



**EVALUATION OF THE REGULATORY REVIEW SYSTEM IN  
TURKEY AND THE DEVELOPMENT OF A NEW MODEL  
FOR IMPROVING THE APPROVAL PROCESS**

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## ABSTRACT

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All regulatory authorities share the responsibility for ensuring patients' timely access to new medicines while maintaining quality, safety and efficacy standards. In addition, healthcare decision-makers must consider the cost effectiveness of medicines and the impact on the national budget. The aim of this study was to evaluate the Turkish regulatory review process and approval times from 2012 to 2015 in order to identify the key issues that need to be addressed. The study included a comparison between the Turkish review process and its quality measures with those of other mid-sized regulatory agencies in Australia, Canada, Saudi Arabia and Singapore to determine the strengths and areas for improvement for the TITCK. To put these issues into context, the pharmaceutical industry experiences of the regulatory environment in Turkey was evaluated as well as patients' knowledge and awareness of the country's regulatory approach to the approval and reimbursement of medicines. Thus, the ultimate aim was to develop an improved review model for the TITCK.

A standardised questionnaire was completed by the TITCK and the four authorities who provided details of their review process for new active substances (NASs) and the quality measures implemented in their assessment procedures. Metrics for medicines approved between 2012 and 2015 were collected from both the TITCK as well as from pharmaceutical companies. A further questionnaire was developed and completed by two hundred and ten patients and the resulting data were evaluated in a unique study.

The comparative study of the TITCK with four comparable regulatory authorities showed that the agency in Turkey conducts a full assessment (Type 3A) for all NAS applications, which is in line with the other mid-sized regulatory authorities, although it does not implement a risk stratification approach. In general, the regulatory requirements in Turkey are aligned with international standards except for certain areas such as the GMP process and pricing. Moreover, the results demonstrated that the approval times in Turkey are longer by two to three months compared to other countries in this study. The TITCK mean approval time for NAS marketing authorisation applications between 2013 and 2015 was three hundred and twenty working days, which exceeded the agency's overall target time of two hundred and ten working days. A similar outcome was identified in the pharmaceutical industry study where the review time was reported to be four hundred and sixty working days and in contrast to the TITCK data this included company response time. Thus, the median time for NASs from first

approval in the world to TITCK approval was identified to be approximately three and a half years. This supported the main findings from the patient study that new medicines become available in Turkey later than other developed countries. Finally, an evaluation of the TITCK decision-making process showed that the essential elements of Good Review Practices (GReP) are implemented, although they are not formalised.

The key issues from these four studies were reviewed with the TITCK experts during a focused workshop. As a result, a new improved review model for the TITCK was proposed. This model utilises the available resources while providing suggested improvements to enable the TITCK to achieve its overall target approval time for NAS applications in a consistent, transparent and predictable manner. These included optimising the TITCK organisational capacity, aligning their requirements with international standards, streamlining the review process, implementing GReP and a structured approach to the Benefit-Risk assessment of medicines. In this way, patients' access to medicines would be enhanced and the new model would support the goal of the TITCK to become an international centre of regulatory excellence in the region.



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## **List OF ABBREVIATIONS**

<b>AIFD</b>	: Research-Based Pharmaceutical Companies in Turkey
<b>APG</b>	: American Pharmaceutical Group
<b>B-R</b>	: Benefit-Risk
<b>CEC</b>	Clinical Evaluation Committee
<b>CMC</b>	: Chemistry and Manufacturing Control
<b>CIRS</b>	: Centre for Innovation in Regulatory Science
<b>CNS</b>	: Central Nervous System
<b>CPP</b>	: Certificate of Pharmaceutical Product
<b>CVS</b>	: Cardiovascular System
<b>CTD</b>	: Common Technical Document
<b>EBS</b>	: TITCK Information Management System
<b>EFQM</b>	: European Foundation of Quality Management
<b>EM</b>	: Emerging Market
<b>EMA</b>	: European Medicines Agency
<b>EU</b>	: European Union
<b>EURDs</b>	: List of European Reference Dates
<b>GDP</b>	: Gross Domestic Product
<b>GMP</b>	: Good Manufacturing Practice
<b>GReP</b>	: Good Review Practice
<b>HSA</b>	: Singapore's Health Science Authority
<b>HTP</b>	: Healthcare Transformation Program
<b>HTA</b>	: Health Technology Assessment
<b>ICH</b>	: International Conference on Harmonisation
<b>IEIS</b>	: Pharmaceutical Manufacturers' Association of Turkey
<b>IND</b>	: Investigational New Drug

<b>IP</b>	: Intellectual Property
<b>ISPAT</b>	: Investment Support and Promotion Agency of Turkey
<b>IT</b>	: Information Technology
<b>MAA</b>	: Marketing Authorisation Application
<b>MHRA</b>	: Medicines and Health Products Regulatory Authority
<b>MOH</b>	: Ministry of Health
<b>NAS</b>	: New Active Substance
<b>NCE</b>	: New Chemical Entity
<b>NDA</b>	: New Drug Application
<b>PMDA</b>	: Pharmaceutical and Medical Devices Agency (Japan)
<b>PMS</b>	: Post-Marketing Surveillance
<b>QA</b>	: Quality Assurance
<b>QALY</b>	: The Quality-Adjusted Life-Year
<b>QC</b>	: Quality Control
<b>QDM</b>	: Quality Decision-Making
<b>QP</b>	: Quality Policy
<b>PBRER</b>	: Periodic Benefit Risk Evaluation Report
<b>PSMF</b>	: Pharmacovigilance System Master File
<b>PSUR</b>	: Periodic safety update report
<b>PV</b>	: Pharmacovigilance
<b>RC</b>	: Registration Committee
<b>R&amp;D</b>	: Research and Development
<b>RMP</b>	: Risk Management Plan
<b>SC</b>	: Scientific Committee
<b>SFDA</b>	: Saudi Food and Drug Authority
<b>SGK</b>	: Social Security Institution

<b>SmPC</b>	: Summary of Product Characteristics
<b>SPPS</b>	: Cardiff School of Pharmacy and Pharmaceutical Sciences Research Ethics Committee.
<b>SOP</b>	: Standard Operating Procedure
<b>TGA</b>	: Australian Therapeutic Goods Administration
<b>TITCK</b>	: Turkish Medicines and Medical Devices Agency
<b>TOPRA</b>	: The Organisation For Professionals in Regulatory Affairs
<b>TÜFAM</b>	: Turkish Pharmacovigilance Centre
<b>US FDA</b>	: United States Food and Drug Administration
<b>WHO</b>	: World Health Organisation
<b>YASED</b>	: International Investors' Association

## GLOSSARY OF TERMS

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**Adverse event:** any unfavourable and unintended sign in a patient or clinical investigation of a subject administered including a symptom or disease associated with the use of a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

**Approval:** a regulatory authority in one or more markets (a product can be legally marketed when the authority grants a licence and subject it to pricing / reimbursement issues) licenses the active substance.

**Authorisation phase:** Includes practices carried out when satisfactory outcomes of the evaluation phase have been reached. These are the product pricing process and the final decision making procedures.

**Benefit-risk framework:** a benefit-risk framework is the basis of regulatory decisions in the pre-market and post-market review process. It takes into account the extensive evidence of safety and effectiveness submitted by a sponsor in a New Drug Application (NDA) or a Biologics License Application (BLA), as well as many other factors affecting the benefit-risk assessment, including the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks. This assessment involves both quantitative analyses and a subjective qualitative weighing of the evidence.

**Biological:** A substance isolated from animal tissues e.g. vaccines, hormones, antigens.

**Biotechnological product:** A naturally occurring or modified polypeptide, protein, DNA or RNA product (produced by recombinant DNA or hybridoma technology and expressed in cell lines, transgenic animals or transgenic plants) for therapeutic, prophylactic or *in vivo* diagnostic use in humans. The only types of vaccines included in the biotech category are recombinant vaccines.

**Centralised procedure:** The centralised procedure is used when marketing Authorisation covering the entire EU region is applied for, for example, for new biotechnological medicinal

products and new innovative medicinal products. The applications for marketing authorisation are then submitted to the European Medicines Agency (EMA).

**Clinical trial:** Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product, and/or to identify any adverse reactions to an investigational product, and/or to study the absorption, distribution, metabolism and excretion of an investigational product, with the objective of ascertaining its safety and/or efficacy.

**Drug product:** A finished formulation, for example, a tablet or capsule that contains the active substance, generally in association with one or more other ingredients.

**European Union Member States (EU):** Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

**Evaluation phase:** Includes all the stages that involve the scientific assessment and quality control analysis carried out to ensure that the medicine is safe, efficacious and of the desired quality standard to be given to the patients. This phase consists of three stages, namely, the scientific assessment stage, the sponsor's interaction stage, and the sample analysis stage.

**Good Review Practice (GReP):** A code about the process and the documentation of review procedures that aims to standardise and improve the overall documentation and ensure timeliness, predictability, consistency and high quality of reviews and review reports.

**ICH Regions:** European Union, Japan and the United States of America (USA).

**Indication:** The specific indication for which the active substance for the project is designed. This may represent the cure, alleviation, treatment, prevention or diagnosis of disease in humans.

**Local study:** A study conducted in a single country with the primary aim of providing local experience with a compound.

**Marketing Authorisation (MA):** Legal approval granted to a company by a national (or regional) authority to market a medicinal product in that particular country (or region).

**Marketing Authorisation Application (MAA):** An application by a company for a marketing authorisation to be submitted to each country (or region) in which marketing approval is sought.

**Mutual recognition procedure:** The Mutual Recognition (MR) procedure utilizes the marketing authorisation granted for an active substance by another EU Member State, Norway, or Iceland. The Member State whose assessment is recognized as a basis for marketing Authorisation is called the Reference Member State (RMS).

**National procedure:** The national procedure is mainly used in cases where marketing authorisation is being applied for in a single member state.

**New Active Substance (NAS):** A chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product. The term NAS also includes: an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product but differing in properties with regard to safety and efficacy from that substance previously authorised; a biological substance previously authorised as a medicinal product, but differing in molecular structure, nature of source material or manufacturing process; a radiopharmaceutical substance that is a radionuclide or a ligand not previously authorised as a medicinal product. Alternatively, the coupling mechanism linking the molecule and the radionuclide that has not been previously authorised.

**New Chemical Entity (NCE):** An entity produced by chemical synthesis.

**New Drug Application (NDA):** An application requesting regulatory approval to commercially market a new drug for human use.

**Patients' access:** The active substance is made available for patients in the private and government sectors in any country.

**Patients' access time:** This is the time from the submission of the registration dossier to the Ministerial price approval of the new medicinal product.



**Pricing time:** The time from the registration of a new medicinal product to the Ministerial approval of the product price.

**Preclinical:** *In vivo* and *in vitro* studies to support administration to man.

**Pre-submission:** The last patient visit for the last pivotal study to be included in the regulatory dossier is complete and the dossier is being prepared but has not yet been submitted to a regulatory authority.

**Review time:** The time from the submission of the registration dossier to the registration of the new medicinal product.

**Shared review:** is one where each participating authority takes responsibility for reviewing a separate part of the dossier. A joint review is one where the whole dossier is reviewed by each authority and the outcome is discussed before a decision is taken.

**Strategy:** The direction and scope of an organisation over the long-term; which achieves advantage for the organisation through its configuration of resources within a challenging environment, to meet the needs of the public and to fulfil the stakeholder's expectations.

**Submission phase:** The submission phase involves all the stages and processes carried out by the authorities' administrative staff prior the scientific assessment of the medicine. These include the receipt and validation stage and the queuing stage.

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# **CHAPTER 1**

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## **GENERAL INTRODUCTION**

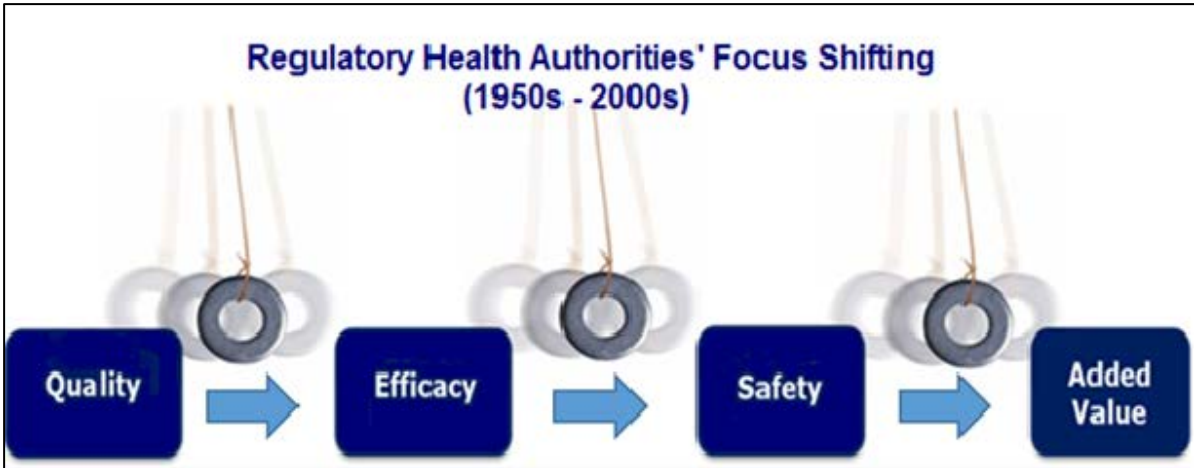
## BACKGROUND

The history of regulating healthcare services and medicines can be traced back in ancient history to Babylon and Mesopotamian times when Hammurabi, who ruled between 1795-1750 BC, was the first to establish a code of laws in relation to medicines and human treatments. This was considered the earliest-known public regulations. (Halwani & Takrouiri, 2006). Similar medical codes and laws can also be found in the ancient Greek Roman times, clearly identified within the Hippocratic Oath. History is full of stories, experiences and events, which demonstrate the eagerness of humanity to develop pharmaceutical and medical sciences and enhance patients' access to better health services, while healthcare authorities focused on how to control and ensure a balance of risks versus benefits for such developments.

Recent years have witnessed an increasing interest in patients' access to medicines by the pharmaceutical industry and Health Technology Assessment (HTA) Agencies (Access to Medicine Foundation, 2016). A new regulated era began in the 1960s, following McBride's publication of "*Thalidomide and Congenital Abnormalities*" in the Lancet in 1962 (McBride, 1962). This was considered a major challenge for the public, national authorities and global healthcare organisations such as the World Health Organisation (WHO). Since 1975, the WHO has made several efforts and published resolutions to support member countries to develop their national regulatory systems and policies to enhance public health and patients' access to medicines in which health authorities play a critical role in assessing the safety of pharmaceutical products as well as quality and efficacy prior to marketing authorisations (WHO, 2015).

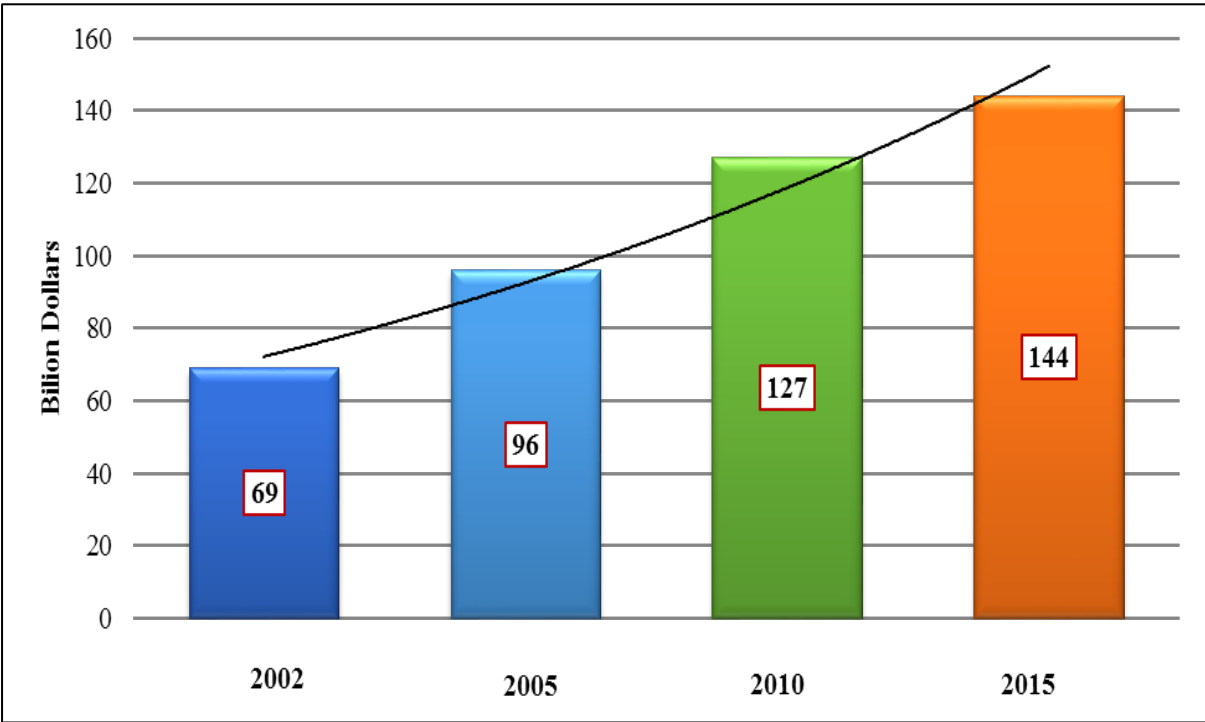
Nevertheless, since the 1960s, throughout the years, the focus of health authorities during the marketing authorisation review process has shown a clear shift from quality to efficacy, from safety to benefit-risk evaluation, and more recently the added value of approved pharmaceuticals (Figure 1.1). This changing and demanding focus for health authorities has also been the main driver for the constant change in the regulatory landscape of the pharmaceutical industry, which is characterised as a very dynamic, rapidly advancing and the most regulated of all industries (Spielberg, 2014).

**Figure 1.1: Shift of health authorities' focus during review and approval process**



Moreover, the need for governments to balance between improving public health and controlling healthcare expenditures, especially those related to pharmaceuticals, has increased all over the world. This was in parallel with the pharmaceutical companies' strategy to introduce new products and treatments, which in turn has led to a steady increase in the research and development costs over decades (Figure 1.2) (Tarmur, 2011).

**Figure 1.2: Total R&D expenditure for the global pharmaceutical industry**



Source: Turkey's Pharmaceutical Sector Vision 2023 Report – AIFD



Bringing new innovative products to the market is a complex process and among millions of compounds in the research and development phase, only a few eventually reach the marketing approval phase. It is estimated that the cost of bringing new drug substance to the market is around \$2.6 billion and takes an average of ten to fifteen years of research and development. (PhRMA, 2015). Thus the main challenge for the pharmaceutical industry, regulatory authorities and payers is to balance the need for new, innovative medicines with the increasing pressure to control the cost of health care expenditure (TUFTS University, 2015).

Global medicines' expenditure has dramatically increased in the last decades due to the increased growth rates in population and aging as well as a better access to medicines around the globe especially in the emerging markets. Accordingly, it is estimated that the global pharmaceutical market will reach approximately \$1.3 trillion by 2018, which is almost more than a 30% increase when compared with 2013 (Aitken, 2014). Furthermore, the total spending on medicines will reach \$1.4 trillion by 2020 (Constantino, 2015).

The significantly increasing healthcare demands, the cost to ensure patients' access to advanced healthcare services and the need for well-being in modern societies has started even to exceed the income in some societies and other developed countries. In Turkey, for example, the healthcare expenditure as a share of GDP has increased 49% since 2002 and public health expenditure, totalled \$18.8 billion in 2005, representing 5.2% of GDP (YASED, 2012)., whereas it increased to \$65.8 billion in 2014 representing 6.4% of GDP (OECD, 2014).

## **The Emergence of Regulatory Affairs**

The increasing level of product and technology complexities together with the constantly expanding number of regulatory agencies, focusing on approval and marketing authorisations, has encouraged several authorities worldwide to issue pharmaceutical laws and regulations to control and regulate the pharmaceutical industry. All over the world, there has been a growing influence of the health authorities' regulations on the pharmaceutical industry at different levels starting from the development phase through the life cycle of a pharmaceutical product to its discontinuation from the market. This level of influence is seen from the change in required standards and the increased demand for data during drug development and the regulatory review. This has led to the new scientific discipline known as "Regulatory

Affairs”; which can be defined as “*a comparatively new profession which developed from the desire of governments to protect public health by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines* (TOPRA, 2014)”.

Establishing the rules and standards for marketing authorisation and review processes of pharmaceutical products means that companies who are developing, manufacturing and eventually applying for a marketing authorisation are equally responsible to ensure that their proposed products for licensing are evaluated appropriately. Additionally, they must be compliant with all the required quality, safety and efficacy standards of health authorities. Currently, with the establishment of health technology assessment agencies with responsibility for reimbursement, pharmaceutical products must demonstrate evidence that they add value to public health and merit the additional cost they bring to national healthcare and social security systems.

## **Global Perspective for Regulatory Science**

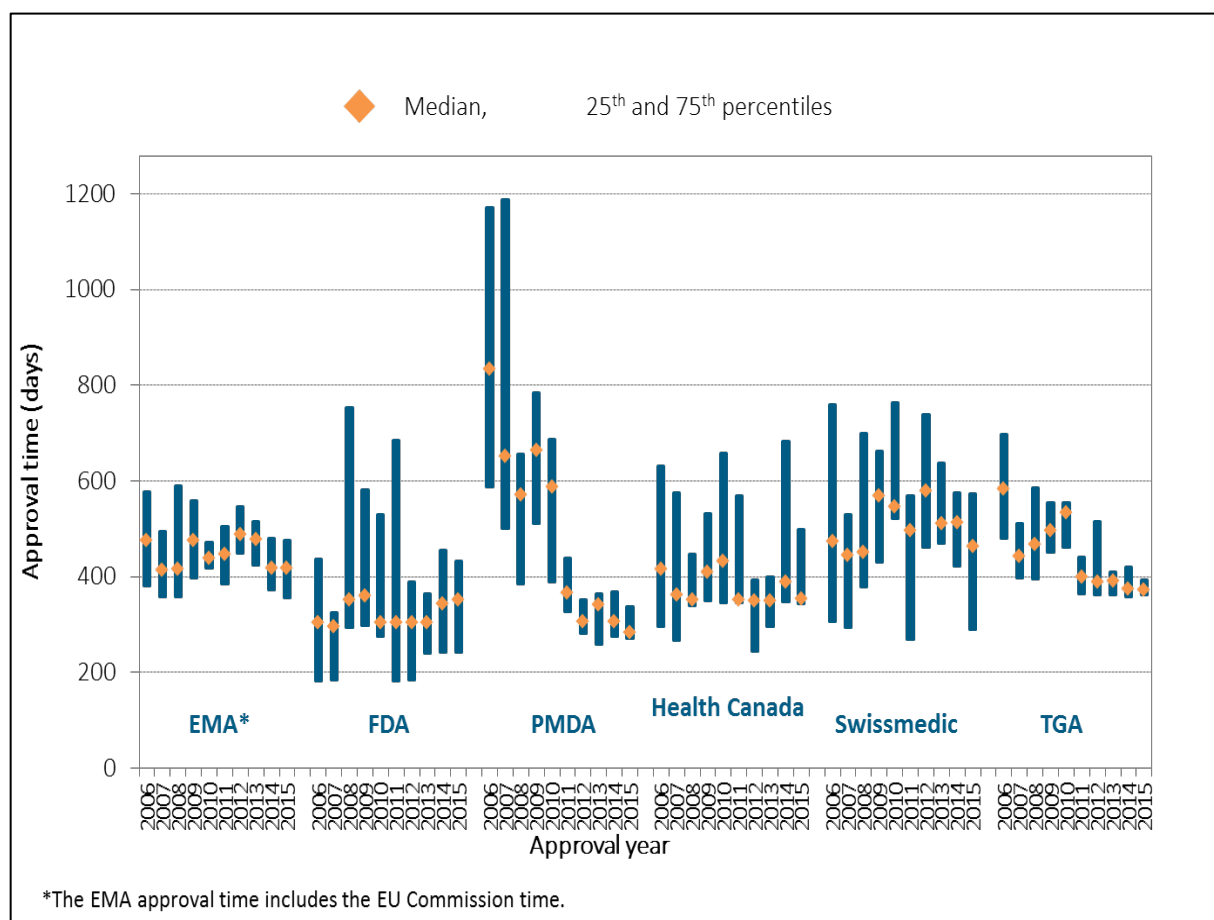
The increasing and different requirements of the regulatory health authorities worldwide brought together the pharmaceutical associations from Europe (EU), United States of America (USA) and Japan with the health authorities from these three regions to think about streamlining this process globally to reduce the cost of development, review and consequently the time to market. As a result, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was established in 1990 with the aim to share and discuss all scientific and technical issues related to pharmaceutical products’ registrations.

One of the main outcomes from the ICH harmonisation effort was the development and implementation of sixty-one regulatory guidelines in the areas of quality, efficacy and safety; eighteen in efficacy, eleven in safety, twelve in quality and ten in the multidisciplinary areas including the cross-cutting topics which do not fit uniquely into one of the quality, safety and efficacy categories (ICH, 2016). These regulations were either adopted or adapted by a large number of countries, which contributed to the harmonisation of the regulatory guidelines worldwide (Cone, 2016). In addition, the ICH generated a standard format for drug applications referred to as the Common Technical Document (CTD), which was proposed by

the industry in 1996 and subsequently adopted by the regulatory authorities. The CTD was an effective vehicle that enhanced the review process and exchange of information globally as well as saving significant resources for the industry. The harmonisation of regulatory requirements brought to the attention of the industry and public, the importance and need for more transparency and consistency to understand the regulators' decisions for marketing authorisations. It has also paved the way to question the different approval timelines for similar products worldwide and the differences of patients' access to innovative medicines and essential treatments.

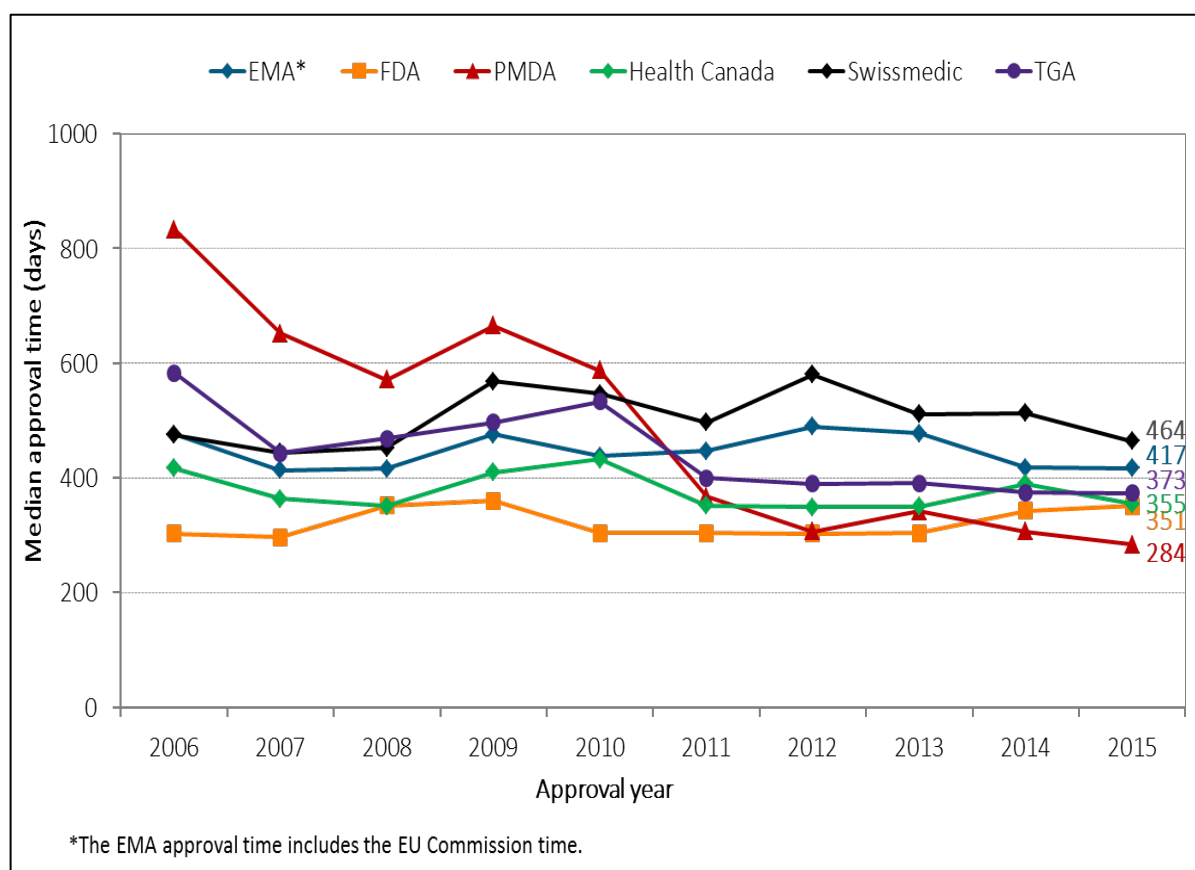
According to Molzon (2010); ever since the adoption of the CTD requirement, the approval timelines of similar new drug products within the major health authorities has become more and more harmonised, while it is still fluctuating dramatically in other countries especially in emerging and developing markets (Figure 1.3 and 1.4).

**Figure 1.3: NASs approval time for major regulatory authorities in 2006-2015**



Source: CIRS, R&D Briefing 59 (Copyright obtained)

**Figure 1.4: Median approval time of NASs in major authorities in 2006 - 2015**

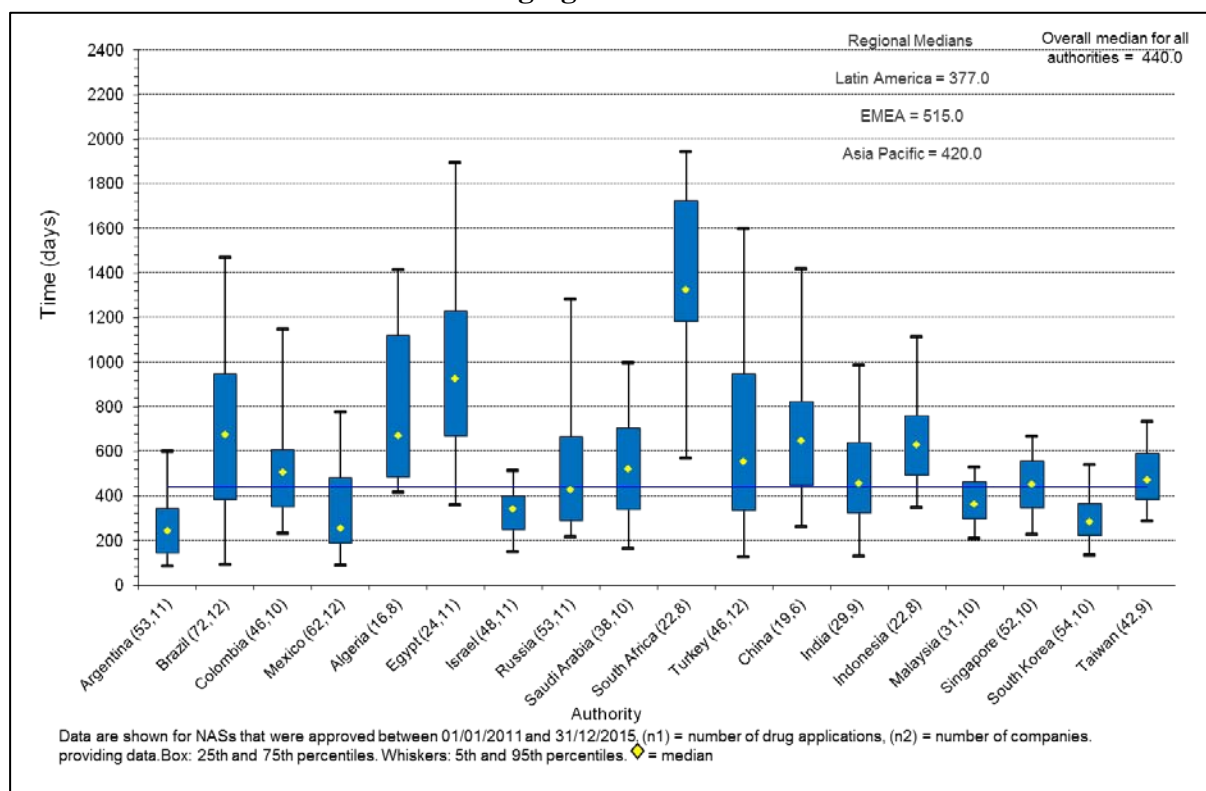


Source: CIRS, R&D Briefing 59 (Copyright obtained)

Figure 1.3 and 1.4 show the median approval timelines (calendar days) of approved new active substances (NASs) from 2006 to 2015 by major health authorities in the EU (EMA), US (FDA), Japan (PMDA), Canada (Health Canada), Switzerland (Swissmedic) and Australia (TGA). The variability of approval timelines reduced among those authorities since 2011 thus presenting an average of ten to fifteen months for approval timelines.

The total approval timelines vary dramatically for the NASs approved between 2011-2015 in the major emerging markets such as Argentina, Brazil, Mexico, Russia and Turkey, Egypt, Saudi Arabia, South Africa, China, India, Indonesia, Malaysia, Singapore, South Korea and Taiwan. Data on the NASs approved in these countries have been analysed based on median approval times in each country, but also the variability of approval times by each authority (Figure 1.5). However, this variability will depend on a number of factors including the type of review whether a verification review such as Argentina or a full review such as in South Africa and Turkey.

**Figure 1.5: Regulatory approval times from date of submission to date of approval for NASs in emerging markets in 2011 - 2015**

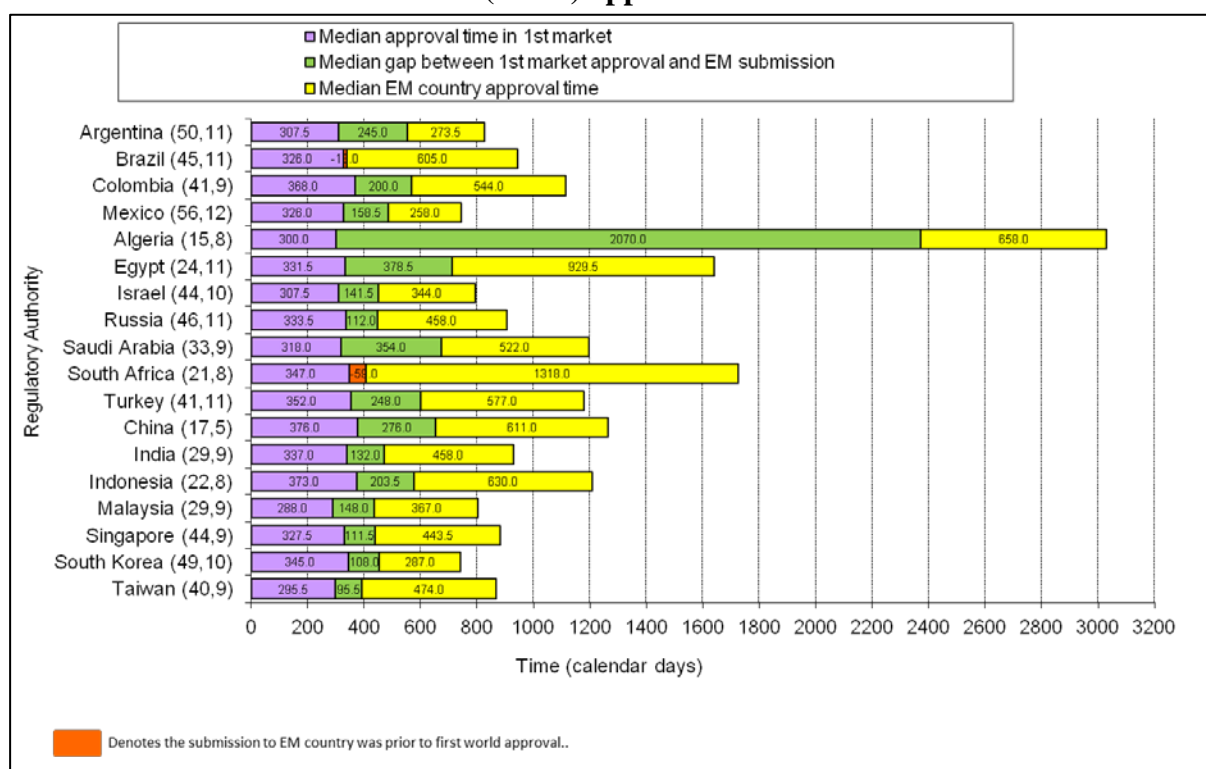


Source: CIRS Emerging Markets Approval Timelines, 2015 (Copyright obtained)

Moreover, Figure 1.6 provides an analysis and comparison of median interval durations for the first regulatory approval for a NAS anywhere in the world, followed by submission and approval for the same compound to one of the Emerging Market authorities. This way, the differences of local requirements for new drug applications in various countries and the variability of the approval timelines and their impact on patients' access to similar products worldwide poses a dilemma of patients' equal rights to access similar treatments worldwide while preserving the national essences and requirements.

Furthermore, unlike most of the emerging markets, NAS applications in Turkey are submitted almost in parallel to first world submissions since prior evidences of approvals are not a pre-requisite for NAS applications. However, the regulatory review process and approvals of NASs submitted between 2011 and 2015 are among the longest in comparison with the other emerging markets after South Africa and Egypt, which consequently delays the availability of NASs in the Turkish market. This is mainly due to the Good Manufacturing Practice (GMP) accreditation process introduced in March 2010 and price negotiations, which both have significant impact on the review and approval process.

**Figure 1.6: Median time to roll out to Emerging Market (EM) countries for New Active Substance (NASs) approved 2010 – 2015**



Source: CIRS Report 2015 (Copyright obtained)

## Key Milestones of the Regulatory Review Process

There are three types of regulatory assessment used worldwide by several authorities. This was agreed as an outcome of the CIRS Workshop on “*The Emerging Markets: Regulatory issues and the impact on patients’ access to medicines*”, organised in Geneva, Switzerland in March 2006. (Walker, et al., 2006). The workshop was attended by several regulators and regulatory agencies worldwide to discuss and evaluate the various types of data assessment methods applied to different applications. Accordingly, the three scientific review models of new drug applications are described below:

### I. Review Assessment Type 1 - Verification model

This model is used by a number of health authorities that lack sufficient resources and capacity to perform a comprehensive scientific review of a new marketing authorisation application (MAA). This model helps reduce duplication of efforts by agreeing that the approving authority will issue a marketing authorisation for any product once the product is officially approved by two or more recognised reference countries. The main responsibility of the local authority is to ensure the “verification” of all data submitted as declared in the

application dossier. This includes the verification review of the product characteristics (formulation, composition and strength) and the proposed labelling information (use, dosage, precautions) for local marketing and that it complies with the reference country(s) authorisation(s). Approval evidence from recognised reference countries, such as the submission of Certificate of a Pharmaceutical Product (CPP), is a pre-requisite for such applications in this review model.

## **II. Review Assessment Type 2 – Abridged model**

This model ensures the optimal use of the available resources by the local authority by not re-assessing the scientific supporting data included in the application of the MAA as long as these data have been evaluated and approved by one or more of the recognised reference countries' authorities. However, the MA application still undergoes an abridged review in relation to the product's use and characteristic in the local market. Therefore, the abridged review model usually contains confirmation of the scientific clinical data but also includes a local review of quality data (CMC) of the product. The review of the quality data is mainly to confirm the product's stability in relation to climatic conditions and distribution infrastructure in the local country.

Moreover, the local review of clinical data might include a benefit-risk assessment in relation to its use in the local ethnic population, medical practice/culture and patterns of disease and nutrition in the country. In the abridged review model, approval by a recognised agency elsewhere is a pre-requisite before the local authorisation can be granted, but the initial application need not necessarily be delayed until formal documentation such as a Certificate of a Pharmaceutical Product (CPP) is available, but must be provided before final authorisation.

## **III. Review Assessment Type 3 - Full review model**

In this model the authority has suitable resources and capacity to perform a full independent scientific review. This includes collaborating with both internal and external experts, to carry out a 'full' review and evaluation of the supporting scientific data (quality, pre-clinical, clinical) for a major application. Full review models, do not require a new marketing application approval in any other country (s) at the time of the submission and thus can carry out an earlier or parallel review to first applications worldwide. However, in some countries,

local regulation requires an evidence of approval in the country of origin or a reference(s) prior to local approval being granted.

## HEALTHCARE SYSTEM AND THE REGULATORY ENVIRONMENT IN TURKEY



Source: [www.wordtravels.com](http://www.wordtravels.com)

Turkey is a transcontinental country that is located at the geostrategic crossroads of Asia and Europe. Eight countries; Bulgaria and Greece border the country to northwest, Georgia to its northeast, Azerbaijani exclave of Nakhichevan, Iran and Armenia to the eastern side, Syria and Iraq to the southeast and the Aegean Sea and Mediterranean Sea to its south border. The current population of Turkey is over eighty million and the growth rate is around 1.29% per year. (World Population Review, 2016). The Gross Domestic Product (GDP) in 2016 was \$735 billion and the GDP per capita in Turkey was last recorded at \$ 9,317 in 2016 (Turkish Statistical Institute, 2016). Moreover, the total public expenditure on health was estimated to be 5% of the total GDP (OECD, 2015).



## **The Turkish Healthcare System – A Historical Perspective**

Historically, the Public Healthcare system in Turkey was officially developed based on western methodologies during the foundation of the Modern Republic of Turkey in the 1920s. The Ministry of Health of the Modern Republic of Turkey was first established in May 1920, with the focus to develop the regulatory framework and necessary legislations in the health care area in addition to restoring the country from the World War I negative health impacts and damages. During that time, the government, with extremely limited resources, provided all health services (Akadagi, 2008).

The period from 1923 – 1946 is considered one of the major milestones in the Turkish healthcare history when significant developments took place in health care services under the leadership of Dr. Refik Saydam who was the Minister of Health. The focus was to establish a central execution, planning, programming and provision point of health services. (Tatar, et al., 2011). Between the years 1946 – 1961 important laws were issued to socialise and further facilitate the health services for all citizens in Turkey. These included the law of *"Socialization of Health Service in Turkey"* No. 224, the *"Turkish Medical Association"* (1953/6023) and the Law of *"Pharmacists and Pharmacies"* (1953/6197).

In the following years, other national plans and programmes to improve healthcare were drafted and approved by parliament. However, many of those programmes failed to reach a legal framework and consequently were never enforced due to the political instabilities and military interventions *"coup d'état"* in 1960, 1971 and 1980. Nevertheless, the essence of those plans and healthcare programmes were the main inspiration behind the latest Health Transformation Program (HTP) in Turkey that started in 2002 (Akadagi, 2008).

Following the last military intervention in September 1980, the health policies in Turkey were mainly shaped by the 1982 constitution, which ensured the equal rights of all citizens to healthcare. For example, article number sixty of the Constitution states; *"Everyone has the right to social security and the State shall take the necessary actions and establish the necessary organization to provide this security"* and article number 56 where the regulatory role of the states in health care was strengthened; *"The State shall regulate central planning and functioning of the health services to ensure that everyone leads a healthy life physically and mentally."* (Constitution of the Republic of Turkey, 1982).

## **The Health Transformation Program in Turkey**

In 2003 the Turkish government implemented the “Health Transformation Program” (HTP) to initiate a new era in the Turkish health care system with the objective to achieve “*Health for All*”. This was identified within an *Urgent Action Plan* to be initiated by the newly elected government in November 2002.

The reforms marked major developments in public access to available health services and treatments (Tarmur, 2011). Subsequently, the scope and objectives of the Health Transformation Program was made officially public in Turkey by the Ministry of Health (Tatar, et al., 2011) and included certain key deliverables such as;

- A fundamental administrative and functional restructuring of the Ministry of Health.
- The establishment of one central point for all health institutions and social security programs to improve the quality of planning and supervising roles of the authorities.
- An enhancement of patients’ access to several health services and facilities.
- An increased efficiency and accreditation of healthcare facilities including pharmaceutical manufacturing sites and health institutions.
- The introduction of the “electronic-transformation” in health information systems to ensure monitoring and traceability mainly in pharmaceuticals’ use and patients’ data.
- The introduction of institutional criteria to promote the rational use and management of medicine and health supplies.
- An increase in the transparency of the decision-making process and data accessibility.

With the implementation of the HTP in Turkey, a number of fundamental and important changes in healthcare policies took place. The program also enhanced the alignment of the Turkish health policies with the European Union (EU) standards that aimed to accelerate Turkey’s EU membership. More importantly, it increased the state governance on approved and reimbursed pharmaceuticals and aimed to establish a central point for all health services, which enabled a better control on the healthcare budget expenditure. Accordingly, the Turkish pharmaceutical industry is mainly a centrally reimbursed market where patients’ access to medicines is mainly attained by having a pharmaceutical product firstly approved by the Turkish Medicines and Medical Devices Agency (TITCK) and afterwards included in the national reimbursement list of the National Social Security Institution (SGK) (Tarmur, 2011).

## **The Turkish Pharmaceutical Industry**

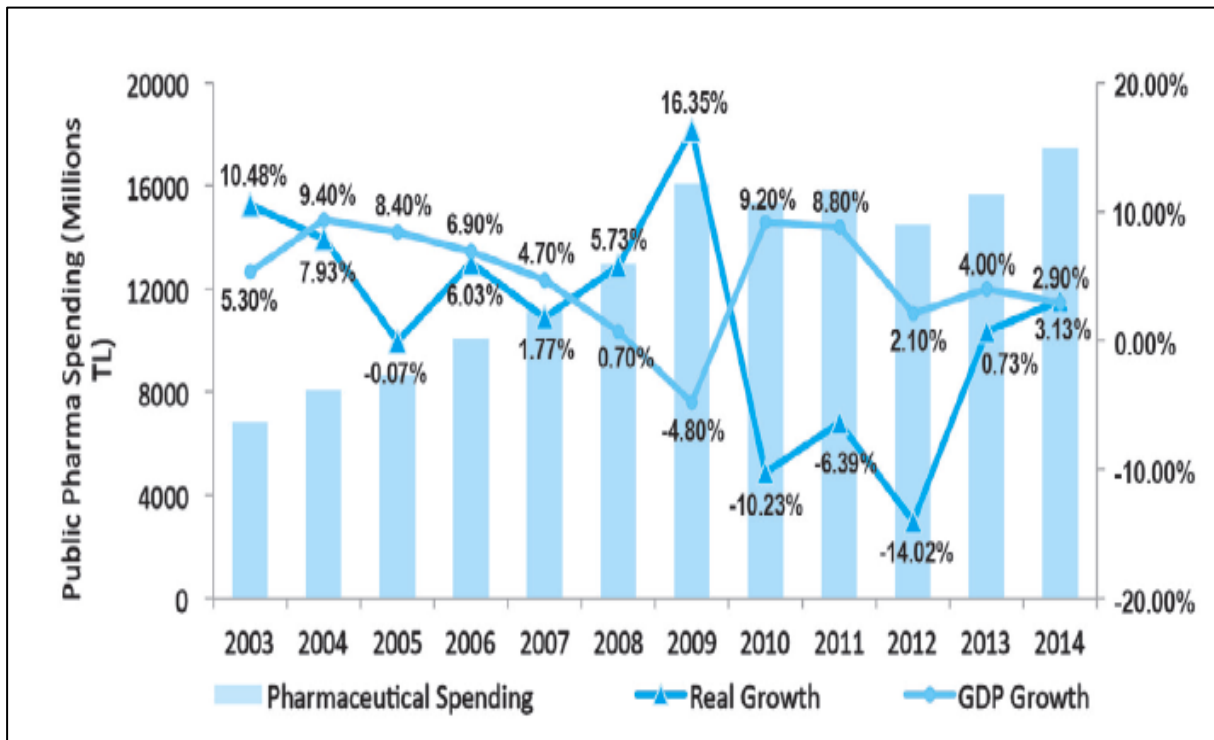
The pharmaceutical market in Turkey is ranked 16<sup>th</sup> among the world's 35 leading pharmaceutical producing countries. (IEIS, 2015). While the provision of healthcare services lies largely within the scope of the state and public institutes, the private sector and pharmaceutical companies (local and multinational) mainly drive the pharmaceutical industry. The market share of originators is approximately 58% and constitutes almost 42% of the total market volume when compared to the generic pharmaceuticals. Since 2002, the Turkish pharmaceutical market has experienced substantial growth, as pharmaceutical expenditure was \$8.87 billion in 2007 compared to \$2.52 billion in 2002 (IEIS, 2015).

Further, this figure reached \$9.82 billion by 2010. Since then, certain governmental measures to control and decrease expenditure volume such as price reductions and health economics criteria for reimbursement were introduced. Therefore, the pharmaceutical market expenditure decreased and reached to approximately to \$8 billion in 2014 (IEIS, 2015). Thus, all those cost reduction practices saved nearly \$6 billion in three years (Figure 1.7).

After 2012, there has been an upward trend in the pharmaceutical spending that reached an average of 2% annual real growth. Furthermore, the pharmaceutical spending in 2009 was 1.7% of GDP compared to 1.5% in 2002 and then dropped to 1% in 2012 and stayed close to 1% in 2013 and 2014 (Figure 1.8) (Gürsoy, 2016).

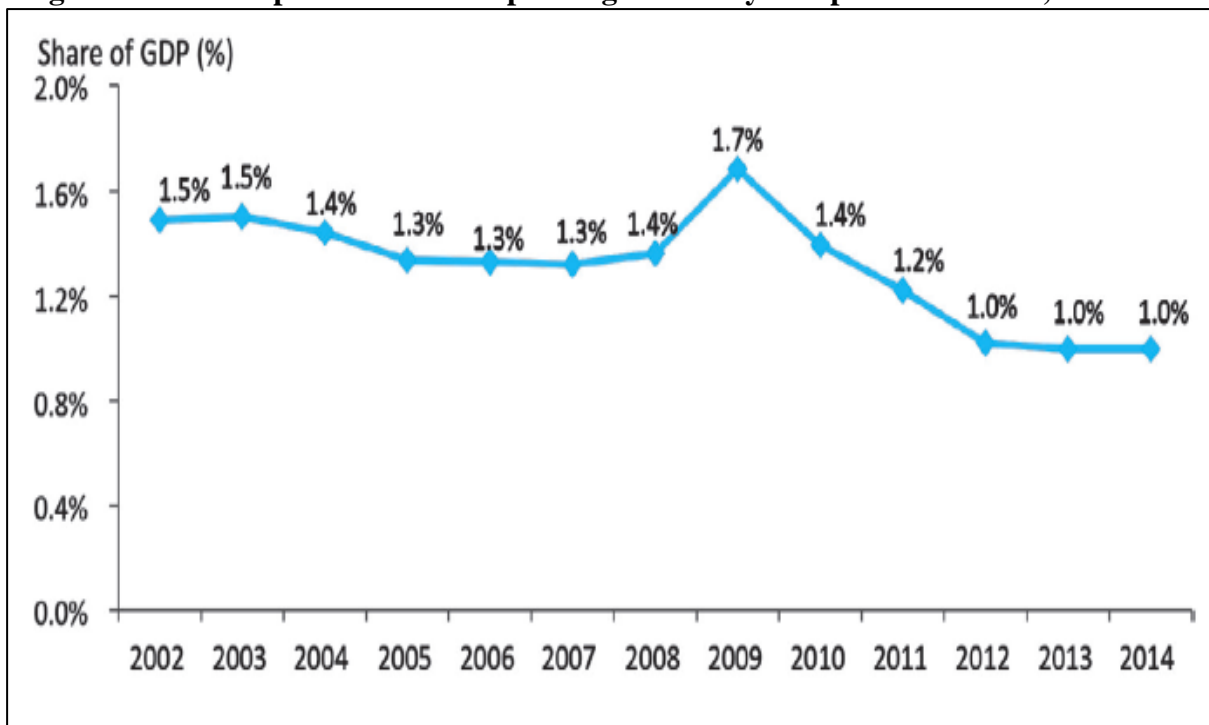
Currently the government's pharmaceutical vision is to make Turkey one of the world's top ten economies in health services by 2023. This plan is to accomplish this by increasing the local R&D expenditure up to 3% of GDP and exports of locally manufactured pharmaceuticals to \$500 billion. According to the Turkish Ministry of Science, Industry, and Technology (AIFD)'s Strategy Report; Turkey should become the Eurasian production base for medium- and high-level technology products (Tarmur, 2011).

**Figure 1.7: Public pharmaceutical spending, real growth and GDP growth in Turkey**



Source: Gürsoy, 2016

**Figure 1.8: Public pharmaceutical spending in Turkey as a percent of GDP, 2002-2014**



Source: Gürsoy, 2016

Prior to 2012, the Pharmaceutical and Pharmacy General Directorate (IEGM) at the Ministry of Health in Turkey was the responsible body for all regulatory activities and control of the pharmaceutical industry ranging from market authorisation, pricing, advertising, inspection and control of medicines at all different levels in Turkey. This is in accordance with the essentials of the “*Law on Pharmaceuticals and Medical Preparations*” (1928) that mandates the regulation of pharmaceuticals and medicinal products in Turkey. Moreover, the Ministry of Finance and the Social Security Institute (SGK), as the main purchaser of pharmaceuticals in Turkey, both play essential roles in determining the reimbursement processes as the basis for the pharmaceutical products.

In 2011 and as part of the HTP, the TITCK was established officially to become the regulatory body responsible for regulating the pharmaceutical and medical device industry in Turkey. This was a positive improvement and brought an expectation for increasing the transparency and scientific developments of the regulatory review and approval processes, while enhancing the quality and timelines of the pharmaceutical regulatory procedures in Turkey.

One of the main roles of the TITCK is to regulate and control marketing authorisations through issuing and enforcing related regulations and requirements for licensing, importing, and marketing pharmaceutical products in the Turkish market. In connection with this, the TITCK is responsible for enhancing the awareness of the pharmaceutical industry for all related regulations accessed from the available official sources, such as the TITCK through the official related websites, official gazette, publications and circulars. Market authorisation is one of the main responsibilities of the TITCK and this process has a number of stakeholders who assist and contribute to the process via several commissions, including academics, pharmacologists and clinicians. The first requirement to apply for a marketing authorisation of a pharmaceutical product in Turkey is for it to be a legal entity registered and located in Turkey whether this is to represent a local manufacturer or a foreign pharmaceutical company. (Ministry of Health Turkey, 1995). The Turkish Patent Law issued in 1995 though not fully providing marketing exclusivity, yet, as per the regulations issued in 2005, the marketing exclusivity of original pharmaceutical molecules is protected for six years after the initial registration of the molecule / product in one of the European Customs Union Zone countries.

## **The Regulatory Review Process in Turkey**

According to the local pharmaceutical regulation in Turkey, a registration approval by the TITCK is required for any pharmaceutical product prior to marketing in the country. This would require an official marketing authorisation application to the TITCK by providing the documents listed under the Licensing Regulation, published in the Official Gazette dated 2005. The regulatory review process in Turkey consists of several milestones and these clarify the key assessments through which a product goes from the time of the application to the TITCK until the patient's access to that specific product. The registration review process, as a step is only one of those milestones that need to be completed which include:

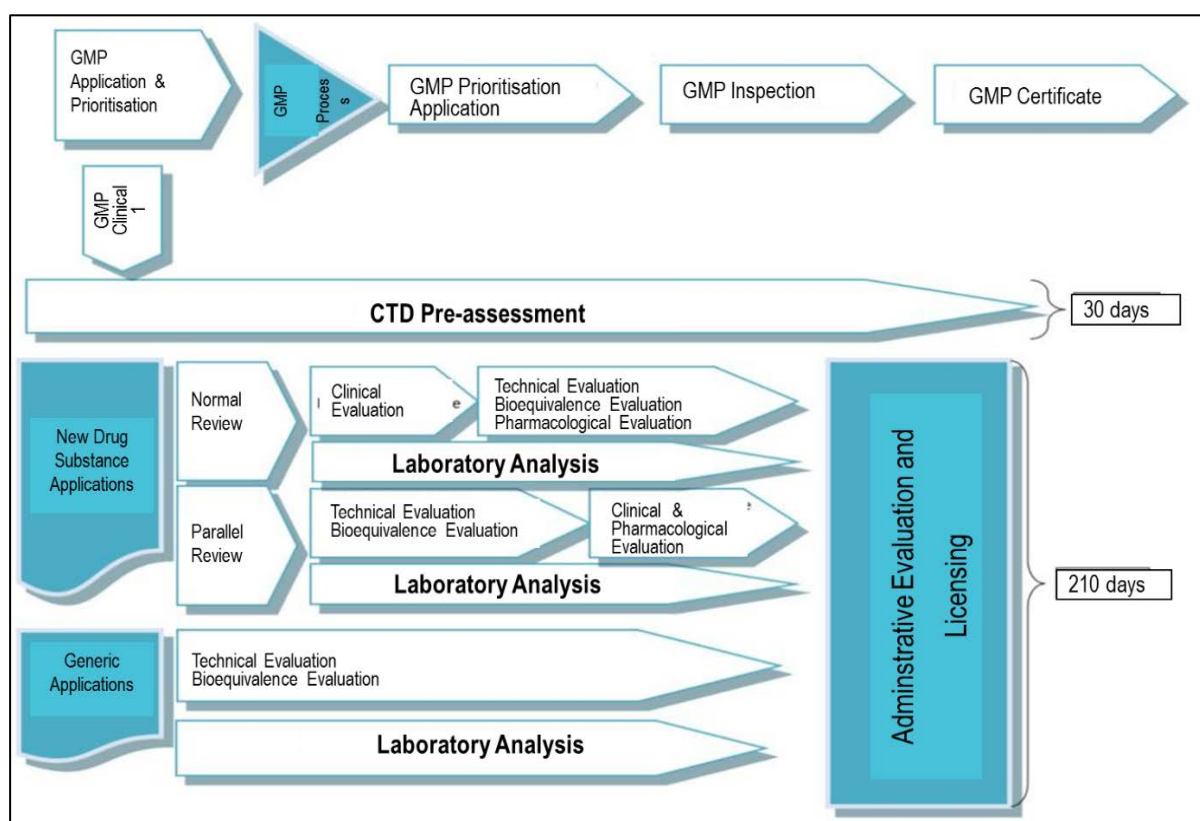
- GMP Accreditation
- Registration review of the submitted application
- Marketing authorisation
- Pricing
- Sales and importation permission
- Reimbursement

### **New marketing authorisation applications and the GMP requirements**

A map of the review process in Turkey is illustrated in Figure 1.9; a general simplified flow chart represents the main milestones of the review process for a New Active Substance (NAS) application from the first step of the preliminary review of the application until the last step when the product is registered. The flow chart also demonstrates the pre-submission steps that need to be completed within the GMP accreditation process.

In March 2010, the Turkish Ministry of Health issued the GMP regulation, which included a pre-requisite step to be fulfilled by all applicants prior to filing for a new drug application or a change to manufacturing site, line or suite. Accordingly, under normal circumstances, the TITCK requires that all pharmaceutical companies, applying for registration of a pharmaceutical product manufactured within or outside Turkey, demonstrate that the manufacturing process and site infrastructure are according to the GMP criteria set by the regulation.

**Figure 1.9: Registration review process for a new drug application in Turkey**



Source: TITCK, 2016

The GMP accreditation process usually requires a “Manufacturing Site Inspection” or Turkish GMP inspection on a product-by-product basis. The inspection comes after an evaluation phase of a submitted GMP application related to an NDA and/or alternative/new manufacturing site application. Unlike many countries in the world, except for highly prioritised applications (TITCK, 2016), the GMP process in Turkey cannot be filed or reviewed in parallel with the new drug registration or site variation process. Therefore, the Turkish GMP accreditation step has a direct impact on the review and market access timelines. Moreover, once a GMP accreditation is granted from the Turkish authority, it is only valid for three years starting from the inspection date and therefore has to be renewed via a separate application, which can be submitted six months before the expiration. Consequently, the GMP requirement and inspection in Turkey has introduced a pre-submission step that takes on average two years leading to a delay and bottleneck in the regulatory review process, which has an average of two to three years when compared with the pre-regulation period prior to March 2010. The GMP process varies in other similar

countries for example in Iran the requirements are similar to the Turkish GMP; however, this could be running as a separate parallel process to the registration review.

In order to obtain an approval from the TITCK, pharmaceutical companies must fulfil a number of regulatory requirements. Firstly the applicant needs to be a legal entity located in Turkey whether a person or a company (Ministry of Health Turkey, 1995). Then an application should be submitted to the TITCK by providing the documents listed under the Licensing Regulation, published in the Official Gazette dated 2005 and which was updated in 2013. Currently, all new drug applications are submitted online to TITCK according to local licensing requirements. The applicant is required to prepare a regulatory dossier in compliance with the common technical document (CTD) with quality, safety and efficacy modules covering both the active drug substance and the finished product. The regulatory application must be organised according to the TITCK Checklist and format and include all the characteristics of the Pharmaceutical Product together with the authorisation status of the medicine in other countries as well as proposed and approved claims and labelling (TITCK, 2005). Following the CTD Pre-Assessment approval, application documents are first assessed by the Clinical Assessment Commission for Medicinal Products for Human Use and then by the Advisory Commissions for Technology, Bioequivalence/Bioavailability and Pharmacology. In addition, laboratory analysis and local risk management plan evaluation should proceed in parallel with advisory commissions.

In 2012 with the new restructuring of the TITCK, a Risk Management Department was established and the Pharmacovigilance Risk Management Unit started to manage and monitor safety risks of all medicinal products. Accordingly, the requirement to submit a local risk management plan is dependent on the nature and safety profile of the product. Submission of Risk Management Plans (RMPs) is mandatory for all biological and biotechnological products during the regulatory review process.

The Registration regulation (2005) Article fifteen states that; *“upon completion of the preliminary evaluation period which is stated to be a maximum of 90 days (including the time period devoted to provide missing documents and answering queries); the regulatory submissions will be evaluated by the agency and need to be concluded within 210 days”*. In general, Turkey evaluates a new drug application based on quality, efficacy and safety similar



to other countries worldwide. However, the regulations contain an exceptional review period of a maximum of one hundred and eighty calendar days to ensure rapid patients' and public access to certain products. This is applicable when the new drug application is related to an innovative pharmaceutical product for treatment or diagnosis, or when a product is considered to be lifesaving from a public health perspective or if the new product or technology is bringing a cost effectiveness benefit to reduce healthcare expenditure (TITCK, 2005).

Additionally, a prioritised assessment and registration review procedure was introduced by the TITCK circular in October 2015 to accelerate the marketing authorisation process for critical applications for certain products such as lifesaving medicines. This was then followed by a guideline issued in April 2016 in order to define the principles of the priority application and review process (TITCK, 2016). According to this guideline, companies are required to submit two separate prioritisation applications for both GMP and registration processes. It is possible to submit both the GMP inspection prioritisation and the registration prioritisation at the same time. Thus, the "Prioritisation Committee" evaluates the innovative medicines' applications based on several criteria including the mode of action, safety, efficacy, additional benefits to patient compliance, impact on the national healthcare budget, the unmet therapeutic need, technology transfer opportunities to Turkey and price. Depending on the assigned registration priority level of the product, the marketing authorisation process could be completed within one hundred and fifty working days for highly prioritised products and within one hundred and eighty working days for prioritised products apart from clock stops in case of notification of deficiency. Also according to the TITCK announcement dated in March 2017, all applications that are not within the "High Priority" or "Priority" status will be included in the "Post-Pre-Evaluation Process Waiting List." However, all applications, which have been granted high priority or priority status, are immediately moved to the "Active Process List," upon paying the "Scientific Examination and Assessment Fee."

When the regulatory application is submitted to the TITCK, this is reviewed at different levels and goes through several assessment stages before approval. Each step of the review process can sometimes contain different sub review processes and can involve external reviewers' assessments as subject matter experts and advisors. Naturally, in cases of questions and queries raised by the TITCK concerning an application, a "clock stop" system is introduced to

the review process. However, the clock stop system can prolong the progress of the review and have an impact on the timeline of the final licensing process.

### **Pricing process**

The pricing process for pharmaceutical products is separate from the marketing authorisation process, yet affects the time of the product to the market. The process is evaluated by a separate independent pharmacoeconomic and pricing commission at the TITCK and can be conducted either in parallel with the application or after the assessment has been conducted by the main technical committee. After assessment by the pricing committee, a sales permit application that enables the marketing of the product could be submitted. The Pricing Commission holds regular meetings and includes several members from the Turkish Agency, Ministries of Health and Finance, Social Security Institute and some other governmental representatives. It has the responsibility to provide to the TITCK with various pricing assessments such as new prices for products, price increases or reductions.

The pricing system in Turkey depends on a referencing process, which was first introduced in 2004, and uses the pricing data from a basket of five EU countries (Italy, France, Spain, Portugal, and Greece) used as the basis for determining the price of an original product. Moreover, a constant exchange rate for Euro into Turkish Lira is determined and applied by the Pricing Commission at TITCK throughout the pricing process, which enables a control on the governmental healthcare expenditure. The pricing rules and referencing process is different for original products compared to generics, as the price of a generic product cannot exceed the original reference price or the highest price of the equivalent generic in the market (TITCK, 2015).

It is worth stating that the pricing regulation sets the highest limits for pricing of pharmaceutical products. Therefore, companies have the option to suggest lower prices to enable the inclusion of their products in the reimbursement list of the Social Security Institute (SGK). Thus, the price labelled on the outer carton of the packaging material shows the official market price based on the pricing process at the TITCK. This means that it reflects the actual price charged to the patient during the purchase of the product as out of pocket or over-the-counter. The discounted price for SGK shows only in the reimbursement price.

When pharmaceutical products are approved, priced and licensed in Turkey, they are subject to a re-registration process once in the 5<sup>th</sup> year counting from the first issuance date of the Registration Certificate. The re-registration requirement in Turkey has also been updated to shift the focus of the TITCK from reviewing the technical aspects to the safety aspects of the products and pharmacovigilance (PV). Accordingly, the submission of a periodic safety update report (PSUR) or a Periodic Benefit Risk Evaluation Report (PBRER) covering fifty-five months data is the main requirement for the re-registration step. Then every three years after the extension of the marketing authorisation validity period, PBRER should be prepared and submitted immediately upon request by TITCK. However, if the drug substance is listed in the current “List of European Reference Dates” (EURDs) and frequency of submission of PSURs” published at the EMA official website, PBRER could be prepared in accordance with this list. Further, according to the latest local pharmacovigilance regulation in Turkey all marketing authorisation applications must include a statement confirming the availability of a local Pharmacovigilance System Master File (PSMF).

### **Reimbursement process**

Turkey is considered one of the efficient centrally reimbursed pharmaceutical markets in the world. In order for any pharmaceutical product to be reimbursed in Turkey, it needs to be approved for the inclusion in the positive list for reimbursement published periodically by the SGK. This requires the submission of a reimbursement application that contains pharmacoeconomic data that support the claim that the new treatment is cost-effective in comparison with alternative treatments available in the market. While this is a mandatory step for original products, the process for generics is relatively easier as the reimbursement application does not require including cost-effectiveness analysis. In general, the conventional reimbursement method requires original products to provide the SGK with a 41% discount of the actual official price approved by the TITCK (Reimbursement Decree 2012). The final assessment for each reimbursement application can take three to four months and the application for the reimbursement of one product can only be submitted twice in a year. Furthermore, an Alternative Reimbursement Model (ARM) with different discount ratios and reimbursement conditions can be utilised and proposed by companies based on confidential terms for certain products such as orphan or highly expensive medicines (Social Security Institution, 2016). The Quality-Adjusted Life-Year (QALY) scores and criteria are not yet considered by the health authorities and SGK during the reimbursement decision process.

According to local regulations, doctors are allowed to prescribe by brand name and the prescribed products can have a higher or lower price than the reimbursed price. In case where a higher priced product is prescribed, the patient needs to agree to pay the difference. Whereas, if it is lower than the reimbursed price, the full cost is covered by the government. In all matters, it is the responsibility of pharmacists to inform the patient of the reimbursement status and provide the lower cost choice so pharmacists are allowed to substitute. Certified chronic disease patients' treatments and in-patients' pharmaceuticals are fully reimbursed. A co-payment of 20% of the reimbursed product has to be paid by the patient at the time of purchase in the pharmacy and this rate is 10% in the case where the patient is retired.

Finally, according to local regulations in Turkey, early access is granted and reimbursed by SGK for life-saving products and orphan drugs on a named patient basis when critical products can be imported and used by patients prior to registration approval and the cost is reimbursed by SGK as per a specific reimbursement protocol (SGK, 2016). Another alternative for early access use of medicines can be provided via compassionate use programs sponsored by companies.

# **AIM AND OBJECTIVES OF THIS RESEARCH PROJECT**

## **Aim**

The aim of the study is to evaluate the pharmaceutical regulatory environment in Turkey in terms of requirements, regulatory review process and timelines and how these are perceived by the TITCK, the pharmaceutical industry and patients.

## **Objectives:**

- Identify the key milestones for the TITCK and the main activities and dynamics in respect to the review process, timelines and scientific assessment models.
- Present the trends for the approved new active substances in Turkey from 2012 to 2015.
- Assess how the TITCK is incorporating good review practices into the assessment and registration processes.
- Determine the similarities and differences in the Turkish Agency's review process in comparison with Australia, Canada, Saudi Arabia and Singapore.
- Evaluate the pharmaceutical companies' attitudes and experiences towards the current regulatory review process and timelines..
- Evaluate the impact of the current regulatory process on patients' access to medicines and identify public awareness with regards to medicines' access.
- Identify the opportunities for the adoption of best practices from other established health authorities leading to a proposed improved model for the regulatory review process in Turkey.

## **CHAPTER 2**

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# **STUDY RATIONALE AND METHODOLOGICAL FRAMEWORK**

## STUDY RATIONALE

The general introduction of this research project gave a historical background of how the pharmaceutical regulatory environment evolved in the modern republic of Turkey and reached its current status. It also highlighted the outcomes of previous studies, which focused on evaluating the regulatory review process, timelines and quality measures in major health authorities such as the FDA (United States of America), the EMA (European Union) and the PMDA (Japan). However, the literature review identified that there is a lack of comparable studies, which provide data on the review models and quality systems of other health authorities such as the TITCK. Hence, the regulatory review process and the performance of the TITCK as an agency have a significant impact on the pharmaceutical industry and patients' access to medicines. To date these have not been adequately evaluated or systematically compared with other authorities. Furthermore, pharmaceutical companies are an important stakeholder and key player within the pharmaceutical regulatory environment where an open dialogue and relationship between the regulatory authorities and pharmaceutical industry can play a key role in fostering innovation and facilitating breakthrough therapies. Thus, the experiences of the pharmaceutical industry towards the regulatory review process and timelines are crucial to assess the efficiency of an authority's review system. Subsequently this can address the key concerns to ensure timely registration approvals in order to meet the increasing demand of patients for high quality, accessible and safe medicines. In addition, patients' awareness of the regulatory environment is believed to be an important aspect and a success indicator of the efficiency in the pharmaceutical system in a country. Nevertheless, no previous study has been conducted to assess the role of patients in the decision-making process of approving and reimbursing medicines in Turkey or the impact of the regulatory environment on their access to medicines.

In light of these aspects, the key issues and focus areas of this study were identified through; a review of published literature and regulations, a series of discussions with pharmaceutical companies' senior staff and TITCK internal and external experts as well as a critical analysis of a fifteen-year personal experience in the pharmaceutical industry. This, as was determined earlier, was coupled with a lack of published evidence regarding the regulatory review process and the quality measures implemented by the TITCK. Thus, no previous studies examined the impact of these processes either on the approval timelines of marketing authorisations of new medicines and/or on patients' access to such medicines.

Accordingly, the study design aimed to collect information and data related to the following:

- Evaluation of the regulatory review process and milestones within the TITCK,
- Assessment of the trends of the TITCK approval times for new medicines,
- Identification and appraisal of the quality measures implemented by the TITCK during the review process,
- Possible solutions for addressing the delays in the registration processes,
- Comparison of the Turkish regulatory review process and its quality measures with other mid-sized regulatory authorities,
- Evaluation of the pharmaceutical companies' experiences towards the regulatory review process in Turkey and,
- Identification of the patients' awareness towards the Turkish regulatory environment and its impact on their access to medicines.

These focus areas led to the conceptualisation and design of four main studies for this Ph.D. research project. These were planned to examine the different stakeholders' views, perceptions and experiences about the regulatory review process of new medicines in Turkey. Accordingly, the methodological framework, underpinning these studies is described in this chapter.

## **METHODOLOGICAL FRAMEWORK**

### **Study Design**

The aim of the study design is to ensure the collection of the appropriate evidences and data to address the study question adequately, logically and scientifically. Therefore, it is important to specify the type of data needed to test a theory, to evaluate a process, or to describe and assess an impact of an observed phenomenon or behaviour. Accordingly, this study employs the quantitative, qualitative, exploratory, descriptive and constructive research methodologies all utilised to evaluate the regulatory review process in Turkey.

### **Types of Study Designs**

**Cross-sectional studies** are also known as transversal or prevalence studies. These are a simple type of observational studies that aim to analyse data collected from a population, a phenomenon or attitude at a specific time with little cost. Moreover, they can be descriptive to



assess a population characteristic, a demographic experience or to describe and evaluate a specific process, or can be analytical to identify the relationship between two variables and investigate the association of a phenomenon with other factors (Trochim, 2006).

**Retrospective studies** look backwards and examine an event or an exposure that took place in the past for which the investigator collects data from past records or databases. However, the data analysis in these studies can be limited and some of its aspects may not be possible to measure. Therefore, these studies are often criticised for being biased and not representative due to the selection of the source for the secondary data (Statsdirect, 2000). Nevertheless, they have their place in a researcher's toolbox when prospective data collection is not possible and / or historical data is needed such as case control studies.

**Prospective studies** evaluate the probability of a phenomenon, a target outcome or interest within a selected group in the future. Thus, the term prospective refers to a selected cohort at present from which an outcome is to be examined in the future. Scientific experiments are generally designed as prospective studies, which depends on the future outcome and of a study conducted as per specific factors to evaluate a certain effect and assess the relationship between variables (Farlex, 2017).

**Longitudinal studies** are observational studies that aim to examine a group of participants for a long period of time, which may take several months or even years to be concluded in order to identify specific correlations between various factors and variables. These studies require continuous follow up and consistent data collection and they do not involve any interventions to the variables (Unite for Sight, 2015).

The cross-sectional study approach was mainly adopted in this study to achieve the aim and objectives concerning the evaluation of the Turkish regulatory review processes and timelines as well as their impact on patients' access to medicines. However, a systematic retrospective approach was also followed for the collection of data from the five regulatory agencies involved in the study and to evaluate the approval timelines for the period from 2012 to 2015.

## Study Participants

The four main studies considered for this research project recruited different target participants in order to generate the required data. The study participants for each study are summarised in Table 2.1.

**Table 2.1: An overview of the study participants**

Study	Study Participants
<b>Study 1:</b> Evaluation of the TITCK review process and timelines.	<ul style="list-style-type: none"><li>• Head of the TITCK,</li><li>• TITCK agency staff and heads of the registration departments and units,</li><li>• TITCK vice president,</li><li>• Ex-TITCK external commission members.</li></ul>
<b>Study 2:</b> Comparison of the TITCK review process and timelines with other mid-sized regulatory agencies.	<ul style="list-style-type: none"><li>• Australia's Therapeutic Goods Administration (TGA),</li><li>• Health Canada,</li><li>• Singapore's Health Science Authority (HSA),</li><li>• Saudi Arabia Food and Drug Administration (SFDA),</li><li>• TITCK.</li></ul>
<b>Study 3:</b> Evaluation of the pharmaceutical companies' attitude towards the Turkish review process.	Pharmaceutical companies operating in Turkey: <ul style="list-style-type: none"><li>• Global companies.</li><li>• Local companies.</li></ul>
<b>Study 4:</b> Patients' awareness of the Turkish regulatory environment and its impact on their access to medicines.	<ul style="list-style-type: none"><li>• Outpatients under treatment with medicines.</li></ul>

## Data collection instruments and procedures

There are two types of data considered as primary data required for scientific research. These can be obtained from various sources using several data collection techniques (The University of Minnesota, 2017), which includes:

- Questionnaires.
- Interviews.
- Focus groups.
- Documents and records available in the public domain or obtained from confidential sources.

## **Questionnaires**

They are tools commonly used within a prospective research design as a method to collect information from a general or a specific group of population of interest either by consecutive / convenient administration or by random sampling. The questionnaire techniques employ the use of a predefined series of questions to collect specific data. Subsequently the responses can be analysed quantitatively or qualitatively, which makes it easier to carry out the analysis and interpret results compared to other techniques.

**Strengths and limitations of questionnaire techniques:** Questionnaire studies are cost-effective and efficient data collection techniques, which can provide accurate generalisable data based on a representative sample of the target population. Therefore, when the target population is very large, diverse in features or geographical located in different areas, such data collection techniques could be the best option to use as a reliable tool and in a timely manner while securing anonymity. However, postal questionnaire studies, do not allow researchers to have a direct contact with the study participants, which may help clarify the questions or help to understand the background behind the responses. Moreover, participants could be hesitant to share information in a written format and return it back to the researcher. This makes achieving a target response rate extremely challenging (NCCP, 2016). In this study, the questionnaire technique was selected as the primary data collection tool due to logistical challenges coupled with the academic desire to recruit participants from a wider field for the four studies.

## **Interviews**

Interviews are one of the qualitative data collection techniques, which can be used in research to explore the different perceptions, views, experiences and attitudes of individual participants (Gill, et al., 2008). Interviews can be conducted in a structured (formal), semi-structured or informal way, either in person or face-to-face or on the telephone. However, the questions asked through interviews should be clear and accurate to enable open-ended responses. However, there are some advantages and disadvantages that may need to be considered when selecting interviews as a data collection technique (Table 2.2) (Businesscom, 2017).

Semi structured interviews were used in this study as a secondary data collection technique which supplemented the collection of factual data and responses from participants related to

the regulatory environment in Turkey. This technique was mainly used in the pharmaceutical industry and patient studies (study three and four) to identify the main themes and to ensure the content validation “often referred to as cognitive debriefing “of the questionnaires during the pilot studies. Furthermore, a number of interviews were conducted with some TITCK staff and external reviewers to enhance the accuracy of the data collected by the standardised agency questionnaire and obtain more information and background to facilitate the analysis.

**Table 2.2: Advantages and disadvantages of interviews**

<b>Advantages</b>	<b>Disadvantages</b>
Can achieve high response rate.	Time-consuming data technique.
Possibility to clarify and ensure the understanding of questions.	Costly, in particular if travelling is required.
Development of a relationship.	The interviewer can bias data, an element of subjectivity.
Can provide better insight, especially about feelings or experiences.	Lack of accurate record keeping
Facilitate in depth analysis with background information.	Difficulty to verify and validate the information provided.

### **Focus Group**

A focus group is an effective qualitative research technique often used to provide data about how a group of people think, feel, behave or act in relation to a specific topic or area of interest. A focus group is conducted by bringing together a group of participants and creating a special environment for them to spontaneously discuss and express their perceptions and experiences regarding a specific topic. This technique depends on facilitating the interaction and active participation of each member; however, the group dynamics can stimulate and affect significantly the nature of the interaction (Mach, et al., 2005). In addition, it may be used in conjunction with other data collection techniques and/or to obtain further data from the interpretations of the participants of initial studies’ outcome or results. This usually allows the generation of additional information for a study on a wider scale. There are different advantages and disadvantages related to this technique, which need to be considered depending on the research question to be answered (Table 2.3) ( Freitas, et al., 1998).

The focus group technique was used twice in this study as a tool to evaluate the perception and attitude of the participants towards the results of the questionnaire studies conducted with the TITCK and pharmaceutical companies. Both focus groups were organised in order to further understand and interpret the results and generate the key issues and messages as well as the focus areas of each study.

**Table 2.3: Advantages and disadvantages of focus group**

<b>Advantages</b>	<b>Disadvantages</b>
Rich source of data to conduct research in a relatively short time.	Requires planning and is difficult to assemble the correct group.
Allows the exploration of more ideas and the generation of data.	Difficult in the data analysis and interpretation.
Allows data collection on a specific topic from a group of participants in a short period of time.	Data are generated in a controlled atmosphere (rather than a natural one).
Relatively cost effective.	Unpredictable in terms of the group interaction.
Quick way to supply data and results (in terms of evidence of the meeting of the group)	Requires intensive effort and attention to capture the data.

### **Existing documents and records**

The analysis of available documents and records can be used as a source for data collection mainly for qualitative research. Analysis of existing documents is an important tool to collect data from a wide variety of sources either available in the public domain or obtained confidentially and therefore it is a good methodology for policy and process evaluation as well as organisational reforms. Examining existing documents or published records has some advantages and limitations where the findings should be confirmed by conducting further studies employing other data collection techniques. Nevertheless, this technique is helpful to define the main themes of the research study and narrow the study question (Trochim, 2006).

Several publicly available documents and regulations were analysed in this study to obtain data regarding the regulatory review process in Turkey. Thus, using this technique facilitated both the design of the sub-studies and the development of the related questionnaire, which included all the necessary questions to address the key issues identified, based on the document analysis.

## **Different Types of Questionnaire Techniques Used in Data Collection**

There are different types of questionnaire techniques that can be used for data collection and thus the choice of the most appropriate method often depends on the objectives of the study, the nature and the size of the target population, the timing of the study as well as the available resources (Mach, et al., 2005).

### **Paper or Electronic mail-delivered**

Paper based questionnaires can be distributed by post as hard copies to a large number of study participants within a specified time. Electronic questionnaires utilise a data collection method where the questionnaires are sent electronically via e-mails and are often quicker and less costly compared to paper based questionnaires. In general, these are excellent data collection tools since participants can respond to them at their convenience and feel more comfortable and truthful when responding to questions anonymously even for controversial issues. Nevertheless, it is usually difficult to get the completed questionnaire back and therefore achieving a high response rate is challenging (Leedy & Ormrod, 2010).

### **Group-administered or interviewer administered questionnaires**

This type of questionnaires involves bringing together a group of participants and asking them to respond to a structured sequence of questions individually. Questionnaires are distributed and collected in-group settings at a defined time, which enables a high response rate. This also facilitates the clarification of unclear questions to all target participants (Trochim, 2006). An example of this type of questionnaire is data collection in an outpatient clinic setting.

### **Telephone-administered**

This method is a rapid and inexpensive tool used to collect data by calling the study participants and recording their responses systematically to generate data for the study. Furthermore, responses can be obtained via an automated system where participants can reply by selecting from a set of pre-defined answer choices via a touch-tone telephone directly linked to a web-based survey system or a voice recognition software (Leedy & Ormrod, 2010). However, language barriers and different time zones are among the main disadvantages of this method, which limits its use for international studies.

### **Web-based**

Web-based questionnaires, also commonly referred to as online surveys, are quick and easy to organise where study participants can complete the questionnaires individually at their convenience and directly on web sites. Web-based questionnaires are cost effective and enable a quick response. Nevertheless, the respondents require a good internet connection to access the questionnaire on the website (Wright, 2005). Paper based questionnaires were used in this research project to collect data from the participants in the patient study, while these were distributed and collected electronically in the regulatory authorities and pharmaceutical companies' studies.

### **Data Source for the Studies**

To achieve the objectives of this study, data were collected from five regulatory health authorities, pharmaceutical companies and patients according to specific criteria.

### **Inclusion criteria**

For the evaluation of the TITCK regulatory review process and approval timelines, the comparison with other regulatory agencies and the pharmaceutical industry studies, the main inclusion criteria was related to data on New Active Substances (NASs) obtained from local and global companies, which have been approved in Turkey between 2012 and 2015. Detailed regulatory information about these products was included in this study such as; *first world approval*, *submission date in Turkey*, *regulatory evaluation time*, and *approval dates* were included in the total approval time. Furthermore, the views and perceptions of patients as well as the pharmaceutical companies on their experiences with the Turkish regulatory environment and in particularly on the registration review process were collected using the different types of questionnaires as well as interviews.

### **Exclusion criteria**

Data related to generic products or those with missing information of submission or approval dates as well as patient questionnaires that did not have a signed informed consent were excluded from this study.

## **Data Collection Procedure**

Questionnaire techniques were used for all four studies; they were applied electronically to regulatory authorities and companies, but as paper copies to patients. Throughout the study confidentiality and/or anonymity was strictly adhered to and only aggregated data were analysed. For example, data related to product approvals and timelines were collected from individual companies “anonymised by using a third party”. Similarly, patient questionnaires were completed anonymously where individual responses were not identified and therefore this did not allow any follow up during data collection and analysis.

## **Data Collection Monitoring and Timeline**

Several face-to-face meetings including those with the head of the TITCK and calls with the units’ coordinators took place to follow-up on the data to be obtained from the TITCK. Participants were asked to provide data related to the regulatory review process, approval timelines from 2012 to 2015 and the quality elements implemented by the TITCK. Collected data were then standardised into a country report in a word document and returned to the TITCK for auditing, correction and comment. In addition, face-to-face meetings with the pharmaceutical companies through the industry association were held to ensure their participation and emphasise the rationale and objectives of the study.

## **Questionnaire Development**

Three different questionnaires were employed during this research project to be used with the different study participants namely;

- The TITCK and other regulatory authorities,
- The pharmaceutical companies,
- Patients.

**Study One and Two:** The first regulatory agency questionnaire was developed based on established questionnaires previously used in an Emerging Markets Programme to evaluate the regulatory process for new medicines and the impact on their availability to patients (McAuslane, et al., 2009). The questionnaire (Appendix I) was reviewed and pre-filled based on publicly available data in order to test the validity of the questions. The questionnaire was administered electronically and aimed to examine the regulatory review processes, approval



timelines as well as the implementation of the quality elements built into the review processes in Turkey, Australia, Canada, Saudi Arabia and Singapore. The questionnaire enabled a standard mapping of the review process and an understanding of decision-making while allowing the comparison among other regulatory agencies.

**Study Three:** The second questionnaire was developed to assess the views and experiences of the pharmaceutical companies with regards to the Turkish review process. The questionnaire was designed following a series of consultation with industry experts and a review of previous surveys of pharmaceutical companies conducted to evaluate the companies' experiences about the TITCK practices, regulations and their interaction with the industry. Accordingly, the main themes of the questionnaire were generated. In addition, a pilot study was conducted with some companies to ensure the content validation and usefulness of the questionnaire.

**Study Four:** The third questionnaire was developed following several discussions with patients and physicians regarding the patients' knowledge and concerns about the pharmaceutical regulatory environment in Turkey. This questionnaire was then piloted among a group of patients and physicians to determine its acceptability, applicability and ensure its content validation.

### **Consensus generating methods**

Chapters Three, Four, Five, Six and Seven aimed to provide both qualitative and quantitative data and evidences to establish a consensus of opinions on the common key issues that currently do not have adequate information. Different consensus methods were implemented throughout the four studies; in order to establish a certain level of agreement mainly in controversial issues where there were insufficient or contradictory data to support certain evidences (Fink, et al., 1984). The ultimate aim of these methods was to measure the extent of the consensus among the four studies and accordingly resolve the disagreement by establishing a consensus development (Holey, et al., 2007). The most commonly used method for generating consensus is the Delphi process, a nominal group technique (expert panel) and the consensus development conference with each having different features (Table 2.4) (Fink, et al., 1984).

**Table 2.4: Features of consensus generating methods**

<b>Feature</b>	<b>Definition/ Use</b>
<i>Anonymity</i>	<i>To avoid dominance; achieved by use of a questionnaire in Delphi and private ranking in nominal group.</i>
<i>Iteration</i>	<i>Processes occur in "rounds", allowing individuals to change their opinions.</i>
<i>Controlled feedback</i>	<i>Showing the distribution of the group's response (indicating to each individual their own previous response in Delphi).</i>
<i>Statistical group response</i>	<i>Expressing judgement using summary measures of the full group response, giving more information than just a consensus statement.</i>

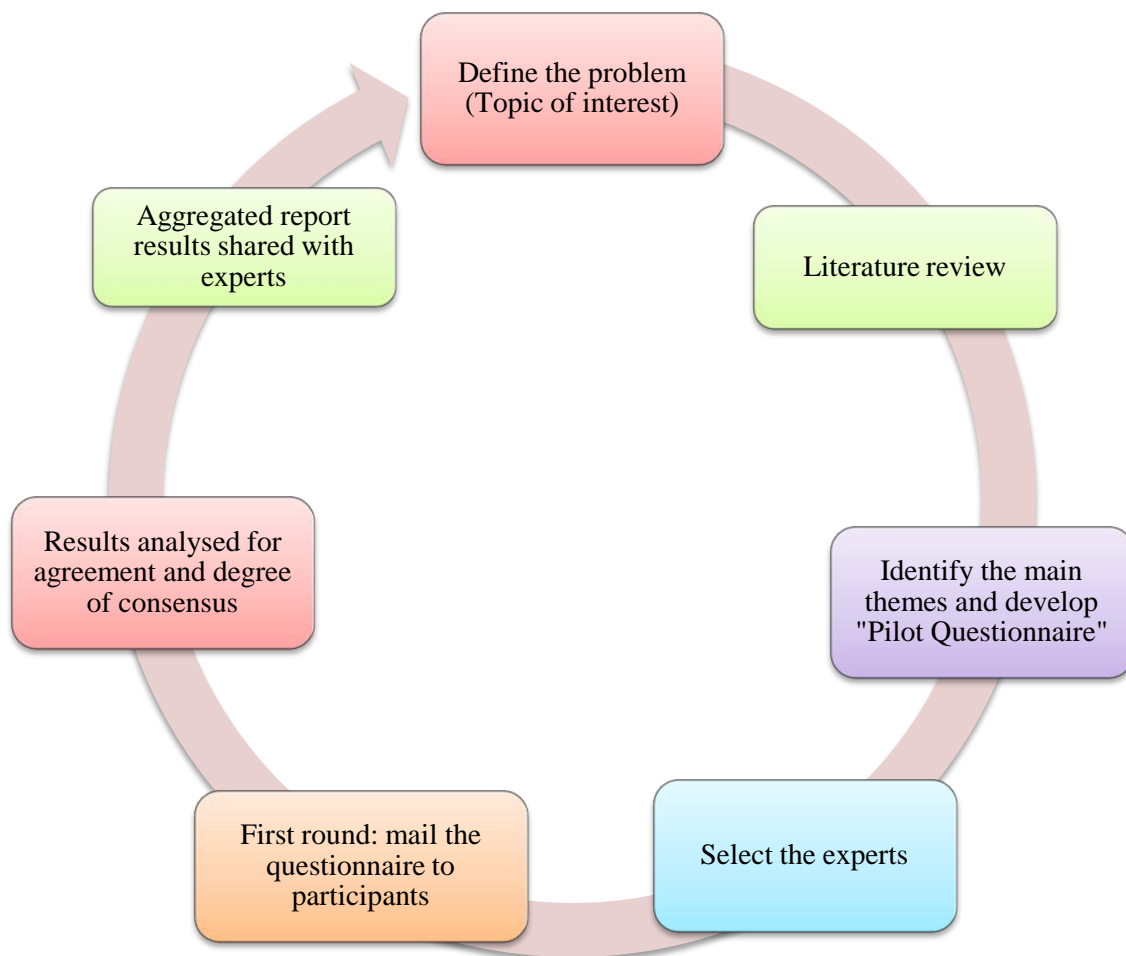
Source: (Jones & Hunter, 1995)

### **Delphi approach**

Delphi approach is a consensus method in which the opinions and views of an expert panel is obtained systematically by sending the questionnaire for individual review for several rounds, followed by sharing the aggregated responses anonymously with the group after each round. The experts are allowed to express their opinions impersonally and following each collective response, they are asked to review their answers in subsequent rounds. Eventually, the Delphi method aims to ensure a consensus after several rounds in order to reach the "correct" response.

The Delphi technique is considered an inexpensive and quick method, since it does not require the physical interaction of experts and the questionnaires round can easily be completed via e-mails. Therefore, there are no geographical limitations when selecting the experts. Nevertheless, the reliability of this method depends on both the number of experts as well as their level of expertise (Fink, et al., 1984). In this study, the Delphi approach was used to a certain extent to develop a consensus of views regarding the content of the questionnaires both in the patient and industry study. The aim was to determine the main topics and themes and accordingly ensure the appropriate data collection to support the scientific evidence required for this thesis (Figure 2.1).

**Figure 2.1: An illustration of the Delphi approach (one round)**



### **Nominal Group Technique**

Nominal Group Technique is mostly used in healthcare and clinical disciplines to confirm the correctness of a specific treatment or clinical intervention and achieve an agreed single objective. It is a structured meeting organisation, which allows a group of experts to collectively brainstorm and think about solving a specific problem. This technique requires the physical interaction of the expert group where each participant is initially asked to individually identify and present their own views regarding the question in a prioritised manner. This is then followed by a group discussion and rating of all the views, which is repeated to achieve a final list or single solution agreed by all participants. The nominal group technique was not used in this research project where several views were to be incorporated.

### **Consensus Development Conference (CDC) method**

Consensus Development Conference is a formal method developed by the US National Institutes of Health (NIH) in 1977, with the aim to evaluate activities and actions regarding a

specific topic by bringing together a selected group of people from all relevant stakeholders. The selected expert panel examine the presented evidences and accordingly prepares a report with a list of recommendations to develop consensus about that topic (Fink, et al., 1984). This method, was not used in this research project, however, it was suggested to be used for future work based on the findings from the different studies in this thesis.

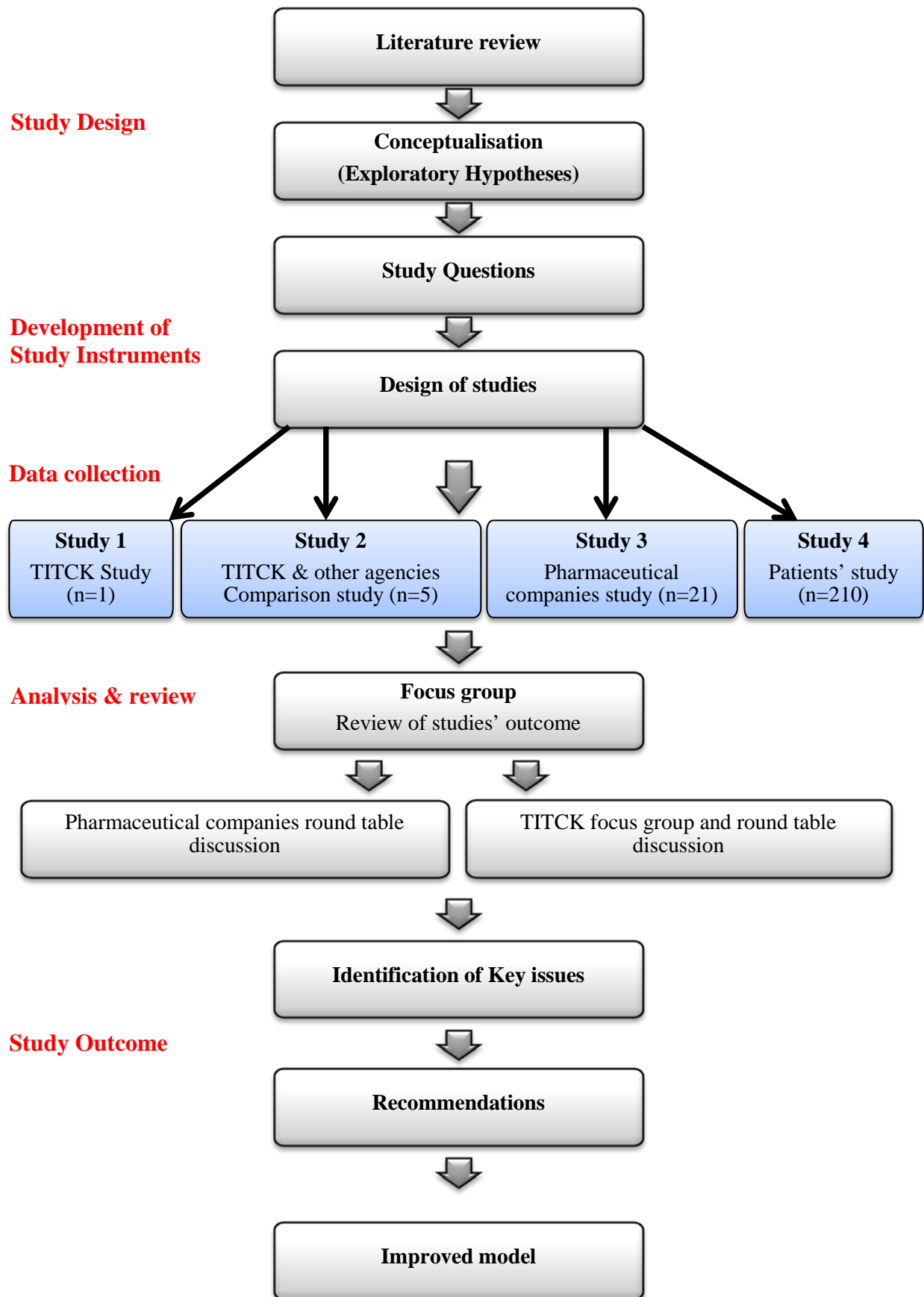
## **Development of the Study Plan**

Chapter one presented a comprehensive review and critical analysis of the literature in the area of the pharmaceutical regulatory environment in Turkey and in particular the TITCK review process. Accordingly, it is believed that there is considerable concern and a systematic gap between the actual and the target approval times of the TITCK registration review process. This was observed by the delayed access of patients to medicines as well as inefficient regulatory performance of the TITCK compared with other developed regulatory authorities. Therefore, the aim of this research was to evaluate and critically analyse this area of concern from all the industry and patients' perceptions. Furthermore, the objective was to understand the regulatory review practices of the TITCK and address these challenges in order to achieve an effective and improved regulatory review. Therefore, the following study plan was developed to capture data on the regulatory environment in Turkey. The plan was then carefully examined to fulfil the objectives of this research, which consisted of four studies each forming a thesis chapter that explores the key characteristics of the Turkish regulatory review process. The study flow chart plan is illustrated in Figure 2.2.

The following methods were used to collect the required data for the four studies:

1. Review of the literature and/publications in relation to the pharmaceutical environment, access to medicines and regulatory review process in Turkey.
2. Identify a list of contacts of key regulatory officials within the TITCK such as the head of the TITCK, vice presidents, registration department heads and unit coordinators.
3. Consult with regulatory experts in the industry, ex-commission members, and external reviewers of the TITCK.
4. Develop a questionnaire to be completed by the TITCK to assess the review process and timelines and compare the review processes, quality tools, and strategic plans with other mid-sized regulatory authorities.

**Figure 2.2: Study flow chart and key milestones**



5. Conduct a comparative study of the TITCK with other mid-sized regulatory agencies using the same agency developed questionnaire.
6. Develop a second questionnaire with the aim to evaluate the pharmaceutical companies' views and experiences with Turkish review process.
7. Data collection from the pharmaceutical industry study and produce a study report discussed with participating companies.
8. Develop a third questionnaire to evaluate the patients' awareness of the pharmaceutical regulatory environment in Turkey.
9. Conduct a comparison and critical analysis of the overall results in order to assess the TITCK regulatory review process and compare the relevant experiences of regulatory authorities, pharmaceutical companies and patients.
10. Conduct focus group and workshop meeting with key regulatory experts and heads of the TITCK in order to evaluate the results and outcomes from the four studies and identify the key areas of improvements.
11. Produce individual study outcome reports as well as an overall focused report with key issues and recommendations following the TITCK workshop.
12. These reports formed the basis of the relevant chapters in this thesis.
13. Develop the proposed improved regulatory review model for the TITCK.

## **Development of the Study Instruments**

The sequence of events to be conducted to achieve the overall aim of this research commenced with an evaluation of the regulatory approval timelines in Turkey. This was a lengthy and challenging process, as it required a sequence of data collection and exchange of information related to the registration review procedures and practices as well as quantitative data of submission and registration approval dates of NASs for the years 2012, 2013, 2014 and 2015. During the course of collecting data on the approval timelines in Turkey, three questionnaires to examine the views and experiences of the TITCK, pharmaceutical companies and patients, with respect to the Turkish registration review process were developed. The first questionnaire was to be completed by the TITCK and distributed among four mid-sized regulatory agencies in Australia, Canada, Saudi Arabia and Singapore. The second was designed to survey pharmaceutical companies in Turkey, which are marketing authorisation holders or applicants of NASs in Turkey. In addition, the third questionnaire was developed and distributed to patients in Turkey who were under treatment with medicines

in order to evaluate their views of the pharmaceutical regulatory system. Two pilot studies were conducted one with three pharmaceutical companies and another one was piloted among thirteen patients and four doctors to assess the applicability, content validity and relevance of the study instrument planned to be used in the studies. The review and approval times for NASs by the TITCK for the years from 2012 to 2015 were obtained directly both from the pharmaceutical companies and the TITCK as well as compared accordingly.

## **Evaluation Process of Questionnaires**

All questionnaires, whether newly developed or created from an existing one, should be reviewed and evaluated in terms of appropriateness, effectiveness and reliability in order to ensure that the questionnaire measures what it purports to measure. For this purpose, the two main methods that are commonly used to develop and evaluate questionnaires are the cognitive and psychometric methods. Thus, an evaluation of the psychometric properties of a questionnaire is essential before it is used and this includes an evaluation of the applicability and acceptability, validity, reliability, consistency, test dimensionality and responsiveness of questionnaire (University of Minnesota, 2017).

### **Evaluation of Psychometric Properties of Questionnaires:**

#### **Applicability and acceptability for use**

Key indicators of the quality of a questionnaire are related to its applicability and acceptability to serve the purpose of the study. Applicability defines the appropriateness and usefulness of a study instrument in terms of its content, use, wording, clarity and simplicity of language, which directly influences the usefulness of the instrument to reach its goals. Furthermore, acceptability is measured by the willingness of study participants to complete and respond to the questionnaire in a timely manner and therefore accept its features related to the clarity, readability and accuracy of questions (Sidani, 2015).

#### **Practicality**

This refers to the level of comfort and convenience of a study participant to respond to a questionnaire and engage in the study. Thus, the practicality of a questionnaire depends on its mode of administration, format and layout, cost effectiveness and the required resources and time to respond to and return the questionnaire. These features if planned and evaluated appropriately in advance can directly influence and increase the response rates.

## **Validity**

The validity of the questionnaire is a key feature that needs to be evaluated prior to the initiation of a questionnaire study. This requires a sensitive investigation of the instrument as it defines the extent to which the questionnaire is capable of measuring for what it is designed. There are different types of validity such as; construct validity, content validity and criterion related validity (Kimberlin & Winterstein, 2008).

- I. Construct validity:** This type of validity is the most accurate and sound method to confirm validity. Construct validity examines the logical relationship of the measures and the variables, that are assessed in the study and therefore includes a comparison between the measures where the identified correlations contribute to the evidence of construct validity.
- II. Content validity:** This type of validity addresses the extent to which the questions in a questionnaire are well developed to provide the important features aimed to be measured in a balanced way. So far, there is no statistical test or measure to assess whether a tool is adequately covering a content area as content validity often relies on the judgment and views of experts. Unless there is a “golden standard” available.
- III. Criterion related validity:** This type of validity aims to provide evidence of how well a new measure correlate with other previously established measures, and produces similar standard outcome at a different time, cost, or method. It is important that these criterion measures are valid themselves.

## **Reliability**

This is the measurement and estimate of how much a measuring instrument would be producing “correct” outcomes with minimum “errors”. Stability and consistency of an instrument are the main parameters that contribute to its reliability. Thus they can always be determined using internal consistency and test-retest reliability measures (Kimberlin & Winterstein, 2008).

## **Sensitivity**

The sensitivity of an instrument can be measured by its ability to identify accurately a small but important change during the course of the study (Kit, 2008). Psychometric properties were considered carefully when the questionnaires of the four studies were designed and developed in order to collect data from the participating regulatory authorities, pharmaceutical



companies and patients. Two pilot studies were planned within the pharmaceutical companies and patients' study with the aim to ensure the practicality, acceptability, content validation and increase the level of confidence about the clarity of the questions. Thus following the pilot study, comments and feedbacks of participants were analysed, consolidated and incorporate into the final versions of the questionnaire.

## **DATA PROCESSING AND ANALYSIS**

In this research project, data were collected as either paper based or electronic questionnaires using postal mail, electronic mail and semi-structured interviews. The responses from the industry and patient studies were first anonymised to ensure confidentiality, then coded and analysed accordingly. Data from all four studies were entered into Microsoft Excel for data processing and analysis. The results were presented either as means and/or as medians (*the value halfway through the ordered data set*). Depending on the data set, different types of graphics ranging from bar charts, frequency tables, pie charts, box and Whisker plots were used to illustrate the results and provide a comprehensive visual tool to understand the relationships between variables. For open-ended questions and free text responses, a manual content analysis was carried out to determine the participants' insights that were then grouped under themes and sub-themes (Wiles, 2008).

### **Data analysis assumptions**

This research project and the four studies that were carried out to underpin the aim and examine the research questions were exploratory in nature and not designed to test a hypothesis. Thus, no statistical test was applied for analysis of the generated data. However, the outcome of the descriptive and qualitative analysis had the potential of generating hypothesis that could be pursued as future studies. Nevertheless, in discussing the outcome of each study, it was decided, in order to contextualise the interpretation of findings as such that the readers would be better able to relate to them, to assume a number of hypothetical hypotheses. It is also hoped that this approach would facilitate the execution of future hypothesis testing studies as a continuation of this research project.

### **Qualitative data analysis**

The processes outlined above resulted in large amounts of qualitative data. Data analysis sought to refine the data into a long-list of items to reflect the research project conceptual

framework in a manner that is transparent and meaningful. Therefore, data analysis was both inductive – discovering new patterns and themes, and deductive - that is, with reference to the evolving conceptual framework to permit moving back and forth between hypothetico-deductive and inductive approaches ensuring that the study aim (s) and prior knowledge were not ignored (Mayring, 2000). Several steps were carried out. First, the accuracy of the transcribed audio-recordings was checked to ensure preservation of the integrity of the generated data. For example, the validity of between 10% of transcribed interviews was checked against corresponding interview recordings.

Data analysis sought to use words and phrases generated by participants to interpret the text data and craft the evolving concepts, themes and sub-themes of the conceptual framework (Hsieh & Shannon, 2005). The data was coded by a trained researcher independently and then discussed the developing themes with the research team to identify areas of consistency, inconsistency and concept saturation; a process which is repeated throughout data analysis. The transparent illustration of developing themes and codes, for example on a thematic map, assisted with communicating data pattern conceptualisation. The thematic prevalence of a concept – that is, the number of participants expressing a concept also assisted with reporting of the results. For example, potential themes were selected for reporting if mentioned by more than 5% of interviewees. Good practice guidance that the process of documenting concept saturation – that is, the point at which no new relevant or important information emerges and collecting additional data will not likely add to the understanding of how study participants perceive the concept of interest and the items in the questionnaire, was followed. The concept saturation was achieved, first through representativeness of the study population and second by continuation of interviews in an additional 10% of the participants before saturation was confirmed.

In this study, several methods were adopted in order to conduct appropriate data analyses for all the four studies. The results and the outcomes of the analysis from each study were put into individual study reports, which were consolidated for further collective analysis and reduced to conclude the key areas of concern to be addressed by a set of recommendation for an improved regulatory review model for the TITCK.

## SUMMARY

- The chapter describes the rationale for carrying out the study to evaluate the TITCK regulatory review process and timelines for the years from 2012 to 2015.
- The various methodologies, techniques and instruments that were used in analysing the data obtained from the TITCK, other mid-sized regulatory health authorities, pharmaceutical companies and patients have been described.
- A detailed description of the developmental technique of the three questionnaires was also provided as well as the methods of data collection and analyses.
- Methodological choices related to database management, data processing and data analyses were evaluated.
- The data collected from the TITCK, the other regulatory authorities were categorised and examined in three major areas, namely, the regulatory review processes, and milestones, the registration and approval timelines and the quality elements implemented within the review process.
- The perception and experiences of the pharmaceutical companies and patients about the regulatory environment and review process were evaluated using various techniques.

## **CHAPTER 3**

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# **EVALUATION OF THE REGULATORY REVIEW PROCESS AND TIMELINES OF THE TURKISH MEDICINES AND MEDICAL DEVICES AGENCY (TITCK)**

## INTRODUCTION

Regulatory health authorities are constantly challenged to improve their capacity to regulate the pharmaceutical industry in order to ensure the timely access of patients to safe and effective medicines as well as to monitor the quality standards and address the potential issues and challenges in the pharmaceutical market (Al-Essa, et al., 2012). Turkey made remarkable progress in its healthcare system and regulations through a series of reforms made under the “Health Transformation Program” (HTP), which was initiated in 2003. Thus over the past decade the HTP has led to the achievement of better health coverage and enhanced patients’ access to health services. Furthermore, the HTP introduced significant changes in all aspects of health regulations including those related to pharmaceuticals and registration processes (Bump, et al., 2014).

However, the pharmaceutical industry perceives the regulatory approval of medicines in Turkey to be a long, bureaucratic and complex process that is affected by a number of variables. Therefore, the regulatory approval process and timelines are still not comparable to other mature health authorities such as the FDA and the EMA since the TITCK is considered to have relatively long approval timelines in comparison to those countries that consequently delays patients’ access to medicines (Kanzık & Hıncal, 2011).

This study focused on the evaluation of the regulatory review process and timelines at the TITCK by assessing the level of adherence to good review practices. In Turkey, all marketing authorisation applications of new active substances are reviewed and evaluated by the TITCK. Once a marketing authorisation application (MAA) is submitted to the TITCK, the file is reviewed at different levels and goes through several assessment stages before approval is granted. Each step of the review process can also include different sub review processes and can involve external reviewers’ assessments as subject matter experts and advisors. The TITCK regulatory review process was closely assessed and evaluated to obtain a deeper insight and identify the key issues to be addressed in order to improve the overall system and facilitate an objective assessment and comparison with other similar mid-sized health agencies in the world.

## OBJECTIVES

The objectives of this study were to:

- Evaluate the regulatory review process in Turkey from the authority perspective.
- Identify the key milestones of the Turkish review process for new active substance applications.
- Identify the model(s) of the review and capture the review dynamics and processes used by the TITCK.
- Assess the review timelines for each step and the availability of internal procedures and quality measures used to ensure consistency, transparency and timeliness.
- Identify the areas for improvement within the Turkish review process.

The key issues addressed in this chapter were to determine the level of interaction of the Turkish Agency with pharmaceutical companies; namely, their openness to scientific advice, pre-submission meetings and discussions during question and answer stages throughout the scientific review process. Furthermore, an analysis of all the registration requirements in Turkey and practices was conducted including the evaluation of fast track review time and clock stop for new drug applications.

## Hypotheses

The hypotheses in this study were incorporated for the purpose of clarity and facilitate the interpretation of the study outcome, as they are qualitative and exploratory in nature. This study examined the following hypotheses

1. The marketing authorisation application requirements for a New Active Substance (NAS) application in Turkey are comparable to international requirements.
2. The approval times for NASs in Turkey are longer compared to other developed countries.
3. TITCK has not embedded Good Review Practices (GReP) into the assessment and registration processes.

## METHODS

The data collection process was conducted using available tools and information to review the TITCK Agency's organisational structure, requirements and relationships with other

governmental regulatory bodies. Thus the aim was to map the review process, steps and timelines available in the public domain as well as to identify in general where the Turkish review system deviates or differs from international requirements. This was then followed by a qualitative and quantitative data collection process which was carried out using a questionnaire provided to the TITCK to identify their review practices and key milestones for the registration application of new active substances and subsequently there was a face to face interview with the head of the TITCK to validate and clarify the responses.

## **Study Participants**


Initially, to facilitate the conduct of the questionnaire, it was pre-filled based on publicly available information and regulations. Subsequently, the pre-filled questionnaire was delivered electronically to TITCK to be further completed and to validate the data provided. A questionnaire (Figure 3.1) was designed to enable details of the regulatory review process in Turkey to be identified and completed by the TITCK (Appendix I).

Additionally, key milestones and quality review measures were addressed in the questionnaire. The questionnaire was previously used in the CIRS Emerging Markets Programme to identify the regulation of new medicines in the Emerging Markets of Argentina, Brazil, China, Egypt, India, Indonesia, Malaysia, Mexico, Saudi Arabia, South Africa, South Korea and Taiwan. This enabled an evaluation of the regulatory aspirations, barriers, problems and priorities, related to the review of new medicines that could have an impact on their availability to patients (McAuslane, et al., 2009).

## **Data Collection**

This study was facilitated by the head of the TITCK and the vice president responsible for the Product Registration and Licensing department. Information on annual application numbers and approval dates from January 2012 to December 2015 were obtained directly from the TITCK. The data were related to NASs including the number of marketing authorisation applications, and the overall TITCK review and approval timelines. Major line extensions were not within the scope of this study, since this term is not available within the Turkish regulations.

**Figure 3.1: CIRS agency questionnaire (Full Questionnaire in Appendix I)**

<p><b>CONFIDENTIAL</b></p>  <p align="center"><b>Regulatory Review Process in Turkey</b>  Review of key milestones, target times and  quality of decision-making in the  assessment and registration process</p> <p align="center"><b>QUESTIONNAIRE</b></p> <p><b>July 2016</b></p> <p><u>Contacts</u>  Emel Mashaki, Pharm.Msc. MBA – Phd Student at Cardiff University  <a href="mailto:emel_mashaki@hotmail.com">emel_mashaki@hotmail.com</a>  <a href="mailto:MashakiE@cardiff.ac.uk">MashakiE@cardiff.ac.uk</a></p> <p>Prof. Dr. Stuart Walker  <a href="mailto:swalker@cirscl.org">swalker@cirscl.org</a></p> <p align="right">Centre for Innovation in Regulatory Science  The Johnson Building, 77 Hatton Garden,  London EC1N8JS, England</p>	<p align="center"><b>REGULATORY REVIEW PROCESS IN TURKEY</b>  Review of key milestones, target times and quality of decision-making in the  assessment and registration process</p> <hr/> <p><b>BACKGROUND</b></p> <p>This questionnaire is designed as part of a PhD project to evaluate the Turkish Regulatory environment and its impact on patients' access to innovative medicines. The aim of the questionnaire is to map the regulatory review process of new active substances within the Turkish Medicines and Medical Device Agency (TITCK) in terms of structure, relations.</p> <p>This questionnaire is designed in association with the Centre of Innovation for Regulatory Sciences (CIRS) and it aims to;</p> <ul style="list-style-type: none"> <li>• Capture the actual registration requirements, review dynamics and practices followed by TITCK.</li> <li>• Identify the review process in terms of type, timelines and availability of assessment framework and procedures.</li> <li>• Identify the interrelations within the agency units and other external reviewers and regulatory commissions.</li> <li>• Understand the decision making process and transparency of the assessment outcomes and review conclusions.</li> </ul> <p>This questionnaire represents the third Phase of the CIRS Emerging Markets Programme which is studying the regulation of new medicines in the Emerging Markets <b>Argentina, Brazil, China, Egypt, India, Indonesia, Malaysia, Mexico, Saudi Arabia, South Africa, South Korea and Taiwan</b> and looking at the regulatory aspirations, barriers, problems and priorities, related to the review of new medicines that can have an impact on their availability to patients.</p> <p>The first phase was initiated in January 2004 to assess the current regulatory environment in some 30 countries, using comparative data, at the country and regional level, in order to identify the key issues for improving review practices and making new medicines available in an efficient and timely manner.</p> <p><b>OBJECTIVES</b></p> <p>The objectives are to:</p> <ul style="list-style-type: none"> <li>• To identify the key milestones and target times for TITCK and the main activities between milestones (for clinical trials applications and registrations).</li> <li>• To identify the model(s) of the review which is being undertaken by TITCK.</li> <li>• To assess how TITCK is building quality into the assessment and registration processes.</li> </ul> <p><b>OUTPUT</b></p> <p>By the end of this questionnaire, TITCK will receive a report from which they can compare their regulatory procedures with those of peer agencies across the regions. This will include an analysis of where time is spent in the review process with the opportunity to identify where time is lost.</p> <p>The outcome will allow an analysis of the quality measures that are, or are not, in place for a certain type of review and provide a baseline for subsequent comparative studies across agencies to establish best practices.</p>
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## Structure of the questionnaire

The questionnaire was divided into three sections:

- **Part 1: Organisation of the agency:** this aimed to provide details of the TITCK's organisational structure and resources. It also explored review model(s) for the scientific assessment of medicines to determine if the quality, safety and efficacy data were assessed in detail by the TITCK or if they used another review model, which depends on the results and verifies the review assessments of other authorities.
- **Part II: Key milestones in the registration of medicines;** this part aimed to explore the review and approval process for new active substances (NASs). As a result, a standard process map with milestones was developed to facilitate the collection of data and illustration of these data in a common format, which simplify comparisons among regulatory agencies. Therefore, the standard process map allowed for the description of the TITCK regulatory review process and for the standardisation of the definitions used.
- **Part III: Building quality into the assessment and registration process;** this part examined the key elements of Good Review Practices (GReP) that contribute to the quality of the decision-making process and measures adopted by the TITCK to improve consistency, transparency, timeliness and competency.

Finally, the questionnaire enabled the interrelations within the agency units and other external reviewers to be identified as well as the availability of an assessment framework and procedures used by the agency internal staff and/or the external reviewers. Following the completion of the questionnaire by the TITCK, data were then transferred into a country report in a word format to create a comprehensive overview of the current regulatory review process. This was provided to the TITCK to enable auditing, correction, discussion and modifications as required.

## RESULTS

The results of this study are presented in three parts:

Part I: Organisational structure of the TITCK.

Part II: TITCK regulatory review process map and milestones.

Part III: Good review practices in the assessment and registration process.

## Part I: Organisational Structure of the TITCK

In 2012 and as part of the healthcare reform programme; the TITCK was established officially in November 2011 to become the official body responsible to regulate the pharmaceutical and medical device industry in Turkey; thus replacing the previously named Pharmaceutical and Pharmacy General Directorate (IEGM). The TITCK operates within the administrative structure of the Ministry of Health to regulate all activities and requirements related to:

- Medicinal products for human use.
- Medical devices and *in vitro* diagnostics.

The scope of activities of TITCK includes; marketing authorisations/product licences, clinical trial authorisations, post-marketing surveillance, regulation of advertising, laboratory analysis of samples, price regulation and Good Manufacturing Practice (GMP) accreditation of manufacturing sites. At present, the total staff in the TITCK is one thousand and eight where more than 25% have a medical background as physicians and pharmacists. In addition, one hundred and forty-seven of the TITCK staff members are assigned as reviewers for applications for marketing authorisations and product licences. The total annual budget of the TITCK for 2015 was calculated to be \$42 million where 47% is allocated for marketing authorisation applications. Thus the source of funding of the TITCK is 30% from the government, whereas the rest is self-funded by fees collected from applicants (TITCK, 2015). For example; for a new marketing authorisation application, several fees are charged where the amount varies depending on the evaluation steps and activities provided by the agency during the review process such as the fees charged for GMP file application, site inspection, review application, analysis and different administrative permission fees such as sales and importation license fees (Table 3.1).

**Table 3.1: Fees charged for review applications – 2016**

2016 – Fees		US\$	Local Currency ( TL)
New active substance		1000 USD	3000 TL
Established ingredient /proprietary product		1000 USD	3000 TL
Generic (non-proprietary) product		680 USD	2000 TL
Indication extension		775 USD	2276,22 TL
Variations	Type II Variation Indication / Label Expansion	400 USD	1148,88 TL

## **Model of assessment in the TITCK**

There are three types of regulatory assessment used worldwide by regulatory authorities. This was agreed as an outcome of the CIRS Workshop on “*The Emerging Markets: Regulatory issues and the impact on patients’ access to medicines*”, organised in Geneva, Switzerland in March 2006 (McAuslane, et al., 2009). The workshop was attended by several regulators and regulatory agencies to discuss and evaluate the types of data assessment methods applied to different applications. Accordingly, the three scientific review models of new drug applications were described as below:

### **I. Review Assessment Type 1 - Verification model**

This model is used by a number of health authorities that lack sufficient resources and capacity to perform a comprehensive scientific review of a new marketing authorisation application (MAA). This model helps reduce duplication of effort by agreeing that the local authority will approve the marketing authorisation of any product once the product is officially approved by two or more recognised reference countries. The main responsibility of the local authority is to ensure the “verification” of all data submitted as declared in the application dossier. This includes the verification review of the product characteristics (formulation, composition and strength) and the proposed labelling information (use, dosage, precautions) for local marketing complies with the reference country(s) authorisation(s). Approval evidence in other countries or recognised reference countries, such as submission of Certificate of a Pharmaceutical Product (CPP), are pre-requisites for such applications and review models.

### **II. Review Assessment Type 2 – Bridging model**

This model ensures the optimal use of the available resources by the local authority by not re-assessing the scientific supporting data included in the application of the MAA as long as these data have been evaluated and approved by one of the recognised reference countries. However, the MA application still undergoes a bridging review in relation to the product’s local use and characteristic in the local market. Therefore, the bridging model reviews the scientific clinical data including a local review of quality data (CMC of the product). The review of the quality data is to confirm the product’s stability conditions in relation to climatic conditions and distribution infrastructure in the local country. Whereas, the clinical review could include a benefit-risk assessment in relation to its use in the local ethnic population, the medical practice/culture and patterns of disease and nutrition in the country. In the bridging

review, approval by at least one recognised agency is a pre-requisite before the local authorisation can be granted, but the initial application need not necessarily be delayed as the CPP can be submitted in some countries prior to approval.

### **III. Review Assessment Type 3 - Full review model**

In this model the authority has suitable resources and capacity to perform a full independent scientific review. This includes collaborating with both internal and external experts, to carry out a ‘full’ review and evaluation of the supporting scientific data (quality, pre-clinical, and clinical) for a major application. Full review models, do not require a new marketing application approval in any other country at the time of the submission and thus can carry out an earlier or parallel review to first world application (Type 3B). However, in some countries, local regulation requires evidence of approval in the country of origin or reference country prior to approval (Type 3A). Within this study, the review and assessment model of the TITCK was explored and the details of the scientific review process identified. Accordingly, the TITCK performs a full review and assessment model for all new active substance applications. Therefore, a new marketing authorisation application can be submitted to the TITCK but they do need to know the registration status of that product anywhere in the world. However, evidence of approval in the country of origin, European Union (EU) or United States (US) must be submitted prior to the final approval by the TITCK. Furthermore, shared/joint reviews have never been undertaken with other agencies by the TITCK.

#### **Data requirements and assessment**

According to the local pharmaceutical regulation in Turkey, a marketing authorisation approval by the TITCK is required for any pharmaceutical product prior to marketing in the country. Thus, in order to obtain an approval from TITCK, pharmaceutical companies must fulfil a number of regulatory requirements; Firstly the applicant needs to be a legal entity located in Turkey whether a person or a company (Ministry of Health Turkey, 1995). Then an application should be submitted to the TITCK by providing the documents listed under the Licensing Regulation, published in the Official Gazette dated 2005 (Özbal, et al., 2012). Currently, all new drug applications are submitted online to TITCK according to local licensing requirements as an electronic submission. Furthermore, the applicant is required to prepare a regulatory dossier in compliance with the common technical document (CTD) with quality, safety and efficacy modules covering both the active drug substance and the finished product and therefore fully aligned with the ICH content requirements as well. The marketing

authorisation application must be organised according to the TITCK checklist and format and includes all the clinical, non-clinical and quality characteristics of the pharmaceutical product together with the authorisation status of the product in other countries as well as proposed and approved claims and labelling. (TITCK, 2005). The CPP is not required at time of application for registration in Turkey. However, a CPP of the assessed product is required prior to final approval, yet other evidence such as an electronic CPP or publication on an official regulatory website can be accepted as an alternative.

Full clinical and efficacy data are required for the application and thus must be submitted in the CTD format with the correct sections (Module 1,2,3,4 and 5) of scientific data. Accordingly, the TITCK performs a complete assessment of these data, mainly the quality and the clinical parts of the product file.

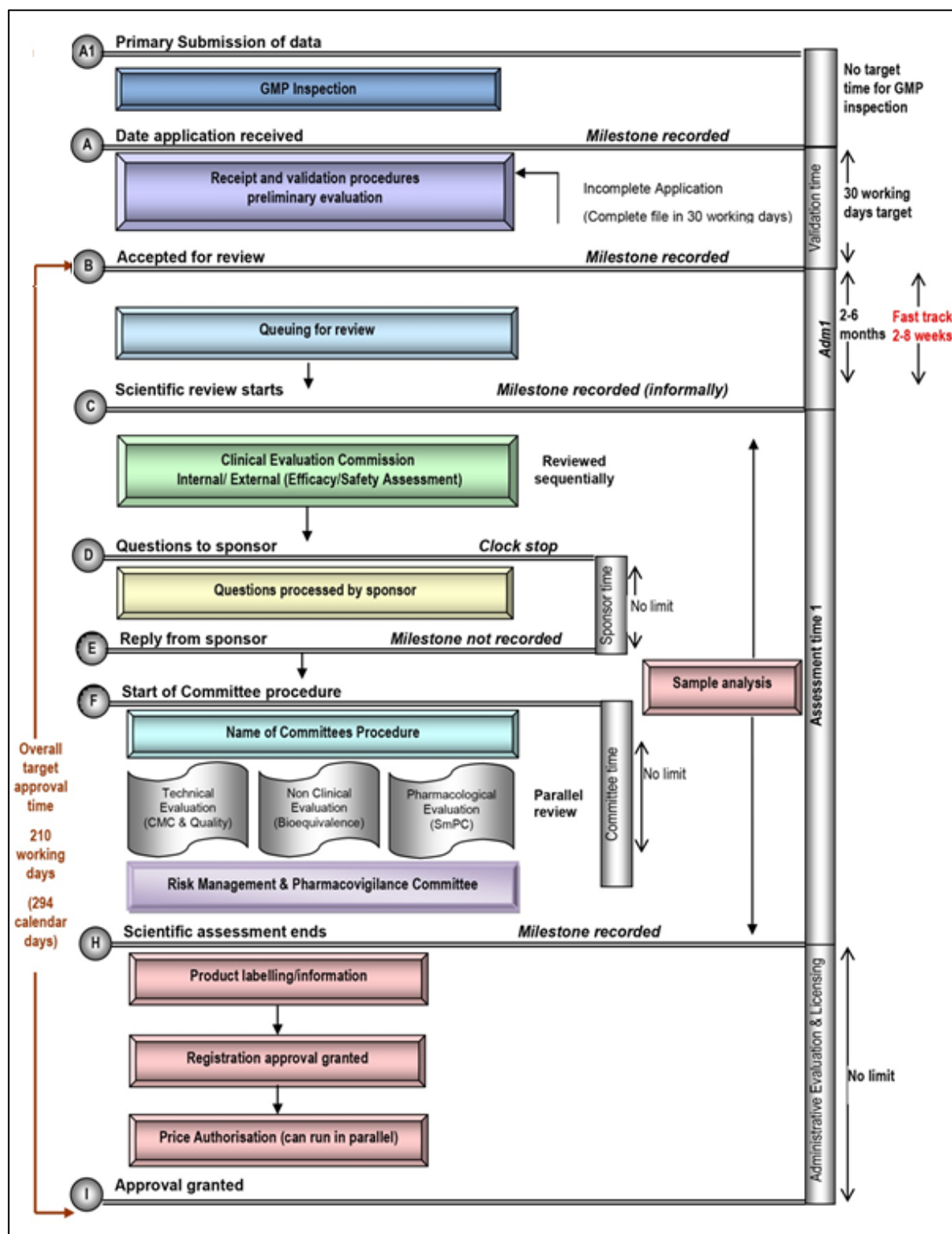
Additionally, the TITCK along with external reviewers perform structured benefit–risk assessments as the first step of the clinical evaluation of the registration review process. Thus, this first clinical assessment always takes into account the ethnic factors, the differences in medical culture/practice, national disease patterns and unmet medical needs even though sufficient data on these criteria are not always supplied in all applications. Similarly, mainly for fast track application products; the TITCK always attempts to obtain additional data from other agencies’ internal assessment reports and publicly available reports such as the European Public Assessment Reports (EPARs) as well as general internet searches and other resources such as local epidemiology studies. Though officially not stated in the regulation; the EMA and the US FDA are regarded as reference agencies. Furthermore, the TITCK takes into account the evaluations of product information leaflets and summaries of product characteristics issued by these reference agencies.

## **Part II: Key Milestones of the Turkish Review Process**

A process map of the TITCK registration review and its key milestones is shown in Figure 3.2. It is a general simplified chart flow that represents the main steps performed within the TITCK during the review process for NAS applications from the first step of the preliminary review of the application until the last step when the product is approved on the first cycle to be on the market. Thus, all steps and processes related to the rejection of an application such as appeals and hearings are not included in the map. Furthermore, the map does not

demonstrate the pre-submission steps that need to be completed within the GMP accreditation process prior to marketing authorisation application.

**Figure 3.2: Registration review process for a new drug application in Turkey**



### **Pre-submission Requirements and the GMP Process**

According to the local regulation, a GMP accreditation by the TITCK for the manufacturing sites of the product must be completed prior to the marketing authorisation application (GMP, 2010). As of September 2014 a principle decision by TITCK (not stated officially in the regulation) enabled a marketing authorisation application for prioritised products (orphan and life-saving products) to be submitted and reviewed in parallel to an ongoing GMP process. Following a decision by the Prioritisation Assessment Committee, these products could also be eligible for an accelerated registration review when conducted in parallel to the GMP process to save time (TITCK, 2016).

The primary step for registration is to submit a complete GMP dossier, which includes quality and manufacturing related data pertaining to the sites, and the product manufactured in the site. The GMP application then undergoes a paper based review process and a categorisation of the application to determine the priority of each application. Following the GMP dossier approval, the applicant is informed about possible dates to conduct the GMP inspection for all new sites and manufacturing lines. If the GMP application is related to a manufacturing site and line that has been previously inspected and approved before by the TITCK, a paper based inspection is carried out instead of a physical one, provided that the tools and equipment are similar to the accredited one. Several GMP inspections to the same site can be combined and performed together.

The GMP inspection process is not predictable in terms of timelines and so far there is no clear official timeline for this procedure. The completion time of the GMP process depends on the classification of the product according to its need and importance in four main prioritisation categories. Benefit-risk evaluation and pharmaco-economic aspects of the product defines the GMP priority category of the product. Products classified as category one and recognised as orphan or lifesaving products obtain first priority to complete the GMP process in an average of twelve months, whereas products categorised as priority four, such as addition of alternative manufacturing sites for the same product, have the least priority from the agency and thus process completion might take longer than thirty-six months. After the GMP inspection (physical or paper risk based) is completed, the applicant is required to follow up and close all the corrective actions on time. The GMP certificate will be issued based on the inspection and corrective action report. GMP certificates are valid for three years in Turkey and must be renewed prior to expiry following the same accreditation procedure.

## **New Product Application**

### **Receipt and validation**

The first milestone in the MAA consists of a preliminary evaluation of the submitted dossier. The submission of the application is carried out electronically where the complete application is downloaded through the TITCK website; this indicates the formal start of the application procedure. Within this step, a validation and pre-review check is performed to ensure the completeness and correctness of the submitted application according to the Turkish regulations. Some items such as the legal status of the applicant, GMP status of the manufacturer and payment of fees, are checked as well. The marketing authorisation application dossier is also checked for acceptability of the file in terms of CTD format with the correct sections (Module 1,2,3,4 and 5) of scientific data. The CPP is not a prior requirement in Turkey since TITCK performs a full review and does not require any prior approvals of the product in the world at the time of submission. However, a CPP or other evidence of authorisation must be provided before the TITCK authorisation is issued, (e.g., copy of authorisation, Internet reference). Legalisation is not required except for certain countries if specifically requested by TITCK. The preliminary and validation step is stated in the regulation to be thirty working days. Therefore, the date of acceptance and uploading of the application is formally recorded. TITCK has to complete the pre-review process within thirty working days and in case of incomplete applications, the applicant is requested to complete the missing data within another thirty days. Article thirteen states: “*The second preliminary review of the application to be conducted upon the remedy of the deficiencies and submittal to the Ministry shall be finalised within thirty days*” (TITCK, 2005). According to Article thirteen, if the dossier is evaluated in a second preliminary review and missing documents are not submitted again, the dossier will be rejected with a letter indicating missing data.

## **Scientific Registration Review Process**

### **Queuing / Backlog**

Upon completion of the preliminary review step, the application is held in a queue to be presented to the scientific committees for further review. The current queue time is approximately two to six months. However, priority products are taken out of the queuing system and thus the time for fast track applications is approximately two to eight weeks. Queuing timelines are not official or standard but rather based on experiences within the TITCK.



## Scientific Assessment

The scientific assessment and review of the application is conducted in two separated parts: efficacy/safety and quality. The main scientific assessment is done by the Clinical Evaluation Commission, which consists of internal and external reviewers officially assigned by the TITCK based on therapeutic expertise. Thus the approval of the application by the Clinical Evaluation Commission is considered the key critical milestone in the assessment procedure. After the completion of this stage, the review process commences by other committees.

## Expert Committees

Six types of committees (total number nineteen) within the TITCK carry out the different scientific assessments (Table 3.2). Additionally, a list of one hundred and twenty external experts are used for the assessment of scientific data and are invited to attend weekly committee meetings held within the TITCK for assessment and review of applications. External experts are mainly responsible for providing a detailed assessment report and recommendation, a clinical opinion on the product and advice to the agency staff on specific technical issues. Accordingly, the TITCK is mandated to follow the committees' recommendations. Moreover, there is no contractual agreement for external reviewers to work within deadlines set by the agency as they are only mandated to sign confidentiality and conflict of interest agreements with the TITCK. Therefore, the review timelines for the committees are not standardised.

**Table 3.2: Scientific assessment committees at TITCK**

Committee name	Number	Roles & Responsibilities	Members
Priority Evaluation Committee	1	Evaluation of priority and accelerated registration review applications before the registration review process starts.	13
Clinical Evaluation Commission	1	Review of safety and efficacy aspects.	30
Technological Evaluation Committee	12	Review of chemistry, manufacturing and control (CMC) and quality aspects.	8-9 per committee
Bioavailability and Bioequivalence Committee	2	Review of non-clinical aspects.	12 per committee
Pharmacological Evaluation Committee	2	Review of product clinical claims and labelling.	24 per committee
Risk Management and Pharmacovigilance Committee	1	Review of product safety profile and risk management plans.	12

## **Scientific Assessment Sequence**

The sequence of the scientific review of the application among the different committees can vary according to the status of the application, where several committee reviews can run in parallel or sequentially depending on the global submission status of the product. Thus, in the case of a parallel MAA submission with the EMA or the FDA; the registration review process starts from the Technological and Bioavailability/Bioequivalence Committees' assessments and then proceeds with the Clinical Evaluation Commission as final stage since this commission requests information mainly from the EMA/FDA and/or other authority's decision and clinical assessment. Quality control analysis, pharmacovigilance review and pricing process can be conducted in parallel and independently to the review process immediately after the Clinical Evaluation Commission's approval. Sample analysis as part of the review and approval procedure must be completed before the finalisation of the regulatory review process. Thus as of March 2015, applicants will have to wait to be informed by TITCK when they can start the sample analysis process and pay the related fees. So far there is no clarity on the timelines.

## **Questions to Applicant**

During the review process, several questions or queries can be raised either by internal or external reviewers regarding the application. Accordingly, questions are sent to the applicant when they arise in each review process by the committees as there is no official time limit for the sponsor to respond. The responding deadline can sometimes be stated in the official question letter. The review 'clock' stops while questions are being answered, but the overall 'sponsor time' is not calculated.

## **Interaction of TITCK with the applicants**

Meetings with the TITCK can be arranged by the applicant to discuss questions and queries that arise during the assessment. Agency meetings with the TITCK do not have an official framework, yet can be held with the TITCK staff at specific times and appointments as announced by different departments of the agency. However, for urgent issues, meetings can also be arranged by the applicant to discuss various issues related to the MAA. Thus the level of contact that companies can have with TITCK staff and experts during development and during the agency's assessment process are limited to some formal contact (possibility of face to face meetings) and some informal contact (possibility of telephone or email contact). In Turkey, pre-application scientific advice meetings similar to those conducted with the EMA

and the FDA are not available to applicants. However, during the review process and interaction with the applicant, general details related to the progress of the MAA file is given and details of technical internal staff that can be contacted to discuss the application during the review may be provided upon request from the applicant. Finally, there are no restrictions or fees required from applicants to conduct meetings with the TITCK.

### **Priority Review and Fast track applications**

A shorter marketing authorisation application (MAA) for generic and biosimilar products is stated in the official registration regulation. Besides this, there is an official procedure for priority/fast track products stated in the registration regulation based on a decision dated in August 2015 and thus a list of applications/products are subject to accelerated review. The accelerated registration review process was introduced by the TITCK via a circular in October 2015 to accelerate the marketing authorisation process for critical applications for certain products such as lifesaving medicines. A list of priority criteria was defined which included life-saving and critical products needed urgently. Moreover a guideline was issued in April 2016 in order to define the principles of the priority application and review process. (TITCK, 2016) . Accordingly, products subject for fast track and accelerated review are first evaluated by the TITCK Prioritisation Committee, which then enables an accelerated review process. Industry experience identified this period to be six months for life saving and critical products.

### **Pricing**

Price negotiation starts during the registration review and licensing process. The pricing process can be conducted in parallel and independently to the review process immediately after the main commission approval. Furthermore, registration approval can be completed prior to pricing approval and this must be granted prior to the sales permission application, which enables the product to be commercially available. The pricing procedure in Turkey is based on reference countries, thus a list of reference countries is assigned every year in January by the TITCK. Currently there are five reference countries for pricing; Portugal, Spain, France, Italy and Greece. Furthermore, the pricing of a new product is calculated based on the lowest ex-factory price in the Euro currency of the reference countries and then converted to the local currency in Turkish Lira (TL) using a constant exchange rate of Euro/TL announced officially every year in January by the TITCK. The exchange rate for TITCK in 2017 was declared to be 1 Euro = 2.3 TL (Ministry of Health, 2015) .

## Decision on the Application and Authorisation Procedure

Upon the completion of all the scientific commissions' review and the assessment by all relevant committees, as well as the finalisation of the quality control analysis and labelling assessment, the marketing authorisation is approved and signed by the Head of the Agency. Once the Marketing Authorisation is issued, the MAA holder can apply for sales permission to enable marketing in the territory and importation permission if required.

## Product Labelling

There is a separate negotiation of the product labelling which includes the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) after the scientific review is completed and before the approval is issued by the TITCK head. Thus the Pharmacological Committee reviews the proposed SmPC and PIL before MA approval is granted. Furthermore, during the sales permission application the final sample of the product, packaging material and labelling are also reviewed and approved accordingly.

## TITCK Review Timelines

The overall approval timeline is set to be two hundred and ten working days in the regulation (Article 15) (TITCK, 2005). *“Article 15- The Ministry shall analyse the registration application which has undergone a preliminary analysis and results to be complete, for checking whether the registration conditions have been fulfilled and shall finalise the process within two hundred and ten days (working days) after the acceptance of the application. However, the aforesaid period shall not include extraordinary circumstances and the period of time throughout which the applicant procures the documents that the Ministry required of it”*. Target timelines for the TITCK review process can be seen in Table 3.3.

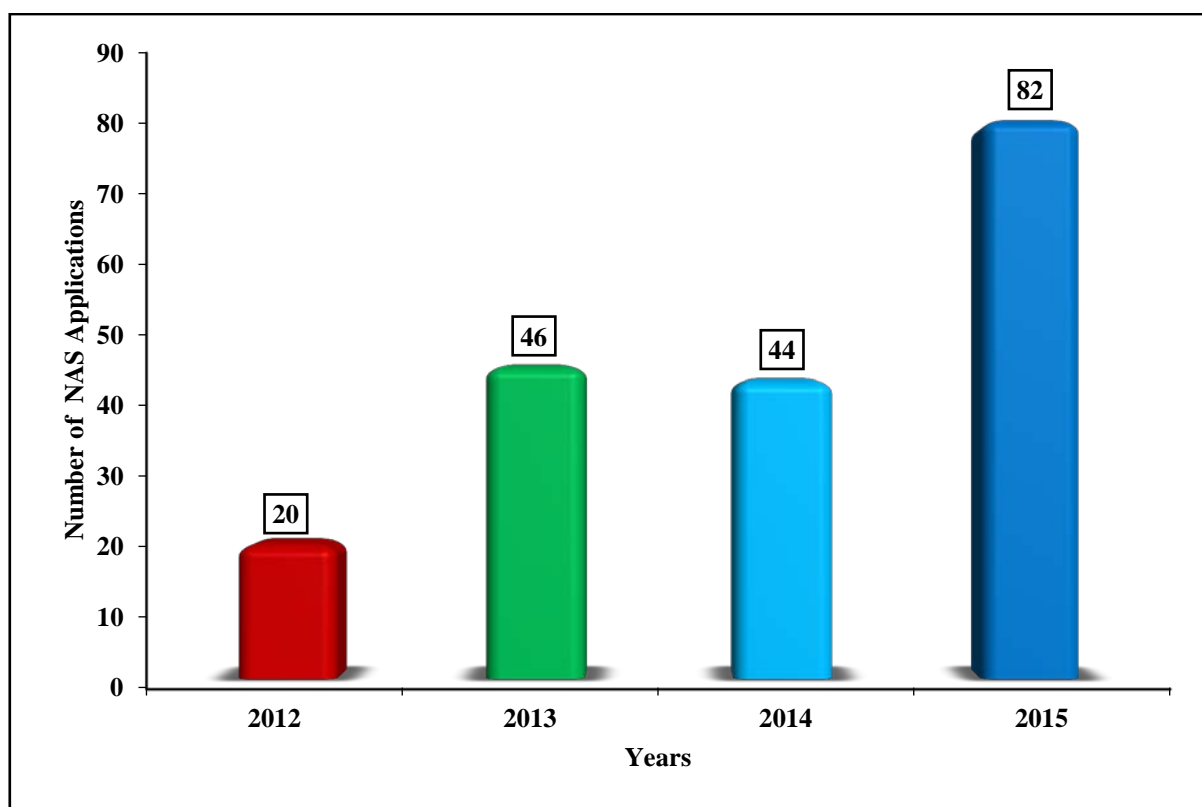
**Table 3.3: Timelines in the review procedure**

Process	Target
Validation	30 working days (42 calendar days)
Queuing / Backlog	2-6 months 2-8 weeks (prioritised review)
Clinical Evaluation Commission	No limit
Sponsor response time	No limit
Expert Committee(s)	No limit
Authorisation procedure	No limit
Overall review time	210 working days (294 calendar days)
Prioritised accelerated review	180 working days (252 calendar days)
Highly prioritised products	150 working days (210 calendar days)

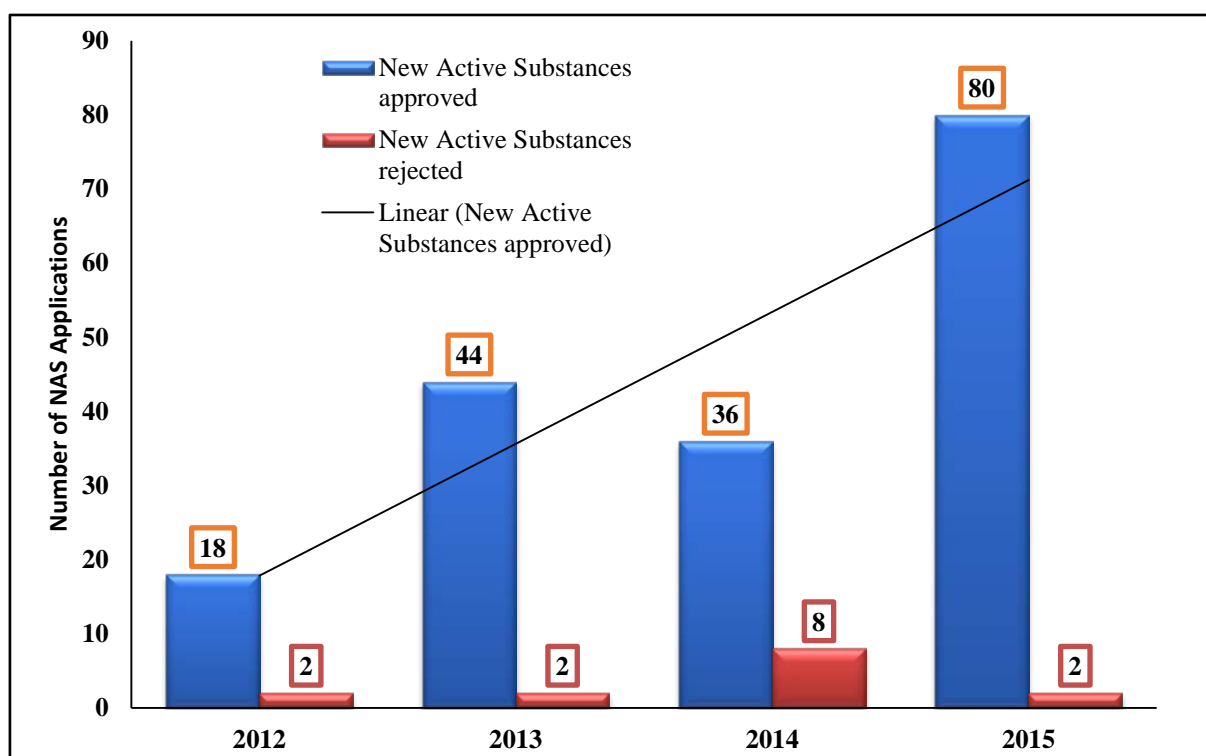
Regulatory authorities are constantly challenged to improve their regulatory performance and accordingly its outcome that is usually evaluated by the number of applications reviewed and approved as well as the approval timelines. However, the regulatory performance of each authority can be affected by several factors including number of reviewers, number and type of applications submitted each year and the quality of the review process (Cone & McAuslane, 2006). Thus, the number of approved products by the TITCK varies each year due to similar factors.

Examining the data obtained from the TITCK for the four-year period (2012-2015), the results showed an overall trend of an increase in the number of NAS applications submitted by the pharmaceutical companies from 2012 to 2015. Thus, the number of NAS applications increased almost four times in 2015 (eighty-two applications) compared to 2012 (twenty applications) (Figure 3.3). Furthermore, the number of NAS marketing authorisations applications that have been approved and rejected by TITCK in 2011, 2012, 2013 and 2014 are shown in Figure 3.4.

**Figure 3.3: Distribution of NAS applications received by TITCK between 2012 and 2015**

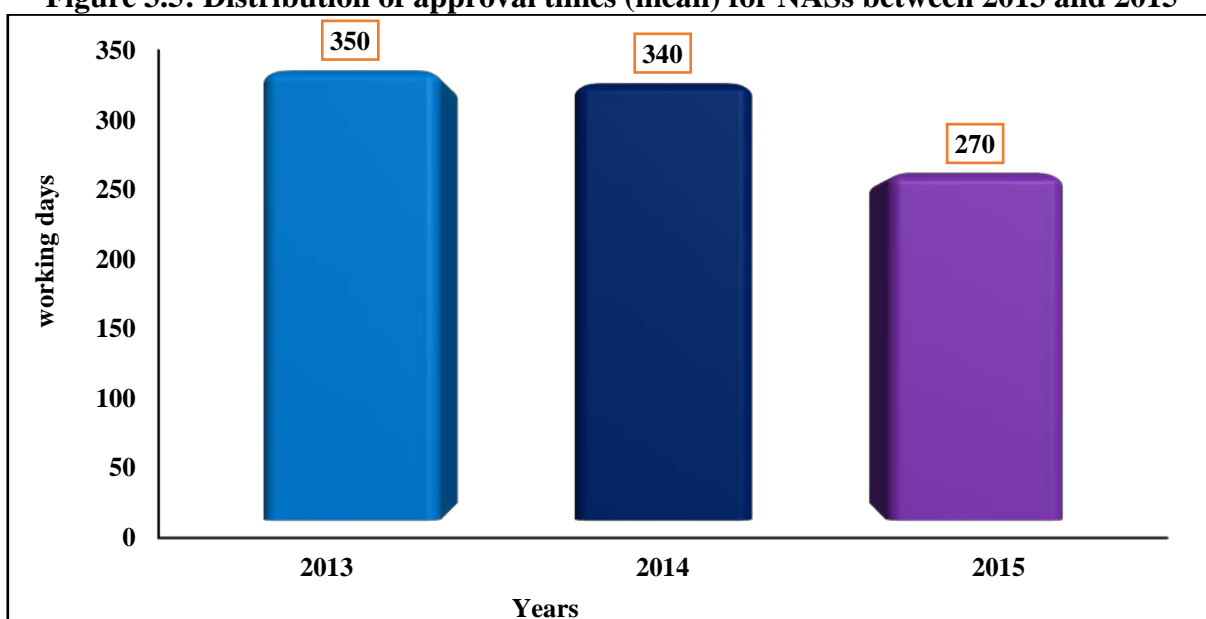


**Figure 3.4: NASs applications approved and rejected by TITCK between 2012 and 2015**



The number of applications that were approved by the TITCK was eighteen, forty-four, thirty-six and eighty applications in 2012, 2013, 2014 and 2015 respectively. In addition, the approval timelines (mean/working days) for NASs from 2013 through 2015 are shown in Figure 3.5 although data for the year 2012 were not provided by TITCK for internal reasons and therefore not included in the analysis.

**Figure 3.5: Distribution of approval times (mean) for NASs between 2013 and 2015**



The highest number of NASs approved in 2015 was eighty with an average approval time of two hundred and seventy working days and only two NAS applications were rejected by TITCK. In 2013, forty-four NASs were approved, with an average approval time of three hundred and fifty working days. In 2014 the average approval time for thirty-six NAS applications was almost comparable to the previous year and was stated by the TITCK to be three hundred and forty working days. However, the highest number of NAS applications that were rejected by TITCK in the last four years was in 2014 with eight NAS applications. The fastest average approval time in the years between 2012 and 2015 was achieved in 2015 with an approval average time of two hundred and seventy working days and the highest number of applications was received in the same year. Thus in 2015, the scientific review and assessment time was reduced by eighty working days from three hundred fifty working days in 2013 to two hundred and seventy working days in 2015, while the number of applications received by TITCK increased by thirty-six applications in 2015 compared to forty-six NAS applications received in 2013. These data demonstrated that the TITCK's performance and efficiency in the review time has dramatically improved in 2015 probably due to the increase in the number of reviewers and committees. However, the efficiency of the review could be further improved if the GMP requirement was conducted in parallel for all NAS applications.

### **Part III: Good Review Practices in the Assessment and Registration Process**

Quality in the assessment and registration process is important to regulatory authorities as it ensures consistency, transparency, timeliness and competency in the review process. Regulatory authorities are continuously developing and implementing a variety of measures to improve and achieve higher quality standards and to meet the expectations of industry and the general public (McAuslane, et al., 2009). Thus usually the quality level of a pharmaceutical product is determined by the product characteristics and the chemical and manufacturing control (CMC) processes that constitute module three "Quality module" in the CTD file. However, recently apart from the timeliness, the quality of the regulatory review and the decision-making process have become important aspects that must be closely monitored and evaluated to determine the regulatory performance and efficiency of an agency (Cone & McAuslane, 2006). The purpose of the third section of the questionnaire was to obtain an insight into the strategies, measures and resources that the TITCK have in place to develop and maintain the quality of their review processes. Accordingly, the results indicated that currently the TITCK seems to have a comprehensive and official internal quality policy

defined as ‘Overall intentions and direction of the organisation related to quality. Nevertheless, the results also identified that Good Review Practice (GReP)<sup>1</sup> is still not implemented by the TITCK but there are plans to establish this within the next two years. However, a number of Standard Operating Procedures (SOPs) are used by the TITCK mainly for the labelling review process, pharmacovigilance assessments and for guidance for scientific assessors. Furthermore, assessment templates that set out the content and format of written reports on scientific reviews are also commonly used. Internal reviewers are provided with a checklist to facilitate the assessment process of applications. Peer review and an additional evaluation of the original assessment by an independent person or committee are not practiced by the TITCK. Furthermore, shared or joint reviews<sup>2</sup> with other regulatory authorities are not conducted within the TITCK and it is anticipated that the agency will not be undertaking such reviews within the next two years.

### **Quality management**

The TITCK has identified the following as the most important measures for the introduction of quality measures within the agency; to be more efficient; to reduce errors as well as to improve communication. Currently, the TITCK have a dedicated department of two staff for assessing and/or assuring the quality of the regulatory process. Thus to monitor and improve quality measures in the TITCK, several activities are undertaken to bring continuous improvement into the assessment and authorisation process. For example, reviewing assessors’ and stakeholders’ feedback through reported complaints, conducting meetings and workshops and ensuring that the necessary action is taken; carrying out internal quality audits (e.g. self-assessments) and using findings to improve the system. Moreover, it was also noted that the TITCK is using an internal tracking system to monitor the progress of application, however, this is not accessible by companies. While external quality audits by an accredited certification body are not conducted either, although the agency might implement this in the near future to contribute to the improvement of the system.

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<sup>1</sup> Good Review Practice (GReP): A code about the process and the documentation of review procedures that aims to standardise and improve the overall documentation and ensure timeliness, predictability, consistency and high quality of reviews and review reports.

<sup>2</sup> A shared review is one where each participating authority takes responsibility for reviewing a separate part of the dossier. A joint review is one where the whole dossier is reviewed by each authority and the outcome is discussed before a decision is taken.



### **Quality in the review and assessment process**

To help improve the quality of applications and the scientific review at the TITCK, several measures and guidelines have been implemented and made through published guidelines accessible through the TITCK's website, industry associations and timely publication of any updates or changes to the regulations in the official gazette.

### **Training and continuing education as an element of quality**

Training and continuing education is an important element of quality to ensure that agency staff are aware of all available quality policies and procedures which will ensure consistency in performance. Within the TITCK, all agency staff receive formal training through various training methods which are mainly carried out through; on the job training, in-house courses, support for post-graduate degrees in the related area, participation in international workshops/conferences as well as placements and secondments in other regulatory authorities. Additionally, there is some degree of collaboration between the TITCK with other agencies in the training area of assessors. For some tasks, the TITCK supports the placements and attendance of agency staff in other international regulatory agencies' inspections, reviews or technical related training to gain real experience. Accordingly, TITCK staff are partly tested on the training given, but completion of the training is not required for professional advancement.

### **Transparency of the review procedure**

Transparency is one of the main areas on which the TITCK focuses to improve and this is derived from the incentive to meet the public need and provide assurances on safety and to increase confidence in the regulatory review system. This study examined 'transparency' in terms of the ability and willingness of the agency to assign time and resources to providing information on its activities to both the informed public (which includes health professionals) and industry. Currently the agency assigns medium priority to transparency. Accordingly, a number of activities to enhance the openness of the regulatory system have been identified. This includes, information provided to the general public on the performance of the agency in terms of the approved products and approved product labelling. This public information can be accessed through the TITCK website.

Furthermore, all MA holders are required to publish a small advertisement in the newspaper about the approval of a new active substance in Turkey. The advertisement has to follow the

TITCK format, to be in black and white, mentioning only the new active substance name. The TITCK uses several facilities to provide information both for the public as well as for the marketing authorisation applicants. For example, transparency to companies is provided through several physical interactions related to the follow up of their application progress, which can be tracked easily by the company representatives in Ankara. However, although an electronic submission system is available, currently applicants cannot access the status of their application under review within the agency as this information is kept internally although companies can, through their company representatives, follow the process by verbal communication with the agency staff on an informal daily basis if required.

The TITCK has an internal electronic system used to track applications that are under review and identify the stage in the process. However, the system does not provide information relevant to the excess of target review time or record the terms of authorisations once granted. Additionally, the TITCK has an archiving system that easily provides information on applications in a way that can be searched within the agency.

Finally, the study identified the TITCK's own perception of its unique positive qualities that it implements in the review of new medicines to make them available for patients. Accordingly, the TITCK identified the following main factors that make a major contribution to the effectiveness and efficiency of the TITCK's review procedures and decision-making processes for NAS applications namely to:

- Follow up all international regulatory authorities' decision-making processes and practices.
- Make available a pool of numerous and various specialties to conduct the scientific evaluation.
- Ensure the availability of well-educated agency personnel with appropriate administrative assessment competencies.

Nevertheless, there are still a number of challenges facing the TITCK that act as barriers to making new medicines available in a timely manner through the regulatory process. These include the limited human resources, insufficiency of physical and technological infrastructure as well as the patent related rights regulations are not aligned with international standards.

## DISCUSSION

The TITCK is a recently established agency within the Ministry of Health, yet it has a long history since 1923 in regulating the pharmaceutical industry when it previously used to be structured as a Medicines Directorate under the administrative structure of MoH. Therefore, it is well recognised that Turkey has an efficient regulatory review system that has enabled for many years the timely registration and patients' access to medicines shortly after their launch in 'major' developed countries like the EU and the USA. However, recent changes in the pharmaceutical regulatory environment including the introduction of local GMP accreditation process in March 2010 has resulted in the approval process and timelines being significantly impacted. This study has evaluated the regulatory review process with its different milestones within the TITCK and identified the key steps, activities and measures of the review process that may have a critical impact on the quality and regulatory performance of the TITCK.

### **Hypothesis 1: The marketing authorisation application requirements for New Active Substances (NAS) application in Turkey are comparable to international requirements.**

The Marketing authorisation application requirements in Turkey follow global guidelines and thus all NAS applications must be submitted to TITCK in compliance with the common technical document (CTD) with quality, safety and efficacy modules covering both the active drug substance and the finished product. These are therefore fully aligned with the ICH content requirements. Moreover, though officially not stated in the regulation the European Medicines Agency (EMA) and United States Food and Drug Administration (US FDA) are regarded as reference agencies. Therefore, this hypothesis is accepted.

### **Hypothesis 2: The approval times for NASs in Turkey are longer compared to other developed countries.**

This study examined the pattern of total regulatory approval times in Turkey between 2012 and 2015 for NAS applications as well as the number of applications received for the same period. Interestingly, the fastest mean approval time was achieved in 2015 when it was three hundred and seventy-eight calendar days (*two hundred and seventy working days*) despite the highest number of applications received (*eighty-two applications*) in 2015 compared to 2012 (*twenty applications*). Whereas in 2013 and 2014 the approval times provided by the TITCK were four hundred and ninety (*three hundred and fifty working days*) and four hundred and seventy-six calendar days (*three hundred and forty working days*) respectively. Similarly, the

TITCK granted eighty approvals in 2015 compared to eighteen, forty-four and thirty-six in 2012, 2013 and 2014 respectively. However, approval times do not include the companies' response time to the questions. These findings demonstrated that the TITCK's performance and efficiency has dramatically improved over the last few years. However, the target time of two hundred and ten working days (*two hundred and ninety-four calendar days*) was still not achieved. Data provided by the TITCK were presented as mean rather than median, which is the way it is presented in other countries.

The approval timeline for the EMA (submission to final approval) including company response time was four hundred and seventeen calendar days in 2015, for the FDA it was three hundred and fifty-one calendar days, for the PMDA it was two hundred and eighty-four, for Health Canada three hundred and fifty-five, for TGA three hundred and seventy three and for Swissmedic four hundred and sixty-four calendar days (Figure 1.4). Therefore, the TITCK should evaluate the resources required and the expected number of applications reviewed in order to meet the target times. This can be achieved by introducing a more collaborative systematic approach between the TITCK and the industry. Thus, pharmaceutical companies should notify the TITCK in advance of the expected number of major regulatory submissions including NAS applications at the time of their annual budget/resource planning. This could facilitate both the planning for the review process as well as enhance the transparency and communication between the TITCK and pharmaceutical companies prior to applications.

Additionally, the TITCK should batch the questions raised during the review process and set reasonable deadlines for companies to respond. Similarly, this would enable companies to better plan their resources and maximise their efforts to reduce the clock stop period during the review of their applications. The findings from the study also suggest that the TITCK could consider collaborating with other regulatory health authorities as well as increasing the amount of available resources to meet the target timelines. On the basis of these findings this hypothesis is accepted.

### **Hypothesis 3: TITCK has not embedded Good Review Practices into the assessment and registration processes.**

This study identified that the TITCK has a relatively sound and robust quality management system and builds good quality measures into its review and assessment system. This includes the use of SOPs and assessment templates as well as incorporating a structured training

system for the TITCK staff. Thus by adapting the EU standards and the international practices and guidelines in the pharmaceutical regulatory area, the TITCK is perceived as a developed regulatory authority that has the ability and scientific qualifications to carry out their own assessments and review processes comparable to other developed regulatory health authorities such as the EMA and the FDA. In addition, the TITCK has developed an electronic submission system that enables companies to upload all regulatory submissions online. Similarly, the electronic system enables the TITCK to perform its activities effectively, while maintaining an internal tracking system of the progress of applications and a good archiving platform for all submissions, reviews and assessments.

The TITCK currently has a number of elements of Good Review Practices (GReP) in place. However, the TITCK may not fully recognise the functions of GReP in their system and that is probably why they have not as yet developed a guidance document on GReP. Consequently, GReP are neither formally embedded in their system nor followed consistently. However, it is recommended that the TITCK should develop formal guidelines for implementing GReP to ensure the consistency and standardisation in their review process. This could be achieved by collaborating with other international regulatory agencies and organisations to identify the best practices in this area as well as establishing a standard training system to ensure GReP are fully implemented by staff at all levels. In the light of the above findings and recommendations this hypothesis is rejected.

In conclusion, a number of exploratory hypotheses were raised in this study to evaluate the TITCK review process, timelines and implementation of Good Review Practices for the period from 2012 to 2015. The findings supported two of the hypotheses with regards to the alignment of the TITCK NAS application requirements with the international standards and the long approval timelines compared to other major regulatory agencies' timelines while rejecting the third one about the full implementation of the GReP. In addition, the results identified that the TITCK review performance was improving over the past four years. They also indicated that while the number of approved applications by TITCK was increasing, there was a decreasing trend in the approval timelines, which is a positive development even though the target timeline of two hundred and ten working days is still not achieved. This study provided for the first time a comprehensive overview of the registration review with all the milestones based on accurate data directly collected from the TITCK. Thus, this facilitates the in depth analysis and understanding of the Turkish review system's strengths and areas of

improvements and therefore enables the establishment of the required action plans by all stakeholders be it the agency or the industry in order to enhance the ultimate target of enhancing patients' access to medicines.

## SUMMARY

- This study has evaluated the regulatory review process and timelines by the TITCK for the first time since it was established as an agency and took over the responsibility for pharmaceutical regulations from the Ministry of Health in 2011. It has identified the key milestones, timelines and evaluated the measures used for GReP and suggested opportunities for an enhanced regulatory review.
- TITCK performs a full review as its assessment model for all new active substance applications. Therefore, a new marketing authorisation application for an NAS can be submitted in Turkey prior to any approval in the world. However, evidence for approval in the country of origin, EU or USA must be submitted prior to the final approval by the TITCK.
- Marketing authorisation applications must be submitted to TITCK in compliance with the common technical document (CTD) with quality, safety and efficacy modules covering both the active drug substance and the finished product and it is therefore fully aligned with the ICH content requirements.
- A local GMP accreditation of all manufacturing sites of the product is a pre-requisite to the marketing authorisation application.
- There is an official procedure for priority/fast track products to accelerate the marketing authorisation process for critical applications products such as orphan drugs and life-saving medicines and products meeting medical needs, which are given priority in the queuing line and assessment process.
- This study identified that the TITCK has a number of quality measures and policies in place to ensure consistency and standard performance including SOPs, review templates and an electronic submission tracking system; however, Good Review Practice (GReP) guidelines have still to be fully developed and implemented.

## **CHAPTER 4**

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# **AN EVALUATION OF THE TITCK REGULATORY REVIEW PROCESS IN COMPARISON WITH REGULATORY AGENCIES IN AUSTRALIA, CANADA, SAUDI ARABIA AND SINGAPORE**



## INTRODUCTION

History is full of examples of unfortunate cases and catastrophes that have triggered the rapid development of modern pharmaceutical regulations that started to evolve in the 19<sup>th</sup> century and progressed mainly after the Second World War (Rägo & Santoso, 2013). The sulphanilamide elixir disaster in 1937, which caused hundreds of deaths mainly children in the USA, was an eye opener for the public towards medicines' adverse events and potential risks. Consequently, this unfortunate event facilitated the establishment of the Federal Food, Drug and Cosmetic Act (FDA – Food and Drug Administration) in the USA and significantly changed pharmaceutical regulations in terms of the approval requirements and process (Jarell, 2012). Another example which further accelerated the development of pharmaceutical regulations was the Thalidomide tragedy in Europe and in almost more than forty-six countries in the world between 1958 and 1960 which led to the birth of approximately ten thousand babies with phocomelia and other birth defects (Fintel, et al., 2009).

As a result, along with the support of the World Health Organisation (WHO) and the involvement of other regulatory authorities; the entire pharmaceutical regulatory and authorisation approval systems were reshaped after the 1960s. Thus, the main goal was to define the minimum standards for drug development and marketing authorisations as well as to promote harmonisation of pharmaceutical regulations across countries to ensure the timely access of patients to safe and effective medicines. For example, the European Commission (EC) introduced several directives after 1975 to regulate pharmaceutical development and set the clinical and non-clinical standards to perform trials with new medicinal products to generate the required data.

Furthermore, the harmonisation of the registration review process and marketing authorisation requirements was established in the EU through the mutual recognition and centralized procedure (Rägo & Santoso, 2013). In parallel, a joint collaboration of regulatory authorities and industry associations from the EU, Japan and the USA led to the establishment of the International Conference on Harmonisation (ICH) in the 1990s. Accordingly, the ICH defined Technical Requirements for the Registration of Pharmaceuticals for Human Use, which focuses primarily on the requirements for new, innovative medicines and facilitated pharmaceutical regulatory harmonisation (ICH, 2016).

The WHO on national, regional, inter-regional and international levels also supported similar harmonisation efforts in both pharmaceutical regulatory requirements as well as review procedures in order to ensure the availability of safe, effective and good quality pharmaceuticals to patients worldwide. Nevertheless, the impact of harmonisation and the level of alignment of each country to the minimum international standards in the regulatory review process remain the key challenge to be measured and identified. However, there is still no consensus or standard definition of the registration review process in terms of methodology, review conduct, stages, timelines and criteria to be employed in the decision making process or even whether countries are actually fulfilling a review process at all or have similar review processes for the same medicines.

On the other hand, individual countries and authorities may have different experiences, competencies and knowledge regarding the regulatory review process, which can add value to other countries if recognised and identified properly. Therefore, through the comparison of various systems and review processes, the best practices can be shared for the benefit of all countries. With this in mind, this study was conducted to compare the current TITCK regulatory review processes and timelines in comparison with other international, mid-sized regulatory health authorities. Thus, the study aimed to identify areas of strength and those requiring further improvement within the TITCK in relation to the review process as well as to assess the level of adherence to good review practices in order to facilitate the TITCK progress toward this goal.

## **OBJECTIVES**

The main objectives of this study were to:

- Identify the regulatory review process model used in the TITCK in terms of process flow, key milestones and timelines.
- Evaluate the key stages in each review process of other regulatory health authorities in Australia, Canada, Saudi Arabia and Singapore to determine the commonly shared milestones and different practices.
- Compare the review process and practices of the TITCK with the regulatory health authorities in Australia, Canada, Saudi Arabia and Singapore.

- Determine the strengths and areas for improvement for the TITCK review process.
- Identify the Good Review Practices (GRoP) implemented by the TITCK to ensure consistency, transparency, timeliness, and predictability of the review process.

## **Hypotheses**

Pharmaceutical regulations and medicines' approval timelines have always captured the attention of both the public as well as local, regional and global stakeholders of the pharmaceutical industry due to the significant impact of these regulations on patients' access to medicines. In Turkey, most of the pharmaceutical regulations are aligned with those of the International Conference of Harmonisation (ICH) Guidelines and the EU Directive 2001/83/EC on medicinal products for human use. The regulations mandate the implementation of the CTD guidelines for preparing the marketing authorization application file and the approval target is set to be two hundred and ten working days (TITCK, 2005).

However, experience from the past fifteen years by the pharmaceutical industry and outcomes of previous studies show that the registration review process and approval timelines in Turkey are still not at the desired level required. Thus from an industry perspective, the TITCK is generally perceived to have relatively long approval timelines in comparison with other mature health authorities such as the FDA and the EMA which consequently delay patients' access to medicines (Kanzık & Hıncal, 2011).

While each country has its own national requirements, it is well recognised that individual health authorities have different expertise, competencies and knowledge that could be of value to other countries by comparing the various review models and sharing best practices. Nevertheless, such comparisons can be of more value and facilitate improvements if conducted among countries with common challenges and similar health agencies' characteristics. Accordingly, a comparison of an emerging market regulatory agency with mature sophisticated health agencies such as the FDA and the EMA may often lead to an unreasonable comparison due to the different characteristics and competencies these agencies possess. For example, in terms of organisational structure, it is known that the FDA has the largest number of reviewers compared to other health agencies and the scope of the FDA's regulatory authority is broad and includes many areas other than pharmaceutical products (FDA, 2016). The EMA is a central networking organisation agency based on twenty-eight member countries representing a population of almost five hundred million. Thus, the review

and decision-making process within the EMA involve many experts from across Europe and the use of a model that depends on a rapporteur and co-rapporteur (EMA, 2016). Therefore, many emerging markets have an interest in comparing themselves with other mature regulatory authorities such as; Health Canada and Australia (Hashan, et al., 2016).

To date, comparative data to demonstrate the performance of the TITCK registration review model with other developed and emerging countries of similar sizes and characteristics have not yet been identified. Therefore, this was the first study to compare the registration review model in Turkey with Australia (TGA), Canada (Health Canada), Saudi Arabia (SFDA) and Singapore (HSA).

The comparative countries were selected to ensure an adequate representation of health agencies of similar characteristics and review models, maturity of the agency as well as agencies of countries from different regions in the world other than those leading agencies in Japan, EU and the USA. Furthermore, the size of population of the selected countries such as Australia and Canada was considered as well. The SFDA is considered one of the most established agencies in the Middle East region and has a leading role in the pharmaceutical regulatory field where it is listed as a reference agency for many countries. Similarly, the HSA in Singapore is a well-developed reference agency to many other agencies in the Asia Pacific region and uses a specific risk stratification model. Within this model, the agency maximises their resources and therefore can be a good model to follow for other emerging markets with limited resources (Hashan, et al., 2016).

In the light of the above, this study examined the following hypotheses:

1. The TITCK review model for NAS applications is similar to that of other mid-sized regulatory authorities.
2. The marketing authorisation application requirements in Turkey are similar to those of other international agencies.
3. The approval times for NASs in Turkey are longer than other countries such as Australia, Canada, Saudi Arabia and Singapore.
4. Good Review Practice (GReP) requirements implemented by the TITCK are comparable to other similar countries, which ensure consistency, transparency, timeliness, and predictability of the review process.

## **METHODS**

### **Study Participants**

The regulatory health authorities who are responsible for the regulation and review process of pharmaceutical products in five countries were included in this study namely; Australia's Therapeutic Goods Administration (TGA), Health Canada, Singapore's Health Science Authority (HSA), and the Saudi Arabia Food and Drug Administration (SFDA) as well as the TITCK.

### **Data Collection Process**

The questionnaire designed and used in this study was completed by the TITCK to collect data related to the regulatory review process of New Active Substances (NASs) including the marketing authorisation applications submission dates, the registration dates and the overall review and approval timelines. The questionnaire had been previously used in an Emerging Markets Programme to evaluate the regulatory process for new medicines in a number of countries and identified the regulatory aspirations, barriers, problems and priorities, related to the review of new medicines that can have an impact on their availability to patients (McAuslane, et al., 2009). The questionnaire was designed to enable the mapping of the process flow and the internal parameters that influence the progress of the review and understand the decision-making process as well as the implementation of GReP and review outcomes in countries like Saudi Arabia (Hashan, et al., 2016).

Moreover, this standard mapping facilitated the collection of important information and allowed the data to be illustrated in a common format to simplify comparisons among other regulatory agencies. The questionnaire was divided into three parts where the introduction aimed to provide details of the TITCK's organisational structure and resources and to explore the review model(s) used for the scientific assessment of medicines. The second part aimed to explore the review and approval process for new active substances (NASs) within the agency through a standard process map which was developed through a previous study of procedures of mature regulatory agencies as well as those of the emerging pharmaceutical markets (McAuslane, et al., 2009).

The standard process map allowed for the description of the review and included common definitions. The last part of the questionnaire documented the activities that contribute to the

quality of the decision-making process and measures adopted by the TITCK as a regulatory agency to build quality into the assessment and registration process in order to improve consistency, transparency and timeliness. Following the completion of the questionnaire by the TITCK, data were then transferred into a country report in a word format to create a comprehensive overview of the current regulatory review process at the Turkish Agency, thus enabling auditing, correction, discussion and modifications if required by the TITCK.

Similar questionnaires had also been completed and validated within the same time frame by Australia's Therapeutic Goods Administration (TGA), Health Canada, Singapore's Health Science Authority (HSA), and the Saudi Arabia Food and Drug Administration (SFDA) (Hashan, et al., 2016). Data were then transferred into a word document with a consistent format and standardised terminology of the questionnaire for the purpose of comparison and to enable the compilation of important information about the structure, processes, and practices of international regulatory agencies. The resulting reports were sent to the authorities for auditing, correction and further comments.

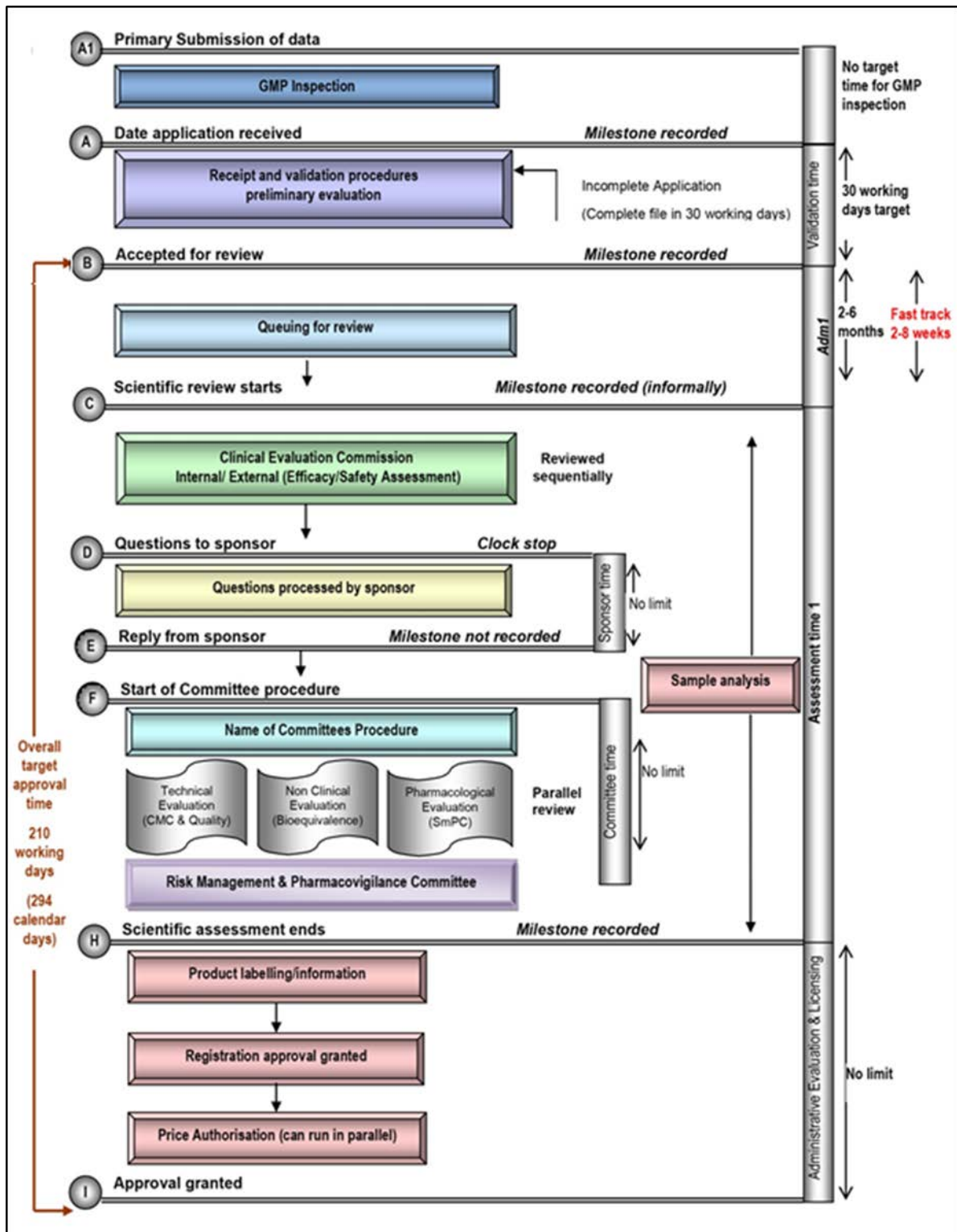
## **RESULTS**

This study identified that each of the five mid-sized regulatory health authority have similar goals for regulating the pharmaceutical industry and establishing the marketing authorisation standards and requirements to ensure the timely access of patients to medicines while safeguarding their safety, quality and efficacy. Process maps of the five countries are presented in a standardised format, which enables appropriate comparisons to be made (Figure 4.1-4.5) Nevertheless; regulatory authorities demonstrate a number of differences within their review systems in terms of processes, timelines and review practices.

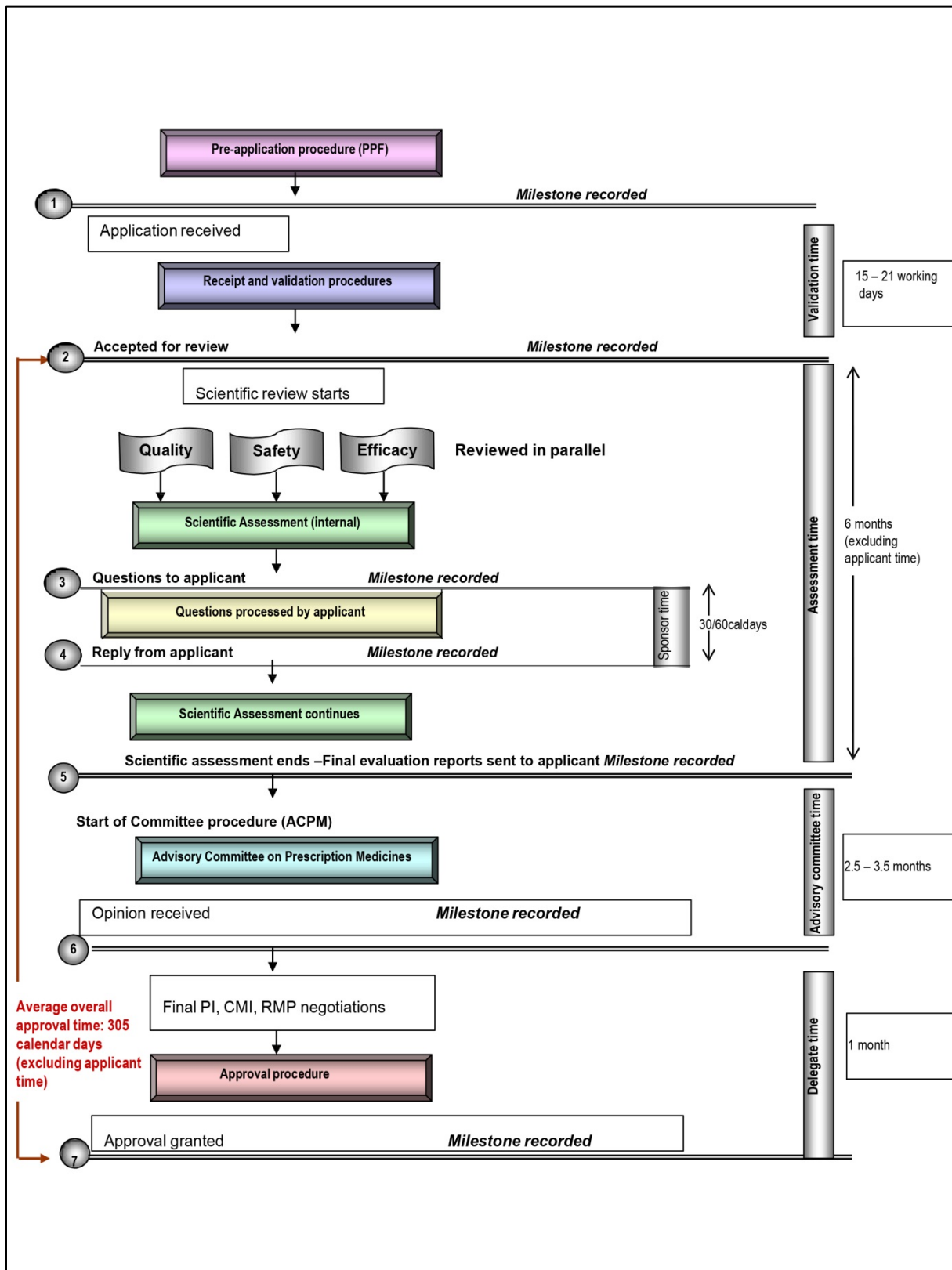
Accordingly, the results of this study as well as the comparative analysis of the review systems are presented in two parts;

- Part I: Comparative assessment of the regulatory review processes and milestones,
- Part II: Good review practices.

Figure 4.1: Registration process map for Turkey

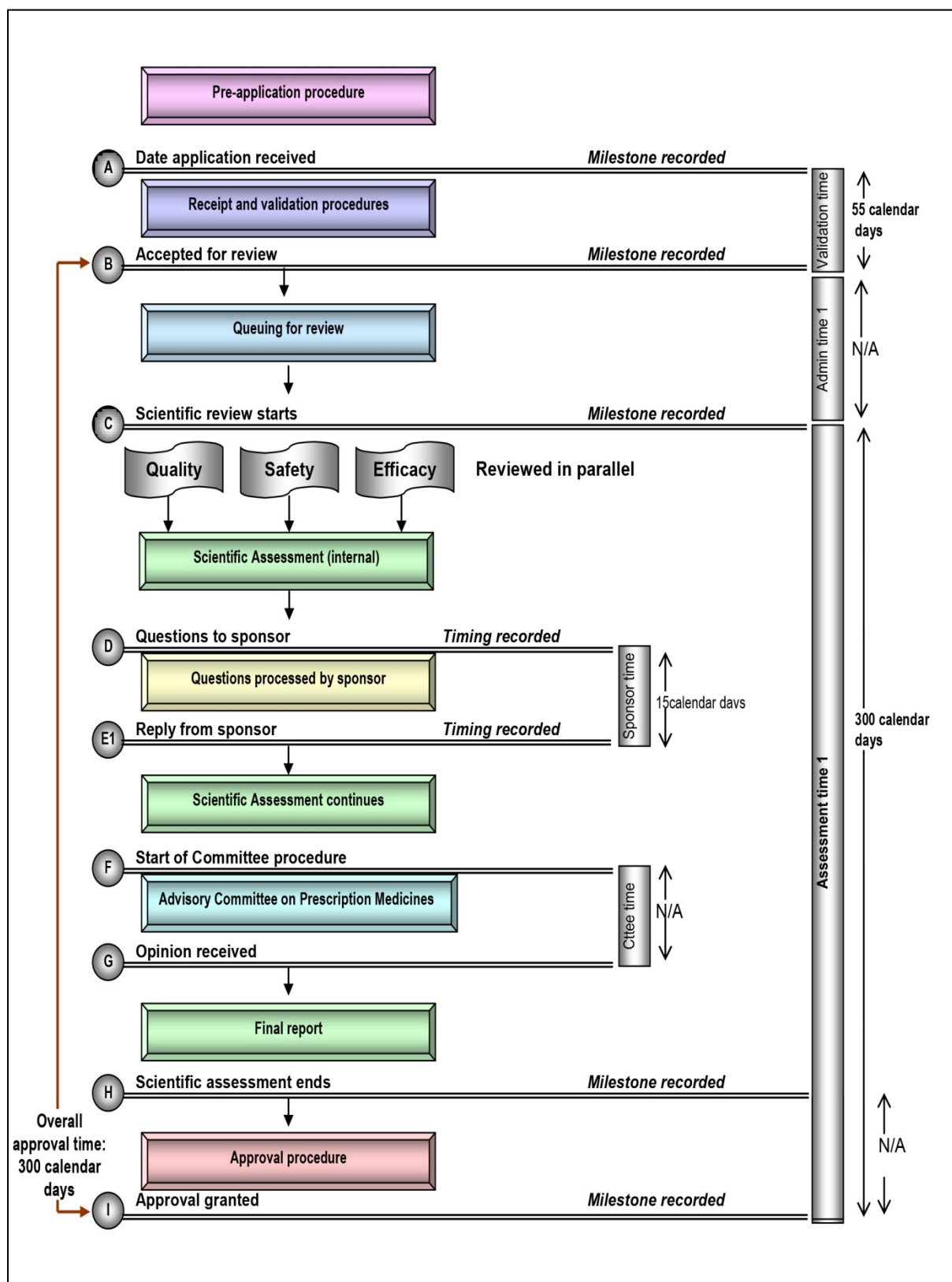


**Figure 4.2 Registration process map for Australia**





**Figure 4.3: Registration process map for Canada**



**Figure 4.4: Registration process map for Saudi Arabia**

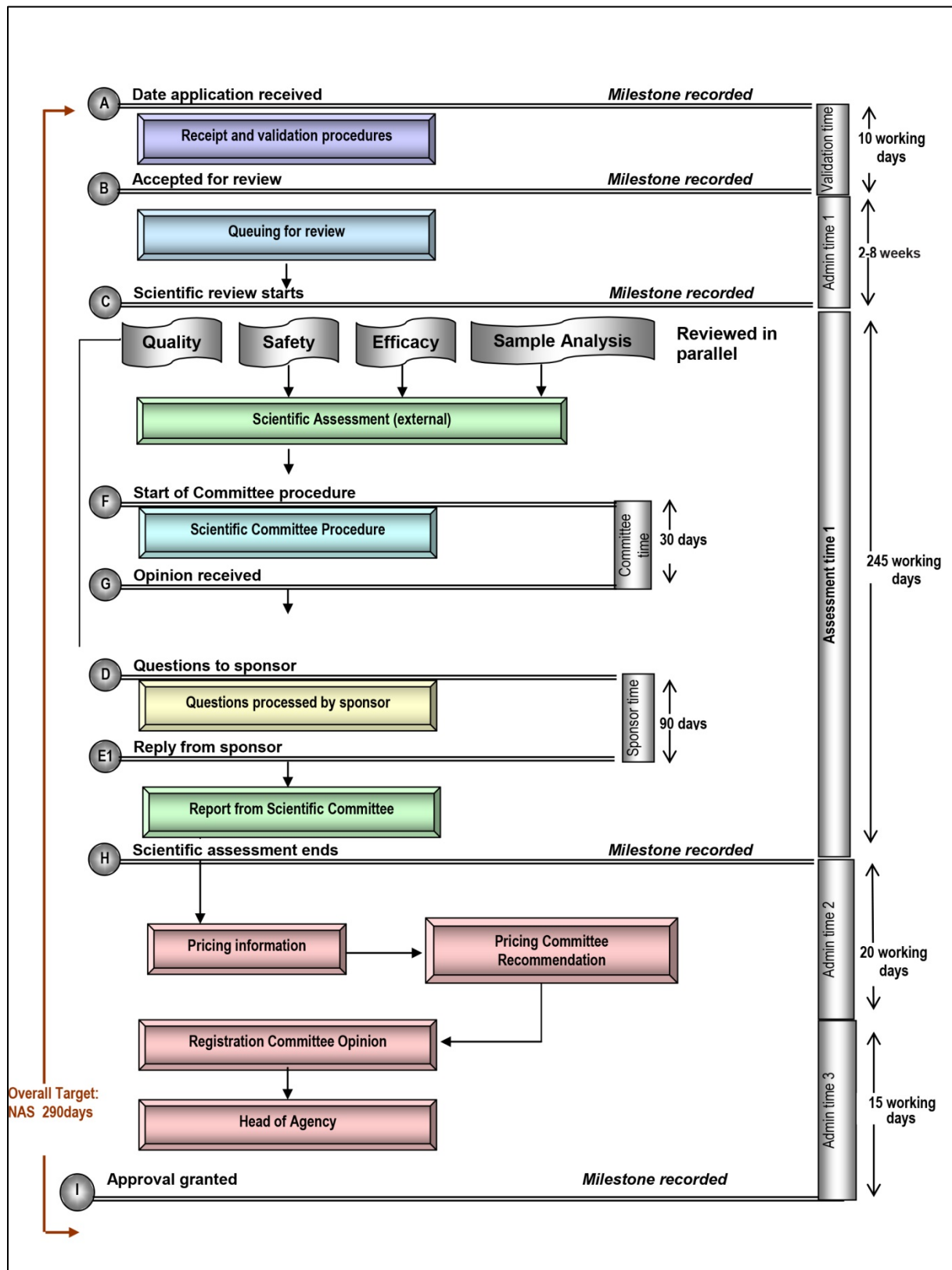
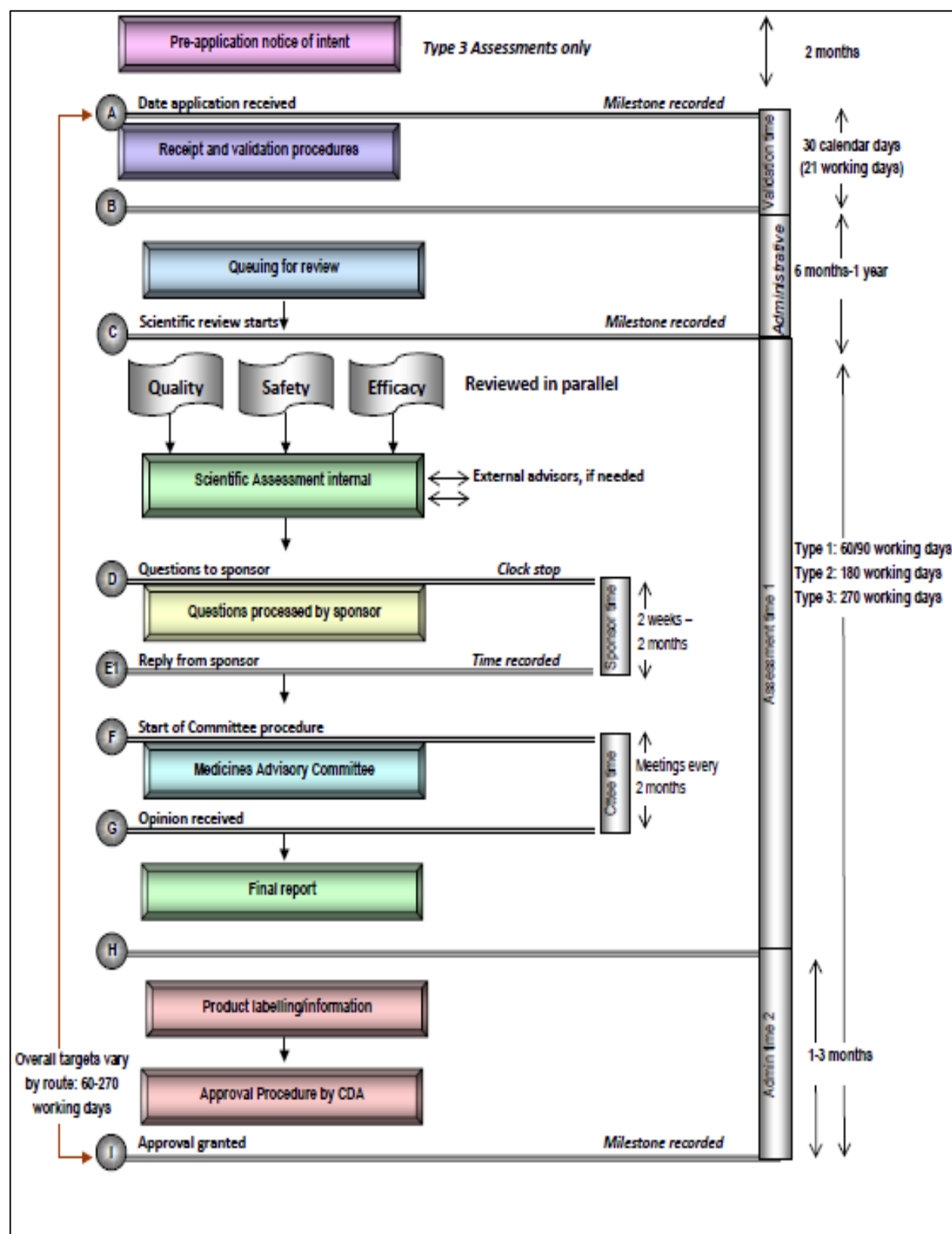


Figure 4.5: Registration process map for Singapore



## **Part I: Comparative Assessment of the Regulatory Review Processes and Milestones**

### **Review model**

Many regulatory health authorities apply a different level of data assessment, according to the type of product and/or its worldwide regulatory status. Accordingly, there are three basic types of scientific review, which have been identified by McAuslane and colleagues for the scientific regulatory review of a product (McAuslane, et al., 2009) and in summary are:

**Type 1 verification model:** this is generally used to reduce duplication of review effort since it requires that the product is authorised by two or more recognised reference agencies, elsewhere. Thus, the responsibility of the agency is only to verify and validate the application for local marketing to ensure that it conforms to that agreed in the reference authorisation(s).

**Type 2 the abridged assessment model:** this conserves resources by not re-assessing scientific supporting data that has been reviewed and approved by at least one reference or competent regulatory agency and includes an ‘abridged’ independent review of the product in terms of its use under local conditions.

**Type 3A and 3B full assessment models:** here the agency carries out a complete scientific review and evaluation of the supporting scientific data (quality, pre-clinical, clinical) for a major application. While for Type 3A assessment, a pre-registration by a reference agency is required, for type 3B; pre-approval by a reference regulatory agency is not required.

Within this study, the review and assessment model of the TITCK was explored and accordingly it was identified that the TITCK performs a full review for all new active substance applications. Therefore, a marketing authorisation application for a new active substance can be submitted in Turkey prior to any approval in the world. However, evidence of approval in the country of origin, EU or US must still be submitted prior to the final approval by the TITCK (Type 3A). In comparison with the other agencies; the SFDA, TGA, HSA and Health Canada utilise a full assessment model (Table 4.1). However, the SFDA requires that a certificate of pharmaceutical product (CPP) is submitted with the application for final marketing authorisation (Type 3A) whilst a CPP submission for some applications is not required for the TGA, Health Canada and HSA (Type 3B). On the other hand, in order to

optimise the use of resources, TGA can conduct an abridged review if requested by the sponsor and if the product has been approved by two or more reference agencies and HSA conducts an abridged review if the product has been approved by one or more reference agencies, or a type 1 (verification model) if the product has been approved by two or more reference agencies.

**Table 4.1: Models of assessment of the five agencies and extent of the scientific review**

Type of review model	Turkey	Australia	Canada	Saudi Arabia	Singapore
Verification review (Type I)	✗	✗	✗	✗ <sup>a</sup>	✓ <sup>b</sup>
Abridged review (Type II)	✗	✓ <sup>c</sup>	✗	✗	✓ <sup>d</sup>
Full review (Type III)	✓	✓	✓	✓	✓
<b>Extent of scientific review</b>					
<i>1. Chemistry, Manufacturing and Control (CMC) data</i>					
Extensive assessment	✓	✓	✓	✓	✓
<i>2. Nonclinical data</i>					
Extensive assessment	✓	✓	✓	✓	✓ <sup>e</sup>
<i>3. Clinical data</i>					
Extensive assessment	✓	✓	✓	✓	✓
<b>Additional information obtained (where appropriate)</b>					
Other agencies' internal review reports	✓	✓	✓	✗	✗
Reports on the internet	✓	✓	✓	✓	✓
General Internet search	✓	✓	✓	✓	✓

<sup>a</sup> The SFDA recently announced that it will conduct a verification review if the product has been approved by the EMA and the FDA

<sup>b</sup> Only if the product has been approved by two or more reference agencies.

<sup>c</sup> Only if requested by the sponsor and if the product has been approved by two or more reference agencies.

<sup>d</sup> Only if the product has been approved by one or more reference agencies

<sup>e</sup> Only for Biological and Biosimilar products

## Data requirements

The TITCK requires full clinical and efficacy data for the application and this must be submitted in the CTD format with the correct sections (Module 1,2,3,4 and 5) of scientific data. Accordingly, the TITCK performs a complete assessment of these data, mainly the quality and the clinical parts of the product file. Additionally, the TITCK performs a structured benefit–risk assessment, examines the influence of the ethnic factors, the differences in medical culture/practice, national disease patterns and unmet medical needs even though sufficient data on these criteria are not always supplied in all applications.

Furthermore, most of the quality elements of the application are assessed by the TITCK through the Good Manufacturing Practices (GMP) accreditation process, where a complete GMP application is submitted for evaluation and a physical inspection of all involved sites is included. The GMP accreditation process is a pre-requisite for all new marketing authorisation and type 2B site related CMC applications. As a result, the start of the review process can be delayed by twelve to eighteen months. An exception is made only for life saving and critical products categorised as priority one where the GMP accreditation process can be conducted in parallel to the review process to save time and accelerate patients' access to these products (TITCK, 2016). However, the GMP process in some countries like Saudi Arabia and Australia may be completed by the submission of a copy of a GMP certificate issued from a reference agency (TGA, 2016). Furthermore, some agencies like Singapore, may conduct an inspection in parallel to the review process according to the ICH GMP and/or PIC/S guidelines (HSA, 2016).

All the comparative authorities in this study require full datasets for the pharmaceutical CMC, non-clinical and clinical sections and conduct a detailed assessment of all three sections for full review. On the other hand, the assessments conducted by the HSA depend on the type of review it conducts, allowing the conservation of resources for use in the review of medicines associated with a high risk for their population. At the TITCK, the sequence of the scientific review of the application can vary according to the status of the application, where several committee reviews can run in parallel or sequentially depending on the global submission status of the product (EMA/FDA). Thus, in the case of a parallel MAA submission with EU or FDA; the registration review process starts with the technical assessment and then proceeds with the clinical evaluation in order to consider any other regulatory agency's clinical opinion or decision mainly from EMA/FDA. Except for the TITCK, the review of quality, safety and efficacy data are conducted in parallel at all four regulatory agencies in this study. Furthermore, the external experts are used on an ad hoc basis by the TGA, HSA and SFDA, whereas Health Canada does not use external experts for dossier review. The external experts are mainly responsible for providing a detailed assessment report and recommendations as well as a clinical opinion on the product.

Pricing data is not required by the TITCK at the time of submission; however, negotiation starts during the registration review and licensing process. The pricing process can be conducted in parallel and independently to the registration review process after the main

clinical assessment is completed. Nevertheless, registration approval can be obtained prior to pricing approval since this is required in later steps prior to the sales and importation permission applications which enable the product to be commercially available. Of the five agencies, only the SFDA requires information related to pricing as part of the marketing authorisation dossier. Thus, pricing evaluations are not part of the technical review at the other comparative agencies.

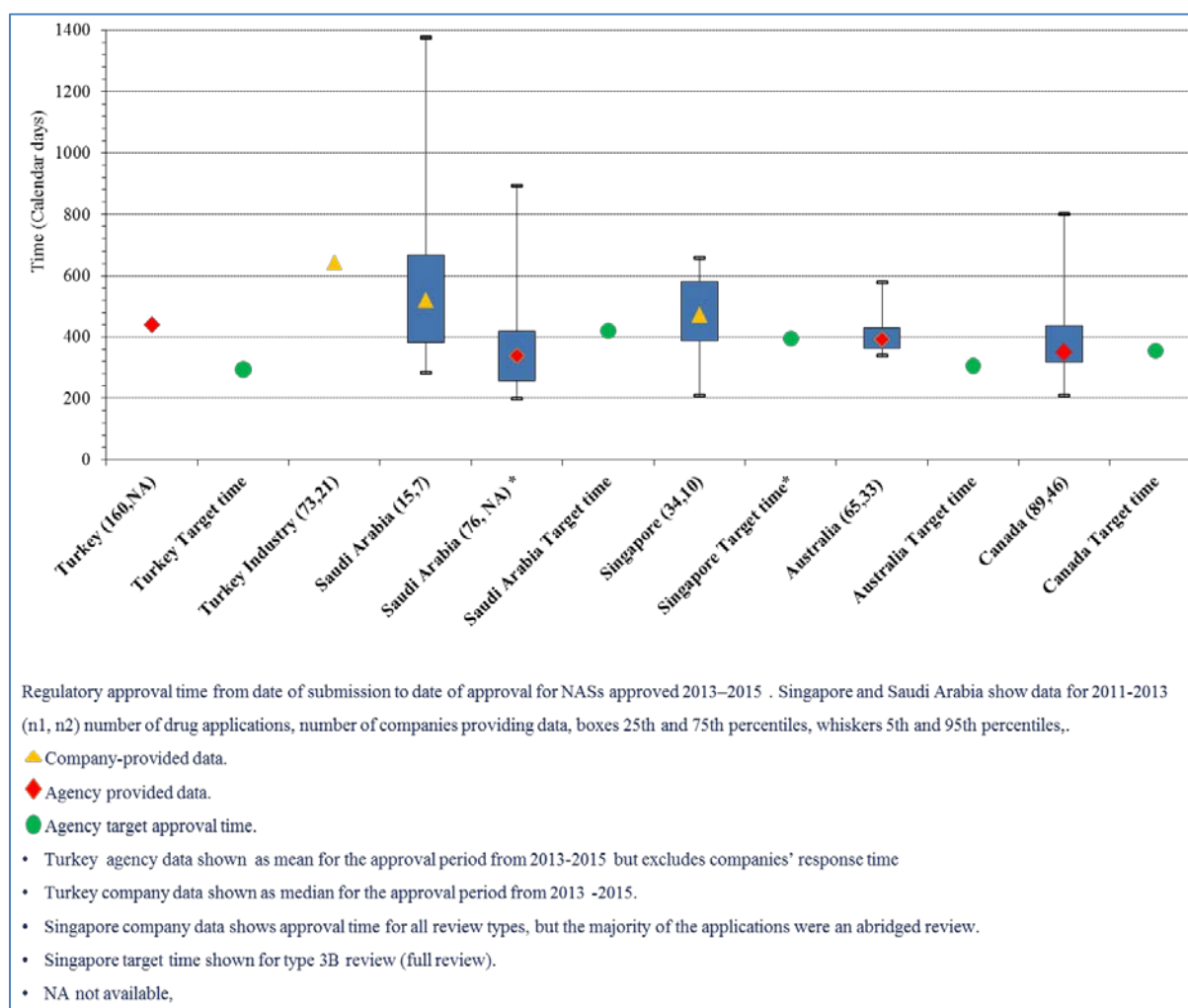
### **Target and approval times**

The TITCK overall approval target timeline is two hundred and ten working days (two hundred and ninety four calendar days) in the regulation, with one hundred and eighty working days for a prioritised accelerated review and one hundred and fifty working days for highly prioritised products. However, prioritised accelerated review and highly prioritised products are not defined in the regulation. In practice, the actual approval timelines are much longer than that stated in the regulation.

The TITCK review process consists of the following common steps: validation of the submitted dossier, scientific assessment, company response and final authorisation. The TITCK target time for the validation is thirty working days. The TITCK mean approval times for New Active Substances (NASs) marketing authorisations applications approved in 2013, 2014 and 2015 were three hundred and fifty, three hundred and forty and two hundred and seventy working days respectively (Figure 3.5).

In comparison, for the SFDA, which conducts a type 3A review, the overall target approval time is four hundred and twenty calendar days (two hundred and ninety working days). Whereas TGA, Health Canada and HSA, which all conduct type 3B reviews have overall target approval times of three hundred and five calendar days; TGA, three hundred and fifty-five calendar days; Health Canada and three hundred and ninety-five calendar days for HAS although these are mainly abridged reviews. While the review times for SFDA were lower than the target time, the review times from 2012-2015 for TGA exceeded the specified target, but for Health Canada approval times were approximately on target during the same time (Figure 4.6).

**Figure 4.6 Regulatory approval times from date of submission to date of approval for New Active Substances (NASs) approved 2013-2015 (Calendar days)**



## Part II: Good Review Practices (GReP)

Building quality measures and the implementation of Good Review Practices (GReP)<sup>3</sup> in the registration review process is important for regulatory health authorities since it ensures consistency, transparency, timeliness and competency in the review processes (McAuslane, et al., 2009) and enables regulatory authorities to achieve timely approvals for new medicines while safeguarding the high quality which may have a significant impact on accelerating patients' access to medicines; thus reducing the costs to both governments and marketing authorisation applicants. Furthermore, the implementation of GReP enhances the global harmonisation and regulatory convergence by facilitating the exchange of best practices,

<sup>3</sup> Good Review Practice (GReP): A code about the process and the documentation of review procedures that aims to standardise and improve the overall documentation and ensure timeliness, predictability, consistency and high quality of reviews and review reports.



assessment reports and outcomes among regulatory authorities that significantly contributes to the better management of resources of regulatory authorities and the timely approvals of medicines (WHO, 2015). Therefore, regulatory health authorities are focusing on improving the quality standards of the review process and implementing the required quality measures to enhance their efficiency and meet the expectations of industry and the general public. This study identified the different quality metrics that have been implemented by the five agencies with the aim of comparing the practices in place to ensure quality, transparency and predictability of the regulatory review process. All five agencies have good review practices (GReP) in place, but implement them informally, except for Health Canada, which has a programme for formal use.

### Quality measures

The quality measures evaluated in this comparative study included the availability and use of: an internal quality policy, GReP, standard operating procedures (SOPs) for assessors, assessment templates, the existence of a quality assurance department, the use of scientific committees and the use of shared and joint reviews with other agencies. The TITCK have six of the seven measures in place, namely an internal quality policy, GReP system, SOPs for assessors, assessment templates, a dedicated quality assurance department and a scientific committee (Table 4.2).

**Table 4.2: The quality measures implemented by the five agencies**

Measure	Regulatory Authority				
	Turkey (6/7)	Australia (6/7)	Canada (5/7)	Saudi Arabia (6/7)	Singapore (5/7)
Internal quality policy	✓	✓	✗	✗	✗
Good Review Practice System	✓ (Informally)	✓ (Informally)	✓ (Formally)	✓ (Informally)	✓ (Informally)
SOPs for guidance of assessors	✓	✓	✓	✓	✓
Assessment templates	✓	✓	✓	✓	✓
Dedicated quality department	✓	✗	✗	✓	✗
Scientific committee	✓	✓	✓	✓	✓
Shared and joint reviews	✗	✓ (Occasionally)	✓ (Occasionally)	✓ <sup>a</sup>	✓ (Occasionally)

<sup>a</sup> Shared and joint review with the GCC countries.

In comparison, SFDA and TGA also each have six of the seven measures in place, whereas Health Canada and HSA employ five. Additionally, Health Canada, TGA and HSA occasionally conduct shared or joint reviews with other regulatory authorities.

### **Transparency and communication**

The transparency of any regulatory health authority can be defined in terms of the ability and willingness of the agency to assign time and resources to providing information on its activities to both the informed public (which includes health professionals) and industry. Thus each regulatory authority may prioritise differently the level of being open and transparent in its relationship with the public, professions and industry depending on the main drivers and incentives of the agency to allocate time and resources to certain activities and practices that facilitate the openness of the regulatory system. For example, the political will in the country, public pressure as well as the press and media attention on the regulatory review system can be among the main drivers of the agency to focus on transparency.

Additionally, agencies may aim to increase the level of confidence in their review system, in order to provide assurances on safety safeguards and to ensure better staff morale and performance (McAuslane, et al., 2009). Information communicated by regulatory health authorities to the public and relevant stakeholders could include: feedback on submitted dossiers, technical staff contact information, pre-submission scientific advice, official guidelines, ability to track the progress of applications, summary of the grounds of approval, approval times, advisory committee meeting dates and the approval of products. The TITCK has only three of these nine parameters in place. This includes, information provided to the general public in terms of information of the approved products and approved product labelling, feedback to industry on submitted dossiers only at the validation step as well as through providing official guidelines to assist the industry.

Furthermore, the TITCK has an internal electronic system to track applications under review identifying the stage in the process, however the system cannot be accessed by applicants, nor does it provide information regarding review timelines. Official pre-submission advisory meetings are also not provided by the TITCK; nevertheless, such meetings can be conducted on request and on an ad hoc basis informally and depending on the case under review. The SFDA has five of these parameters in place, HSA six, Health Canada eight and TGA all nine (Table 4.3).

**Table 4.3: Transparency and communication parameters in the five agencies**

Measure	Regulatory Authority				
	Turkey	Australia	Canada	Saudi Arabia	Singapore
	(3/9)	(9/9)	(8/9)	(5/9)	(6/9)
Feedback to industry on submitted dossiers	✓	✓	✓	✗	✗
Details of technical staff to contact	✗	✓	✓	✗	✓
Pre-submission scientific advice to industry	✗	✓	✓	✓	✓
Official guidelines to assist industry	✓	✓	✓	✓	✓
Industry can track progress of applications	✗	✓	✓	✓	✓
Summary of grounds on which approval was granted	✗	✓	✓	✗	✗
Approval times	✗	✓	✓	✓	✓
Advisory committee meeting dates	✗	✓	✗	✗	✗
Approval of products	✓	✓	✓	✓	✓

Of the five agencies, TITCK, SFDA and HSA do not publish a summary basis of approval, while SFDA, Health Canada, and HSA do not supply advisory meeting dates, or give feedback to the industry on the submitted dossier. Neither the TITCK nor the SFDA share information that is needed to contact their technical staff during the review. The reason behind this approach is possibly the concern of the agencies that stakeholders may influence or apply pressure on the reviewers.

### **Continuous improvement initiatives**

During the past few years, building quality measures into the regulatory review process has become one of the important focus areas for major regulatory authorities and pharmaceutical companies. Thus, regulatory health authorities are devoting more time and resources to build the necessary quality indicators and improve the processes accordingly. Previously, approval times and the speed of the regulators' review were the only indicators of quality used to measure the authority's review performance and process efficiency (Cone & McAuslane, 2006). However, studies have shown that the quality of the regulatory review and decision-making process from receipt of the applications to final approval must also be considered and equally monitored to be improved (Salek, et al., 2012). Reasons for introducing quality

measures within the authority include, enhancing the review process efficiency, minimising the errors, ensuring consistency, reducing costs, achieving stakeholder satisfaction and increasing transparency through improving communication within the authority and with all stakeholders. Accordingly, the continuous improvement initiatives assessed in this study included external and internal quality audits, tracking systems and the review of assessors and stakeholders' feedback. This study identified that the TITCK does not have an internal tracking system to track the different milestones of applications through the various review stages. Moreover, although the TITCK conduct internal quality audits through its dedicated internal quality department, yet the agency does not go through any external quality audits. Accordingly, Turkey has three of these five continuous improvement processes in place while Australia and Singapore have four of these and Saudi Arabia engages in all five continuous improvement processes and Health Canada has three (Table 4.4).

**Table 4.4: Quality improvement initiatives in the five agencies**

Measure	Regulatory Authority				
	Turkey (3/5)	Australia (4/5)	Canada (3/5)	Saudi Arabia (5/5)	Singapore (4/5)
External quality audits	✗	✗	✗	✓	✗
Internal quality audits	✓	✓	✓	✓	✓
Internal tracking systems	✗	✓	✓	✓	✓
Reviews of assessors' feedback	✓	✓	✗	✓	✓
Reviews of stakeholders' feedback	✓	✓	✓	✓	✓

### Training and education

One of the important elements of a quality process is the training and continuing education of staff at the regulatory health authorities as well as of assessors working within the authority, including those employed on a full-time basis as well as those contracted for specific assessments. The type of training and continuing education that can enhance the review process includes international workshops, external and in-house courses, on-the-job training, lectures by external speakers, induction training, sponsorship of postgraduate degrees and placements and secondments.

The TITCK apply all of the training and education elements except for the provision of induction training for new employees and assessors, which is described as being handled

through on-the-job training. In comparison, the SFDA has seven, lacking only the availability of in-house training, whereas Australia, Canada and Singapore employ all eight (Table 4.5).

**Table 4.5: Training and education in the five agencies**

Measure	Regulatory Authority				
	Turkey (7/8)	Australia (8/8)	Canada (8/8)	Saudi Arabia (7/8)	Singapore (8/8)
International workshops/ conferences	✓	✓	✓	✓	✓
External courses	✓	✓	✓	✓	✓
In-house courses	✓	✓	✓	✗	✓
On-the-job training	✓	✓	✓	✓	✓
External speakers invited to the authority	✓	✓	✓	✓	✓
Induction training	✗	✓	✓	✓	✓
Sponsorship of post-graduate degrees	✓	✓	✓	✓	✓
Placements and secondments in other regulatory authorities	✓	✓	✓	✓	✓

### **Enablers and barriers to good quality decision-making**

This study identified the TITCK's own perception of its unique positive qualities and the major impediments it faces in carrying out the review of new medicines and making them available to ensure patients' timely access to medicines. Therefore, the TITCK indicated that the availability of a pool of high calibre employees and good scientific committee experts as well as building close relationships with other international regulatory authorities' to share good decision-making processes and practices, are factors that make a major contribution to the effectiveness and efficiency of the review. Whilst other agencies provided a diverse set of enablers as part of their questionnaire responses, there was some consistency among all five countries. Moreover, the study revealed the main challenges encountered by the TITCK that act as barriers to a good quality review system and to making new medicines available in a timely manner with limited human resources include physical and technological infrastructure as well as the patent related rights regulations are not aligned with international standards. Questionnaire responses from the comparative agencies indicated that incomplete submissions and lack of experienced staff were considered barriers to an effective and efficient authority. In summary, the key features of the TITCK review process compared with TGA, Health Canada, SFDA, and HSA are presented in Table 4.6.

**Table 4.6: Key features of the five agencies' review process**

<b>Marketing Authorisation</b>	<b>Turkey</b>	<b>Australia</b>	<b>Canada</b>	<b>Saudi Arabia</b>	<b>Singapore</b>
Certificate of a Pharmaceutical Product (CPP) is required at time of submission	✗	✗	✗	✓	✗
Medical staff: More than 20% of the review staff are medically qualified	✗	✓	✗	✗	✗
Review times: The authority sets targets for the time it spends on the scientific assessment of NAS application.	✗	✓	✓	✓	✓
Approval times: The authority has a target for the overall time for the review and approval of an application.	✓	✓	✓	✓	✓
Questions to sponsors are batched at fixed points in the review procedure.	✗	✓	✗	✗	✓
Company response time: Recording procedures allow the company response time to be measured and differentiated in the overall processing time	✗	✓	✓	✓	✓
Priority Reviews: The agency recognises medical urgency as a criterion for accelerating the review and approval process for qualifying products.	✓	✗	✓	✓	✓
Parallel processing: The different sections of technical data (Quality, Safety, and Efficacy) are reviewed in parallel rather than sequentially.	✗	✓	✓	✓	✓
Price negotiation: Pricing discussion is separate from the technical review and does not hold up the approval.	✓	✓	✓	✗	✓
Sample analysis: The focus is on checking quality in the market place and requirements for analytical work do not hold up the marketing authorisation.	✗	✓	✓	✓	✓

## DISCUSSION

In today's world, enhancing patients' access to new medicines is of critical importance for all health authorities and stakeholders. However, the expected improvement in patients' access to medicines cannot be realised in many countries around the world due to several reasons including stricter pharmaceutical regulations, long approval timelines, increased payer pressures and complicated legal practices.

In Turkey, the registration review process of pharmaceutical products is conducted in accordance with the “*Registration Regulation of Human Medicinal Products*” which was amended in 2009 and thus sets forth the principles, procedures, and policies regarding the registration of medicines, with the aim of achieving the desired efficacy and safety as well as the required quality (Ministry of Health, 2005). One of the main goals and focus areas of the Turkish health authority in the past decades was to ensure alignment with international standards and build a robust high quality regulatory health agency comparable to other mature developed health agencies, in order to ensure the timely access of patients to medicines.

**Hypothesis 1: The TITCK review model for NAS applications is similar to that of other mid-sized regulatory authorities.**

The TITCK currently performs a full review (Type 3A) for all new active substances and a marketing authorisation application for a NAS can be submitted in Turkey prior to any approval in the world although, a pre-approval by a reference regulatory agency is a prerequisite for marketing authorisation final approval. During the review process, the TITCK conducts a full assessment of the data, but mainly for the clinical and quality parts where a complete GMP application and inspection process is included as a pre-requisite for the application. This may also run in parallel to save time for life saving and critical products. Taking into consideration the limited resources within the TITCK and the relatively large number of applications received by the agency, the TITCK might need to utilise and conserve constrained resources more efficiently. One method for the conservation of regulatory resources is the use of a risk stratification approach for the review (Alsager, et al., 2015). With this approach, agencies such as HSA, TGA and Health Canada may conduct an abridged review in certain circumstances where products have been approved by one or more reference agencies. Therefore, they are able to conserve resources for a full review for products that have not been previously reviewed or medicines associated with a high risk for patients.

Additionally, the TITCK could benefit more from joint reviews or assessment outcomes of other regulatory health authorities mainly for the clinical part thus reducing the pressure and review load of the assessors. This option could be explored with agencies of similar size and resources such as Health Canada, SFDA or TGA. Moreover, the TITCK can equally benefit from the GMP assessment and accreditation process of other regulatory health authorities. One method for this collaboration is by becoming a full member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) which was established with the aim to harmonise

GMP accreditation procedures in the world by setting common standards for the GMP process, the provision of related training to inspectors and the development of required competencies for the assessment among regulatory authorities to increase mutual confidence (PICS, 2016). In May 2013, the TITCK applied for a full membership to PIC/S. Such a membership will enable the TITCK to benefit from the co-operation and networking between regional and international organisations in this area and rely on other inspectors' assessment. This could save the time and resources of their own agency by relying and using other reference agencies' GMP approvals similar to the SFDA. Another suggestion would be for the TITCK to conduct the GMP process in parallel to the registration review procedure similar to Health Canada, HSA and TGA in order not to further delay the application and therefore the authorisation process.

Finally, it appears from this analysis that the full review of the TITCK is in line with the other mid-sized regulatory agencies. However, the TITCK does not have a risk stratification approach as some other agencies. In addition, the GMP accreditation procedure is not fully aligned with the globally implemented process. In the light of these findings, it would appear that this hypothesis is rejected.

**Hypothesis 2: The marketing authorisation application requirements in Turkey are similar to those of other international agencies.**

In Turkey, the submission of a CPP at the time of application is not required; however, a CPP or evidence of approval in the EU, the USA or another country is required for final authorisation. This is similar to countries like Mexico, and China that also require proof of prior marketing authorisation before final approval (McAuslane, et al., 2009). Other agencies employ the use of alternate evidence of market authorisation such as information from other agency websites. However, other mid-sized agencies in countries like Australia, Canada and Singapore do not require a CPP when they perform a full assessment of the application while SFDA requires a legalised CPP for regulatory submissions although this is not mandated by the World Health Organisation (WHO, 2017).

In cases of a NAS submission to TITCK in parallel with other developed agencies like the EMA and the FDA, the agency proceeds with the review process but relies on the approval of those agencies to grant its final approval. Therefore, it is suggested that a regulatory agency like the TITCK who conduct a full assessment may also consider abolishing the need for a



CPP or any evidence of prior marketing authorisation approval. This could be implemented initially for critical and lifesaving products in order to ensure patients' access to these medicines as soon as possible regardless of its registration status in the world. However, most of these medicines become available to patients in Turkey based on the assessment of the clinical data only and even prior to any licensing, as part of the early access programs (TITCK, 2009). Similarly, the TITCK requires that the data submitted with the NAS application are in accordance with the ICH guidelines and the CTD (common technical document) format including all its five modules of quality, non-clinical and clinical. Therefore, marketing authorisation application dossiers provided by global companies do meet the TITCK requirements since the content of the dossier with the exception of module one data is aligned with those of other developed agencies.

Like the SFDA, the TITCK requires information relating to pricing as part of the review process and this includes the reference price lists for the drug product in five countries namely; Portugal, Spain, France, Italy and Greece. Nevertheless, the final marketing authorisation approval does not depend on the pricing negotiation. In contrast, other pre-marketing administrative steps such as final packaging and labelling approval, sales and importation permission do rely on prior price approval. Comparatively, price evaluation is not part of the review process at TGA, Health Canada or Singapore. Currently, price negotiation is a complex process in Turkey where a number of other government departments get involved in the decision-making process such as; the Social Security Institute (SGK), Ministry of Finance, and Under-secretariat of Treasury as well as the Ministry of Development (TITCK Price Decision, 2015). Thus, the price approval of a medicine is subject to the evaluation and consensus agreement of stakeholders other than the TITCK and thus does not include any scientific regulatory assessment. In the established agencies such as; the EMA, the FDA and Health Canada, pricing is conducted as an independent separate process after the marketing authorisation approval. Therefore, the agency is only responsible for the scientific regulatory assessment of the application and does not get involved with pricing or reimbursement discussions. In this way the regulatory review and assessment is conducted only on the basis of the scientific judgement of data. Accordingly, it is suggested that the TITCK should not perform pricing assessment as part of the review process, but rather initiate the process separately and preferable in parallel or following licensing. In the light of the above, apart from the pricing process, the marketing authorisation application requirements in Turkey are similar to those of other international agencies although an evidence of approval

elsewhere is still required prior to authorisation. Accordingly, with an exception that an authorisation is required elsewhere prior to final approval, this hypothesis is accepted.

**Hypothesis 3: The approval times of NASs in Turkey are longer than other countries such as Australia, Canada, Saudi Arabia and Singapore.**

The TITCK mean approval times for NAS marketing authorisation application were identified to be four hundred and seventy-six, four hundred and ninety, three hundred and seventy-eight calendar days for the years 2013, 2014 and 2015 respectively. These exceeded the agency's overall target time of two hundred and ten working days (two hundred and ninety-four calendar days). This suggests there is room for improved timeliness, consistency and process predictability in the system. Part of the delay in approval could be attributed to the time taken by the sponsoring company to respond to agency questions. Therefore, setting target timelines for question and answer phases and enhancing the dialogue and transparency between the TITCK and the industry could improve the quality of dossier submissions and reduce the number of agency questions raised during the review process.

The mean approval time of the TITCK for NAS applications in 2015 is two hundred and seventy working days (thirteen months) excluding companies' response time instead of two hundred and ten (ten months), which indicates that the TITCK did not meet its target approval time. Further, industry experience also shows that question and answer phases can take fifteen months with an average of ten to fifteen questions received for each NAS application thus an average of two to four months to close each question. Therefore, it is suggested that the TITCK batch their questions and set target response timelines for companies. Moreover, companies should keep a systematic record of the number of questions received and response times. Additionally, delays in approval may also be related to the structure and working procedures of the committees where most of the review and assessment decisions are taken 'leaving only administrative and technical parts of the application to be reviewed by internal assessors'. Therefore, the TITCK may consider delegating the review and assessment of some variations or extensions to internal assessors in order to reduce the number of dossiers assessed by committees and enhance the committees' review thus allowing them to focus on new product applications and major clinical or quality variations.

The approval times at the TGA in 2015 is three hundred and seventy-three calendar days and therefore exceeded agency target times. Whereas, Health Canada approval time is three

hundred and fifty-five, which is approximately the same as target times for this period. The reason for this is because the agency makes vigorous efforts to keep to target times to avoid the penalties of up to 50% of user fees as mandated by the User Fees Act if target times are not met (Hashan, et al., 2016).

The TITCK has established target times for the authorisation procedure and overall approval, whereas the SFDA, the TGA, Health Canada and the HSA set separate target times for validation, scientific assessment, and authorisation as well as overall approval times. Defining target timing for individual milestones within the review facilitates planning for both agencies and sponsoring companies, and this permits the identification of the most appropriate areas for improvement. Although currently the TITCK has a manual system, they are planning to convert this into an electronic internal tracking system to monitor the various milestone timelines'. However, so far the timelines and different milestones are not available to stakeholders in a systematic formal way. Establishing an electronic tracking system with target timelines would enhance the efficiency and continuity of the review process while enabling the TITCK to monitor the timelines between milestones as well as to observe the time between first-in-world approval and approval in Turkey.

In conclusion, it would appear that the approval timelines in Turkey are not only presented as mean rather than median as the other countries in this study, but do not include question and answer times and therefore they are not comparable with the approval times of other agencies such as the FDA, the EMA (Figure 1.4). Furthermore, it might appear that the TITCK has longer approval timelines compared to other countries; this was also confirmed by the industry study data on approval times, which will be discussed in details in chapter five. Therefore, the results are inconclusive due to the fundamental difference of not being able to compare median and mean approval times.

**Hypothesis 4: Good Review Practice (GReP) requirements implemented by the TITCK are comparable to other similar countries, which ensure consistency, transparency, timeliness, and predictability of the review process.**

Good review practices (GReP) facilitate a timely and high-quality regulatory review and enable regulatory convergence, which can have a significant impact on resource conservation as well as patients' access to medicines. Thus previous studies demonstrated that building quality and GReP into the regulatory review process is as significant regulatory performance

indicator as the approval the timelines (Cone & McAuslane, 2006). In relation to this, the World Health Organization has set the standards of GReP with the aim to guide national and regional regulatory authorities (WHO, 2015). Similar to other comparator agencies, the TITCK in this study employ many of the essential elements of GReP. However, the good review practices implemented by the TITCK are currently still not formalised and require an enhancement in some areas such as; transparency to stakeholders, training tools such as induction courses for new assessors and building an electronic tracking system available to stakeholders. By adapting the standards of the global guideline of good review practices and monitoring its implementation within the TITCK, it could be formalised to become a mandatory system to improve and ensure consistency, timeliness and review process predictability.

Furthermore, the TITCK may consider providing other elements which can contribute to enhance transparency in the review process as well as the quality of applications, such as, the provision of a summary basis of approval; thus communicating to the companies, patients and healthcare providers the agency decision making process. In providing a rationale for the publication of summary basis of approval, Health Canada describes, in its website what the Summary Basis of Decision (SBD) documents are for. Therefore, they inform the public in a general way why Health Canada authorized certain drugs and medical devices in the country based on regulatory, safety, effectiveness and quality considerations. Accordingly, it states that this: “... *improves the transparency of the drug and medical device regulatory review processes. They also give Canadians improved access to information about decisions to authorize products for sale in Canada*” (Health Canada, 2016).

Finally, the TITCK is not currently implementing a structured framework for the evaluation of the benefit-risk (BR) assessment of medicines, which is the key step in the review process for NASs. Thus, the assessment process depends largely on the reviewers' performance and experiences, which may vary significantly as some reviewers, could be more experienced and keen to improve the quality of the review performance compared to others. Therefore, to enhance the quality and standardisation of the review process, the TITCK can consider the implementation of a structured peer review process that is practiced by many mature agencies. For example, in Australia the TGA uses a multi-layered peer review process during which applications are reviewed for a second time by senior reviewers to ensure that an optimal decision is made (Al-Essa, 2011). It is also recognised that establishing such a BR framework

would require a high level of expertise and time. Therefore, it is suggested that the TITCK should consider adopting and implementing the Universal Methodology for Benefit-Risk Assessment (UMBRA) framework as this has been positively assessed by several mature agencies and currently under evaluation by agencies in the emerging markets (Walker, et al., 2013). In addition, the TITCK could also gain benefit by reviewing the assessment templates of other regulatory authorities worldwide, which may demonstrate to the TITCK as to how the benefits and risks are assessed in their review processes. In relation to the good review practice elements, Turkey is comparable to other countries and therefore, this hypothesis is accepted. However, with regards to transparency and communication, these are areas that could be improved.

## SUMMARY

- This study has evaluated the regulatory review process and timelines by the TITCK for the first time since it was established as an agency when it took over the responsibility for pharmaceutical regulation from the Ministry of Health in 2011. It has identified the key milestones, timelines and evaluated the measures used for GReP and provides opportunities for an enhanced regulatory review process.
- A comparison of the current TITCK processes and practices with those of similar medium-size regulatory agencies such as the SFDA, the TGA, Health Canada and the HSA has enabled the development of several proposals to assist the agency in its efforts to become an internationally recognised reference agency.
- In general, the TITCK review model and the marketing authorisation requirements of applications are similar to other regulatory agencies' review model and requirements. Therefore, this model enables the review of NAS applications in parallel to other developed regulatory agencies such as the FDA and the EMA. However, the requirement of a prior approval or a CPP at the time of final authorisation may still delay patients' access to medicines.
- The TITCK could conserve resources and reduce the time in the review process, by exploring the possibility of introducing shared or joint reviews with other similar regulatory authorities. The resulting delay caused by the current GMP process, could be avoided by the TITCK collaborating with other agencies or becoming a member of an international organisation such as PIC/S, which they have already applied for, and following the standard schemes in the GMP accreditation process. Accordingly, the TITCK could benefit from the inspection outcomes and GMP certificates issued by other regulatory health authorities in relation to the same manufacturing sites and quality data.
- The TITCK could reduce approval times by redefining the pricing process and separating it from marketing authorisation. This will enable the TITCK to better present its review performance both locally to the public and other stakeholders as well as to reduce the timescales between Turkey and first approvals in the world.

- Good Review Practices are implemented informally to a certain extent within the TITCK. However, GRePs need to be established as a formal system and become mandatory and carefully monitored during implementation. Furthermore, it is recommended that the TITCK define target times for each review milestone in addition to the predefined overall authorisation procedure approval timing. Moreover, it should improve internal tracking systems to monitor these milestones and thus enable this information to be available to all stakeholders.
  
- The TITCK is currently lacking a number of elements that contribute to transparency and communication. These would include publicly available summaries of the basis for approval, developing standards for scientific and advisory meetings for applicants prior to submission as well as developing relationships with other reference agencies to encourage training through secondments and job shadowing.

## **CHAPTER 5**

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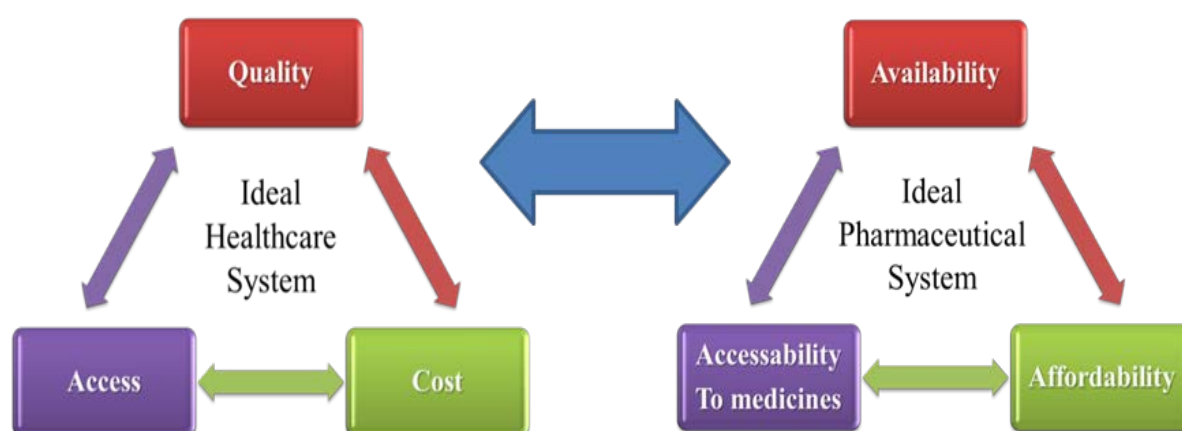
# **EVALUATION OF THE ATTITUDES AND EXPERIENCES OF PHARMACEUTICAL COMPANIES TOWARDS THE TURKISH REGULATORY REVIEW PROCESS**



## INTRODUCTION

An ideal healthcare system consists of three fundamental characteristics, which are cost, quality and access. All three aspects are equally crucial to establishing an efficient healthcare system where individuals can easily access high-quality healthcare services at an affordable cost while the system provides the expected return on investments for all involved companies within the industry (Figure 5.1). Access and cost are usually determined by health authorities' policies and regulations and therefore have direct impact on the quality of the healthcare (YASED, 2012).

**Figure 5.1: Fundamental aspects of an ideal healthcare and pharmaceutical system**



Similarly, the key to an ideal healthcare system is its relationship to a good pharmaceutical system, where it relies on the availability of assured quality, safe and affordable medicines to patients (SPS, 2011). This barrier to an adequate and timely access to medicines often results from the lack of the availability of medicines mainly due to price policies and poor governance in the pharmaceutical system which significantly affects the affordability of medicines and ultimately the efficiency of the healthcare system as well as the pharmaceutical investments within the system (Mhlanga & Suleman, 2014). Since 2002 the healthcare system in Turkey has undergone significant developments with respect to their services and patients' access to medicines. This was due mainly to the introduction of the Health Transformation Program (HTP), which resulted in an improved access to higher quality healthcare services including medicines. This has been accompanied by several developments in the pharmaceutical industry, which significantly increased in the last decade and witnessed many major changes in policies and regulations (ISPAT, 2014). Along with these developments such as an increase in R&D investment, manufacturing sites and the establishment of

international subsidiaries in Turkey, the government, in parallel, has initiated a number of measures to control the increasing healthcare budget mainly for pharmaceuticals and to enable a sustainable financing source for wider coverage. This is because the increasing higher consumption of pharmaceuticals has created pressure on the national budget due to the wider scope of social security and increased patients' access (YASED, 2012).

However, restricting costs and healthcare expenditure can have a negative impact on patients' timely access to innovative and high cost medicines as well as on the pharmaceutical industry's profitability and investments. These changes in the pharmaceutical regulatory environment can act as a barrier to new medicines reaching the market in a timely manner. For instance, the regulatory environment in Turkey imposes major challenges to pharmaceutical companies in many areas such as the local GMP process and the pricing procedure. This is despite the alignment of the Turkish regulations with the European directives and the standards of the International Conference of Harmonisation (ICH). Yet, the registration review process is perceived to be a complex one and thus suffers from a significant backlog and delay in approvals. In theory, the approval timeline for a new medicine in Turkey is stated to be two hundred and ten working days, nevertheless, recent examples from the industry identified that major delays occur during the approval process due to the increasing requests mainly for clinical data and the recently introduced GMP inspection requirements. Consequently, six years ago it took eighteen months to three years for a new medicine to be approved in Turkey (Kretschmer, 2011). Therefore, it is important for the pharmaceutical industry to have a clear understanding of the registration review process with all its quality aspects and practices implemented by the regulatory authority. This is essential if the key issues are to be addressed effectively in order to enhance approval timelines and patients' access to medicines. Similarly, it is important to identify pharmaceutical companies' experiences of the review process and take into consideration industry experts' opinion about the issues and challenges.

The aim of this chapter is to assess the experiences and attitudes of the pharmaceutical companies in Turkey towards the regulatory registration process, the requirements of the TITCK and their timelines. This also includes an evaluation of the level of interaction with the TITCK and the process review in terms of predictability, transparency and consistency. For this purpose, a questionnaire was designed to evaluate the current attitudes and experiences of pharmaceutical companies. This study aimed to identify the major issues and

challenges faced by pharmaceutical companies during the regulatory review process and in obtaining marketing authorisation approvals for innovative medicines. This research was designed to be complementary to the other two studies that evaluated patients' perception of the regulatory environment and the review system of the TITCK.

## **OBJECTIVES**

The main objectives of this study were to:

- Determine the attitudes and experiences of pharmaceutical companies towards the Turkish regulatory review process.
- Identify the key issues companies are facing in the Turkish regulatory environment.
- Evaluate the changes in the regulatory approval timelines and processes between 2012 and 2015.
- Identify the improvements that the pharmaceutical industry would like to see to ensure that the medicines' approval process is both efficient and effective.
- Assess the impact of the current regulatory process on patients' access to innovative medicines.

## **METHODS**

The experimental method used in this research was similar to the other studies that examined both the patients' perspective as well as that of the TITCK in relation to the pharmaceutical regulatory environment in Turkey. This was to ensure consistency in the data collection for all three studies from the different perspectives and facilitate the comparison, which would contribute to the identification of areas of improvement within the system. Therefore, a descriptive research method was utilised to describe the experiences of pharmaceutical companies towards the regulatory review process and timelines. Accordingly, the questionnaire was designed as a cross-sectional study aimed at collecting data during a specific time period to evaluate the current industry perspective.

### **Questionnaire Development**

In this study the main objective and emphasis was to develop a tool to collect data in line with the objectives. For this purpose, the questionnaire was designed to be utilised as a qualitative research method and was carried out in three phases:

- Phase 1: Identification of the main themes and development of the first version of the questionnaire.
- Phase 2: Pilot study and content validation.
- Phase 3: Development of final version of the questionnaire.

**Phase 1: Identification of the main themes and development of the first version of the questionnaire.** The main themes of the questionnaire were generated firstly by reviewing previous surveys of pharmaceutical companies by the pharmaceutical industry association on an annual basis with the aim of obtaining the general status of the companies' experiences about the TITCK practices, regulations and their interaction with the industry. The main topics, not covered by the association's annual survey, were also identified. Thereafter, a face-to-face meeting with the regulatory affairs and market access committees of the Research Based Pharmaceutical Companies' Association (AIFD) was organised in order to identify the main areas of need for the industry and generate the themes required for the questionnaire. Accordingly, a total of four main themes were identified and the first version of the questionnaire was designed in four parts with the following headings:

- Theme 1: General questions and company details.
- Theme 2: Local requirements in Turkey and regulatory metrics.
- Theme 3: Regulatory review process.
- Theme 4: The way forward for TITCK.

The questionnaire included twenty-two questions mainly as multiple choice and five open-ended questions with the aim of collecting detailed information and opinions from the companies during the pilot study.

#### **Phase 2: Pilot study and content validation.**

A pilot phase for this study was designed to identify areas of improvement in terms of structure, terminology, deletion and/or addition of questions to ensure that these were comprehensive and easy to understand. Thus, the initial questionnaire was completed by three pharmaceutical companies, who were representative of the core team of the Regulatory Affairs Committee within AIFD. Upon completion of the questionnaire by each company representative, participants were asked to provide their input to specific questions (Table 5.1).

**Table 5.1: Pilot phase questions for content validation**

▪ In general how did you find the questionnaire?
▪ How do you evaluate the language of the questionnaire?
▪ Are there any questions which you found difficult to answer, and if so, which ones? Please state briefly why you think they were difficult?
▪ Are there any repetitive questions in the questionnaire?
▪ Are there any questions you think are not relevant in this questionnaire?
▪ Are there any other questions you would like to add to the questionnaire?
▪ Do you think that this questionnaire is relevant to pharmaceutical companies?
▪ How long did it take you to complete this questionnaire? Please state in minutes.

Following the pilot phase, a face-to-face meeting with an experienced regulatory affairs industry representative was organised to evaluate the responses and inputs from the participants. The analysis identified areas for improvement in terms of structure, wording, terminology used, deletion and/or addition of questions. These were then reviewed to see if they could be merged with other questions or need to be modified. For instance, two companies stated that they had difficulty in answering the question related to the agency's transparency and suggested to address this topic in several questions.

Furthermore, companies suggested including some questions related to the TITCK communication strategy in terms of consultation, scientific advice and question and answer processes. One company was hesitant to answer the question related to areas of improvement and therefore this question was clarified and limited to a specific period of time. As a result, the questionnaire was modified and further twenty-one questions were added to obtain the views of the companies about the TITCK transparency, communication, decision-making process and the applicability of a structured benefit-risk framework (Table 5.2).

**Table 5.2: Added questions as a result of the pilot study**

<b>Topic</b>	<b>Questions added to main study</b>
Communication with TITCK	Questions: 7, 8, 9, 28, 29, 30, 31, 32, 40, 41 & 42.
TITCK additional requirements	Questions: 20, 21, 22, 35 & 39.
Implementation of Good Review Practices	Questions: 23, 37 & 38.
Availability of benefit-risk framework	Questions: 33 & 34.

### **Phase 3: Development of final version of the questionnaire.**

The review of the questionnaire and analysis of the companies' feedback during the pilot study was critical to the design of a more effective questionnaire as an assessment tool for the main study. Thus, the final version of the questionnaire comprised forty-six questions, mainly

as closed or multiple choices to ensure a statistical standardisation and facilitate the objective analysis for comparison and the time to complete the questionnaire was recorded to be thirty minute. Furthermore, the questionnaire included ten open-ended questions to identify potential views from the industry regarding developments in the regulatory environment, requirements and review process (Figure 5.2).

**Figure 5.2 Pharmaceutical industry questionnaire**

Turkish Pharmaceutical Companies' Questionnaire	
<b>Part I. General Questions</b>	
1. How many years has your company been present as a legal entity in Turkey	<input type="checkbox"/> 0 - 5 Years <input type="checkbox"/> 6 - 10 Years <input type="checkbox"/> 11 - 15 Years <input type="checkbox"/> 16 - 20 Years
2. Please state the number of new active substances (NASs) your company has currently in the "registered status" in Turkey: .....	
3. Do you have a local production facility in Turkey	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Other.....
4. How many employees do you have in your local organisation in Turkey.....	
5. Please characterise the nature of your Regulatory Affairs (RA) unit in Turkey.	<input type="checkbox"/> In-house <input type="checkbox"/> Outsource <input type="checkbox"/> both <input type="checkbox"/> others (regional/head office of company)
6. How many employees do you have in your Turkey RA unit (state number please):.....	
7. How would you rate the consultative process of the TITCK with the industry before a major regulatory change or issuance of a regulation is announced?	<input type="checkbox"/> Excellent <input type="checkbox"/> Good <input type="checkbox"/> Satisfactory <input type="checkbox"/> Poor
8. How valuable would it be to have a structured framework for regular consultations?	<input type="checkbox"/> Very valuable <input type="checkbox"/> Valuable <input type="checkbox"/> Not valuable
9. What impact does the efficiency of the TITCK have on your company's willingness to increase its investment in Turkey (i.e. R&D, manufacturing)	<input type="checkbox"/> Major impact <input type="checkbox"/> Moderate impact <input type="checkbox"/> Minor impact <input type="checkbox"/> None
<b>Part II. Local Requirements in Turkey and Regulatory Metrics</b>	
10. How would you evaluate the clarity and enforcement of the local requirements for New Drug Applications (NDA) in Turkey	<input type="checkbox"/> Clear, strictly listed and enforced <input type="checkbox"/> Listed requirements but not fully enforced and subject to various interpretations <input type="checkbox"/> Requirements are unclear
11. How would you rate the alignment of the Turkish NDA regulations with the EU	<input type="checkbox"/> Local regulations are fully aligned with EU <input type="checkbox"/> Local regulations are partially aligned with EU <input type="checkbox"/> Local regulations are not aligned with the EU,
Industry Questionnaire version 7.0	
5	

Please describe how they are not aligned.....

.....

.....

**12. How do you see the current local GMP requirements enforced since 2010**

- ☐ I see the current GMP requirements as a necessary and scientific step
- ☐ I do not see the added value of the GMP step. It is a delaying step to approvals
- ☐ I agree with the GMP requirements as long as it is a parallel process to NDA and not delaying the review

**13. What was the average delay in months for NDA submissions since the GMP requirements were introduced in 2010..... Months**

*Please provide the range (shortest to longest delay in months).....*

**14. How do you believe the nomination process of departmental heads and reviewers at TITCK is determined**

- ☐ On scientific abilities and merits
- ☐ On administrative expertise
- ☐ I have no information

**15. How do you assess the scientific competency of the reviewers**

- ☐ Excellent
- ☐ Good
- ☐ Satisfactory
- ☐ Poor

**16. How do you rate the ability of the agency to assess biological / biotechnology applications**

- ☐ Excellent
- ☐ Good
- ☐ Satisfactory
- ☐ Poor
- ☐ I have no information

**17. How many New Active Substances (NAS) do you currently have under review at TITCK**

Please state number: .....

**18. List all of the New Active Substances (NAS's) chronologically for which your company received approval from January 2012 until March 2015.**

Drug Substance	General Therapeutic Indication	Date of First World Wide Approval	Date of submission to TITCK	Date of Approval by TITCK	Date of Sales permission approval
NAS 1					
NAS 2					
NAS 3					
NAS 4					

19. What do you believe should be the maximum time in months for the regulatory review of New Active Substances by the TITCK

☐ 6 months      ☐ 9 months      ☐ 12 months      ☐ 24 months      ☐ other;.....

20. In general, does TITCK request more information today than 3 years ago for regulatory submissions of NAS's?

☐ Yes      ☐ No      ☐ Not sure

21. If 'Yes', are these additional requests aligned with international regulatory requirements?

☐ Yes      ☐ No      ☐ Not sure

22. If 'No', please indicate for which sections of the file the questions were outside international requirements (tick the box(es) that applies)

Areas of dossier	Questions which are outside International requirements	If yes, please specify
Non clinical data	<input type="checkbox"/>	
Clinical efficacy	<input type="checkbox"/>	
Clinical safety	<input type="checkbox"/>	
Quality/ CMC data	<input type="checkbox"/>	
Pack, labelling or prescribing information	<input type="checkbox"/>	
Administrative data	<input type="checkbox"/>	

23. Do you believe that TITCK is in line with global best regulatory good review practices

☐ Yes      ☐ No      ☐ Not sure

If no, please give details:.....  
.....  
.....



### Part III. Regulatory Process

**24. How would you evaluate the transparency of the review process of NAS's**

- ☐ Review process is transparent and files can be tracked from submission to final approval
- ☐ Review process is relatively transparent; Files can be tracked from TITCK's letters / Q&A
- ☐ Review process is generally transparent for the main milestones but the decision making process within each milestone is not transparent
- ☐ The review process is not transparent.

**25. How do you perceive the regulatory review process in Turkey**

- ☐ Predictable ☐ Unpredictable

**26. In practice, do you face challenges in sequential submissions to the TITCK**

- ☐ Yes ☐ No ☐ It depends on the submission

**27. What do you think are the major sources of delay in the TITCK in approving new medicines? (Tick all that apply)**

Source of delays	High	Medium	Low
Resources	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Expertise	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Process efficiency	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Insufficient meetings	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Type of questions raised	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lack of consultation with applicant company	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lack of statutory timelines or other performance criteria for reviewers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other, please name:.....			

**28. How would you describe the ease of communication with TITCK on issues relating to your file?**

- ☐ Excellent ☐ Good ☐ Satisfactory ☐ Poor ☐ Not sure

**29. Have you ever been provided with scientific advice by TITCK prior filling an NAS?**

- ☐ Yes ☐ No

**30. If yes, did the advice reduce the number of questions asked during the review?**

- ☐ Yes ☐ No ☐ Not sure

**31. At what stage of the submission did you have the most communication with TITCK?**

- ☐ Pre-submission ☐ During review

**32. How do you set a time and agenda for a meeting with TITCK?**

- ☐ Online ☐ Through an official liaison in Ankara ☐ Directly with the reviewer ☐ others:...

33. Do you believe the TITCK has a structured approach to decision-making?

☐ Yes ☐ No ☐ Not sure

34. Do you believe that utilising a structured benefit-risk framework (B-R)<sup>2</sup> would be beneficial to the agency and company when the TITCK is reviewing the dossier?

☐ Yes ☐ No ☐ Not sure

35. What are your views with regard to the recent requirement by TITCK for a risk management plan for NASs

☐ Reasonable ☐ Unreasonable ☐ I had no experience

36. If you have had to provide TITCK a risk management plan, how did it impact your review process and approval timeline?

	Positive impact	Negative impact	No impact
Timelines			
Review process			

#### Part IV. The Way Forward for TITCK

37. Where would you suggest that the TITCK make improvements to their regulatory review processes?  
Give details

38. Have you made proposals to the TITCK for streamlining the regulatory process? (either as an individual company or through an industry association)

☐ Yes ☐ No

If yes, what were they and how were your proposals received? Give details.....

.....  
.....

39. Do you believe that the regulatory requirements by the TITCK are increasing?

☐ Yes ☐ No

If yes, please give details:.....

<sup>2</sup> The benefit-risk framework is the basis of regulatory decisions in the pre-market and post-market review process. It takes into account the extensive evidence of safety and effectiveness submitted by a sponsor in a New Drug Application (NDA) or a Biologics License Application (BLA), as well as many other factors affecting the benefit-risk assessment, including the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks. This assessment involves both quantitative analyses and a subjective qualitative weighing of the evidence.

**40. Are you satisfied with the level of industry-TITCK communication/dialogue on regulatory issues affecting the sector?**

☐ Not Satisfied      ☐ Satisfied      ☐ Highly Satisfied

**41. Does the TITCK have a long-term strategy with respect to regulatory environment?**

☐ Yes      ☐ No      ☐ Not sure

**42. If yes, how would you assess the TITCK's communication policy of its long-term strategy?**

☐ Excellent      ☐ Good      ☐ Satisfactory      ☐ Poor      ☐ Not sure

If poor, please give details

**43. What are the three most important positive developments at the TITCK since 2011?**

1. ....
2. ....
3. ....

**44. What are the three most important negative developments at the TITCK since 2011?**

- 1.....
- 2.....
- 3.....

**45. Please List three major factors that could contribute towards an effective and efficient agency**

1. ....
2. ....
3. ....

**46. List three factors that you see as barriers to making a new medicine available in a timely manner through the regulatory process.**

- 1.....
- 2.....
- 3.....

**Thank you for completing this questionnaire**

Name / Signature:	Company / Position:
Date:	Email address :

## Study Participants

The questionnaire was distributed to all pharmaceutical companies operating in Turkey who have experience with the regulatory process for New Active Substance (NASs) as a marketing authorisation holder or applicant, which were the study inclusion criteria. Therefore, all other pharmaceutical companies were excluded from this study. Hence, the questionnaire was distributed to:

- **International pharmaceutical companies:** this included thirty-eight innovative pharmaceutical companies officially registered as full members of the AIFD.
- **Local pharmaceutical companies:** the questionnaire was sent to the three local companies who are involved in the registration of NAS through the Pharmaceutical Manufacturers Association of Turkey (IEIS).

## Questionnaire Administration and Data Collection

The questionnaire was sent via e-mail to companies by the industry associations. The deadline for returning the questionnaires was stated in the e-mail to be two weeks, nevertheless, follow-up e-mails were sent out again after a further two weeks. The communication pack was accompanied by:

- The study questionnaire (Figure 5.2).
- A cover letter providing brief information about the study, expected outcome and instructions on how to complete the questionnaire and the required timeline.
- A confidentiality agreement (Appendix II).
- List of abbreviations and definitions used in the questionnaire study.

Following a request from pharmaceutical companies a “Question and Answer” document was prepared to encourage their participation (Appendix III). The data from the participating companies were collected and anonymised by a third party to ensure confidentiality and avoid any potential conflict of interest. All completed questionnaires were returned directly to the third party where they were blinded and subsequently analysed appropriately to generate a study outcome report that was provided to the companies. Important aspects of this study were communicated to the TITCK as planned and agreed by the companies.

## RESULTS

The results of this study are presented in four parts:

- Part I: General questions and company details.
- Part II: Local requirements in Turkey and regulatory metrics.
- Part III: Regulatory review process.
- Part IV: The way forward for TITCK.

### Part I: General Questions and Company Details

The questionnaire was distributed to thirty-eight global pharmaceutical companies and three local companies. Accordingly, a total number of twenty-one completed questionnaires were received with a response rate of 51% (Table 5.3).

**Table 5.3: List of companies that participated in the study**

International companies	
1) Abbvie	11) Glaxo Smith Kline
2) Alexion	12) Janssen (Johnson & Johnson)
3) Allergan	13) Merck Sharp & Dohme
4) Astra Zeneca	14) Novo Nordisk
5) Astellas	15) Pfizer
6) Bayer	16) Roche
7) Boehringer Ingelheim	17) Sanofi
8) Bristol-Myers Squibb	18) Shire
9) Celgene	19) Takeda
10) Eczacıbaşı-Baxalta	20) UCB
Local companies	
21) IDE İlaç Danışmanlık ve Eğitim	

Throughout the study, several meetings were conducted with the industry associations and pharmaceutical companies in order to encourage their participation and clarify all aspects regarding the study. Nevertheless, some companies were hesitant and did not participate for several reasons. This was despite, the mitigation actions that were taken to address these concerns (Table 5.4).

**Table 5.4: Companies’ participation objections and mitigated action plans**

<b>Companies concerns</b>	<b>Mitigation actions</b>
<b>Legal concerns</b>	<ul style="list-style-type: none"> <li>▪ Confidentiality agreement was attached to the questionnaire.</li> <li>▪ Third party directly collected and blinded the data for the analysis.</li> </ul>
<b>Sensitivity of the requested data</b>	<ul style="list-style-type: none"> <li>▪ Written confirmations within the confidentiality agreement and cover letter which ensured that;</li> <li>▪ Commitment to all terms of confidentiality and that no outcome reports or data would be shared with the authorities before discussion and agreement with the participating member companies.</li> <li>▪ No outcome or individual company data would be disclosed in the public domain or be available to a third party.</li> <li>▪ External reports or presentations of the data would include only anonymised figures.</li> </ul>
<b>Unwilling to participate</b>	<ul style="list-style-type: none"> <li>▪ Seven face-to-face/online meetings were organised with industry associations to encourage participation and obtain their support.</li> <li>▪ One online meeting between the European Federation of Pharmaceutical Industries and Associations (EFPIA) and AIFD was organised to emphasise the importance of the study and encourage participation.</li> <li>▪ Headquarters of international companies were informed about the study to obtain their endorsement and support at their affiliate level in Turkey.</li> </ul>
<b>Lack of awareness of the study objectives</b>	<ul style="list-style-type: none"> <li>▪ Three face-to-face meetings were organised with the companies to present the study elements and clarify all questions and concerns.</li> <li>▪ Preparation of a “<i>Question and Answer</i>” document for companies.</li> </ul>
<b>Lack of time</b>	<ul style="list-style-type: none"> <li>▪ Questionnaire pack was sent out to companies in two rounds.</li> <li>▪ Deadline to collect responses was extended three times.</li> </ul>

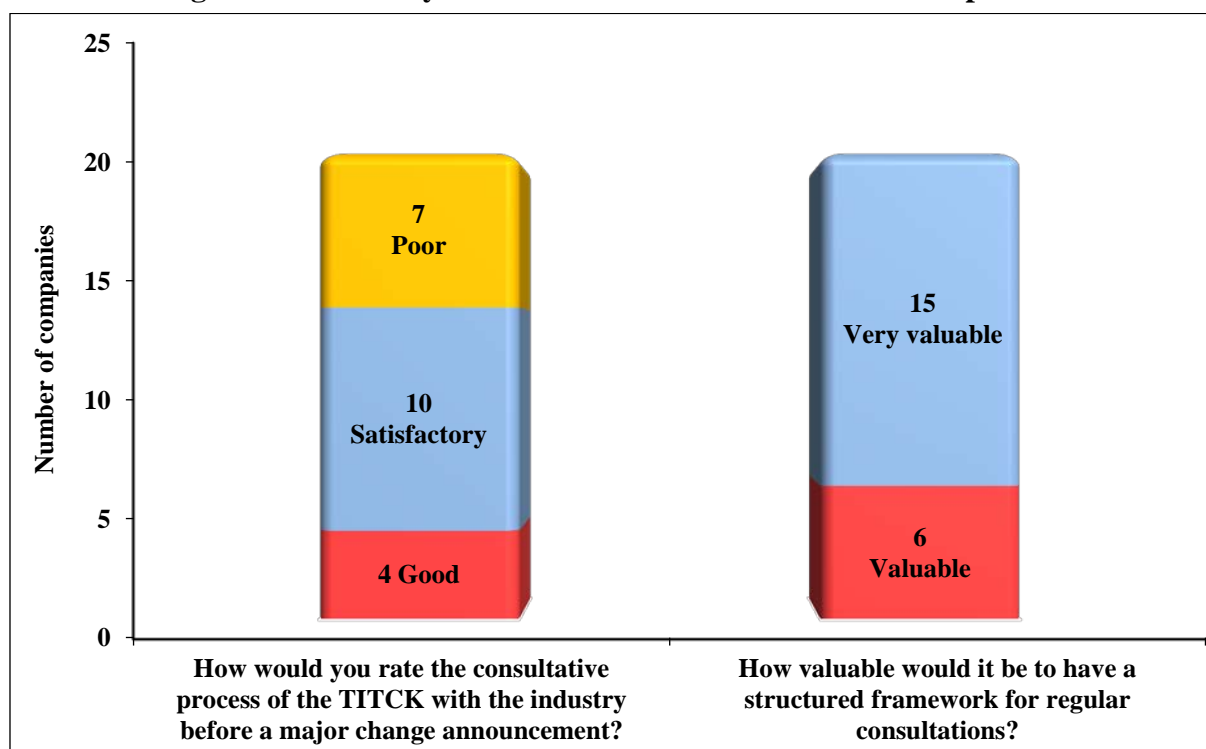
Details about the responding companies were analysed in order to obtain a clear understanding of their main characteristics as well as their views of the pharmaceutical regulatory environment in Turkey (Table 5.5). The majority of respondents were international companies who had been operating in Turkey for more than fifteen years and therefore had extensive experience of the authority’s review process. Moreover, the analysis identified that half the companies were marketing authorisation holders of between one and ten NASs and fourteen (67%) had no manufacturing site in Turkey.

**Table 5.5 Background of the responding companies**

Company characteristics /Percentage (n = 21)			
<b>Company Presence in Turkey</b>		<b>Number of employees</b>	
0-5 years	2 (9%)	1-50 employees	3 (14%)
6-10 years	6 (29%)	51 - 99 employees	2 (9%)
11-15 years	0 (0%)	100 - 499 employees	11 (52%)
16-20 years	13 (62%)	500 – 999 employees	3 (14%)
		>1000 employees	2 (9%)
<b>Registered NASs by Company</b>		<b>Number of regulatory staff</b>	
0-10 NASs	10 (48%)	1-4 employees	8 (38%)
11-50 NASs	4 (19%)	5-9 employees	9 (43%)
51 - 99 NASs	5 (24%)	10 – 14 employees	2 (9.5%)
>100 NASs	2 (9%)	≥ 15 employees	2 (9.5%)
<b>Owning local production facility</b>		<b>Nature of the regulatory unit</b>	
Yes	3 (14%)	In-house	18 (86%)
No	14 (67%)	Out-source	0 (0%)
Other ( <i>Contact manufacturing facility</i> )	4 (19%)	Both	3 (14%)

Ten companies evaluated the general consultative process of the TITCK mainly prior to issuance a new regulation or announcement of a major change to be satisfactory; while seven stated that it was poor and only four companies indicated that it was good (Figure 5.3).

**Figure 5.3: Industry evaluation of the TITCK consultative process**

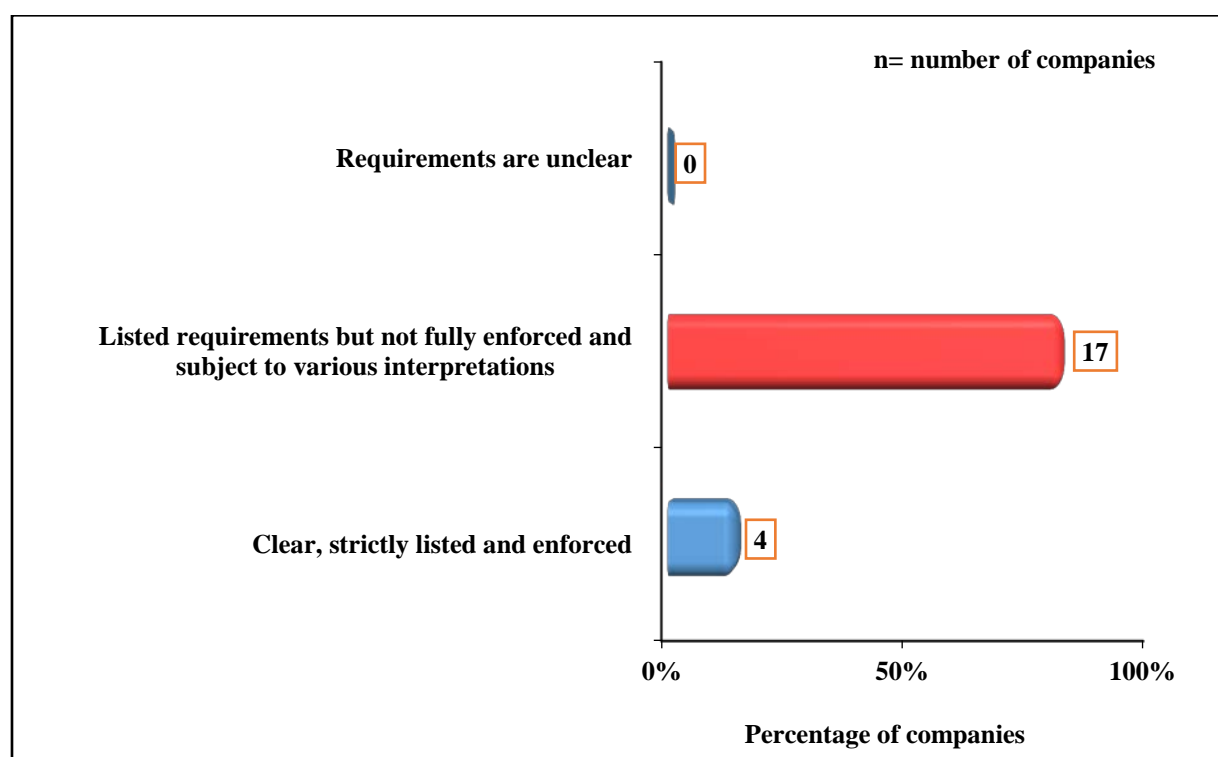


Furthermore, the majority of companies (n=15) stated that it would be very valuable to have a structured framework for regular consultation with TITCK. Thirteen companies (62%) indicated that the efficiency of the TITCK has moderate impact on their company's willingness to increase its investment in Turkey in areas such as research and development and manufacturing while six (29%) evaluated this impact as a major impact and only one as minor.

## Part II: Local Requirements in Turkey and Regulatory Metrics

The second part of the questionnaire included the companies' understanding of the local requirements in terms of clarity and enforcement of regulations for a New Drug Application (NDA) in Turkey. Thus, the majority (n=17) stated that in general the local requirements for NDA applications are clearly listed; however they are not fully enforced and subject to various interpretations. Only four companies reported that the related local requirements are clear, strictly listed and enforced (Figure 5.4).

**Figure 5.4: Clarity and enforcement of the local NDA requirements**



All companies agreed that local requirements are only partially aligned with those of the EU. However, companies provided nine main areas where local regulations are not aligned such



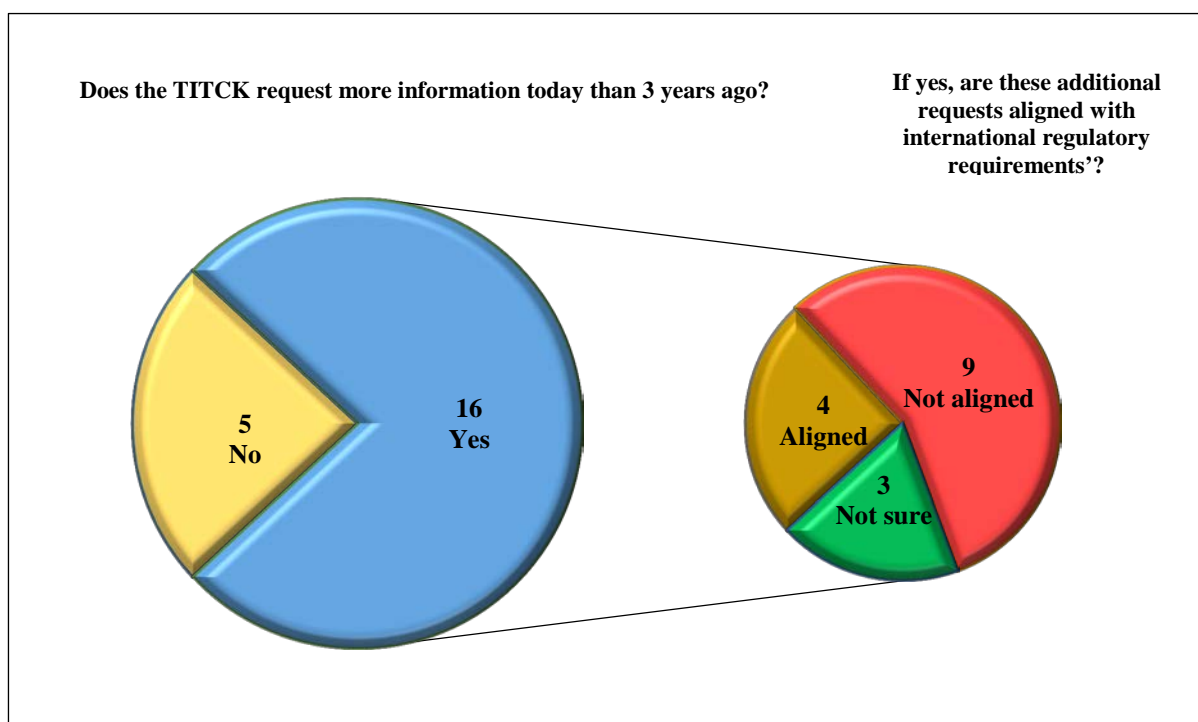
as; Turkish GMP process, product quality control and laboratory analysis; post marketing variation requirements, orphan drug requirements and pricing (Table 5.6).

**Table 5.6: Companies' description of how local regulations are not aligned with EU**

<b>Deviation area</b>	<b>Examples of companies' quotes why not aligned</b>
<b>1.GMP requirement</b>	<ul style="list-style-type: none"> <li>○ <i>GMP inspection requirement for sites renewals is not aligned.</i></li> <li>○ <i>Parallel GMP process to the registration review is allowed only for prioritised products in Turkey; however this is applicable for all applications in EU.</i></li> </ul>
<b>2.Product quality control and analysis</b>	<ul style="list-style-type: none"> <li>○ <i>Analysis of the product in registration review is not aligned. This is carried out after approval as a market control in EU, however in Turkey; it is required during the registration process.</i></li> </ul>
<b>3.Variation regulation</b>	<ul style="list-style-type: none"> <li>○ <i>The post marketing variation guideline is not aligned.</i></li> <li>○ <i>Variation guideline is not updated and aligned with EU.</i></li> </ul>
<b>4.Biosimilar regulation</b>	<ul style="list-style-type: none"> <li>○ <i>Biosimilar regulation lacks the related guideline that defines the requirements for each therapeutic group.</i></li> <li>○ <i>Biosimilar guidelines are not in line with EU.</i></li> </ul>
<b>5.Orphan drug regulation</b>	<ul style="list-style-type: none"> <li>○ <i>There is no orphan regulation in Turkey.</i></li> <li>○ <i>Orphan drug regulation is not yet published.</i></li> </ul>
<b>6.Line extension</b>	<ul style="list-style-type: none"> <li>○ <i>Line extension regulation is not applicable in Turkey.</i></li> <li>○ <i>Line extension guideline is not published yet in Turkey.</i></li> </ul>
<b>7.Pricing</b>	<ul style="list-style-type: none"> <li>○ <i>Pricing procedure is based on fixed exchange rate that does not reflect the real current exchange rate.</i></li> </ul>
<b>8.Administrative requirement</b>	<ul style="list-style-type: none"> <li>○ <i>Sales permission requirement is not aligned with EU.</i></li> <li>○ <i>Additional CTD Module 1 documentation is required only for Turkey.</i></li> </ul>
<b>9.Others</b>	<ul style="list-style-type: none"> <li>○ <i>Lack of Supplementary Protection Certificate.</i></li> <li>○ <i>Duplicate submission cannot be made on behalf of the same company.</i></li> </ul>

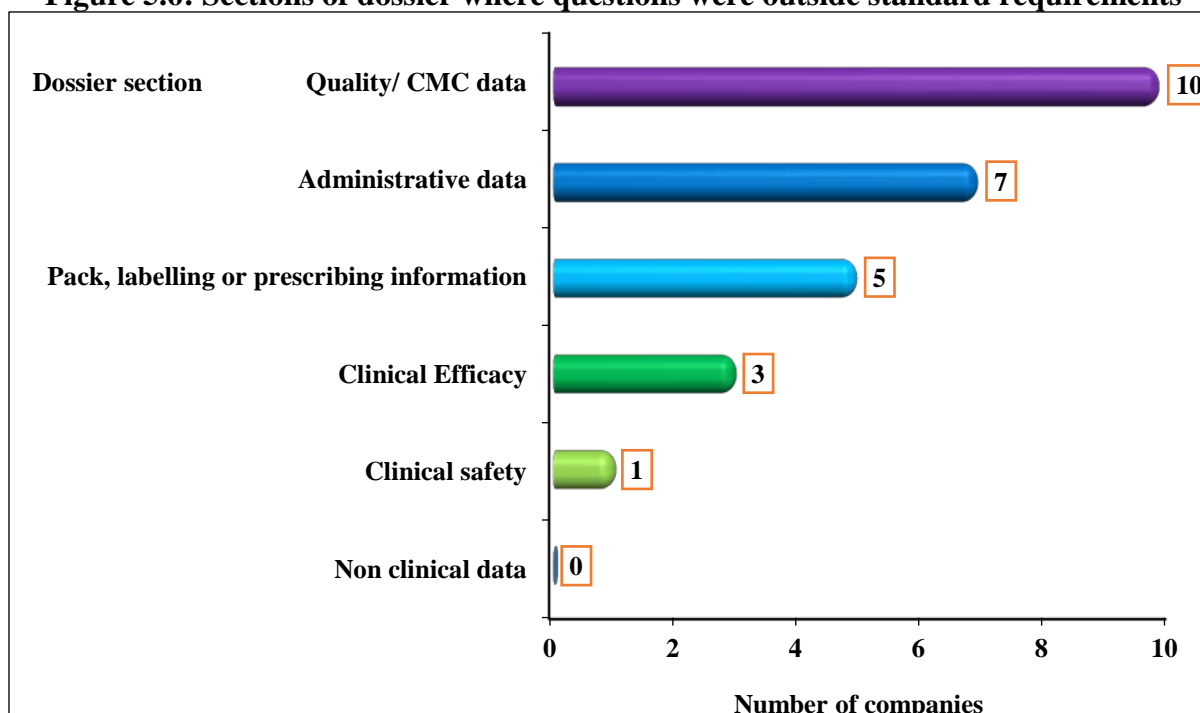
Sixteen companies (76%) indicated that in general, the TITCK request more information today than three years ago for regulatory submissions of NASs. However, nine of these stated that additional requests are not aligned with international regulatory requirements, while four companies stated they are aligned and three being unsure (Figure 5.5).

**Figure 5.5: TITCK requests that are outside international requirements**



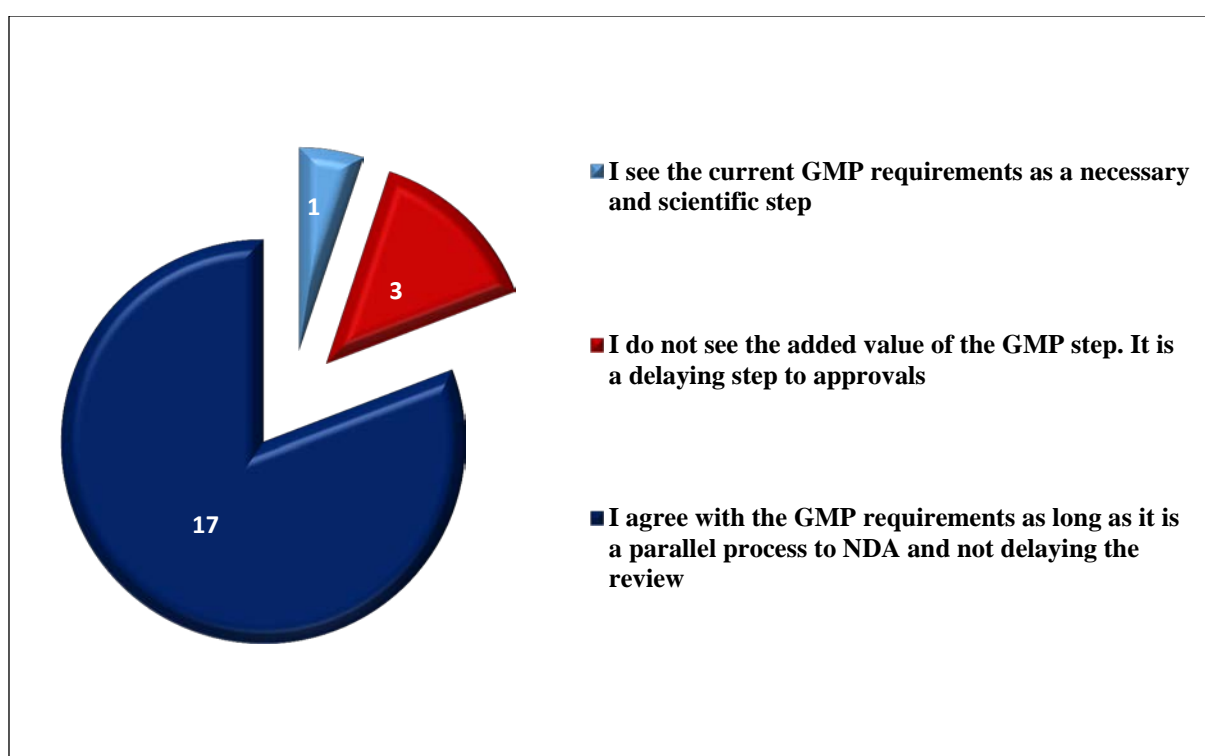
The majority of the companies indicated that quality, Chemistry, Manufacturing and Control (CMC) and administrative data were the most frequent sections of the dossier for which TITCK requested additional information outside expected requirements and that the TITCK has never requested additional data relating to the non-clinical section (Figure 5.6).

**Figure 5.6: Sections of dossier where questions were outside standard requirements**



Companies evaluated the current TITCK Good Manufacturing Practice (GMP) requirement introduced in 2010 that mandated the local accreditation of all manufacturing sites for pharmaceutical products. The GMP accreditation step is still a pre-requisite for all new drug applications except for those evaluated as prioritised products such as orphan and lifesaving medicines. Accordingly, most of the companies (n=17) stated that they agree with the GMP requirements as long as they are conducted in parallel to the registration as subsequently this would not delay the review (Figure 5.7).

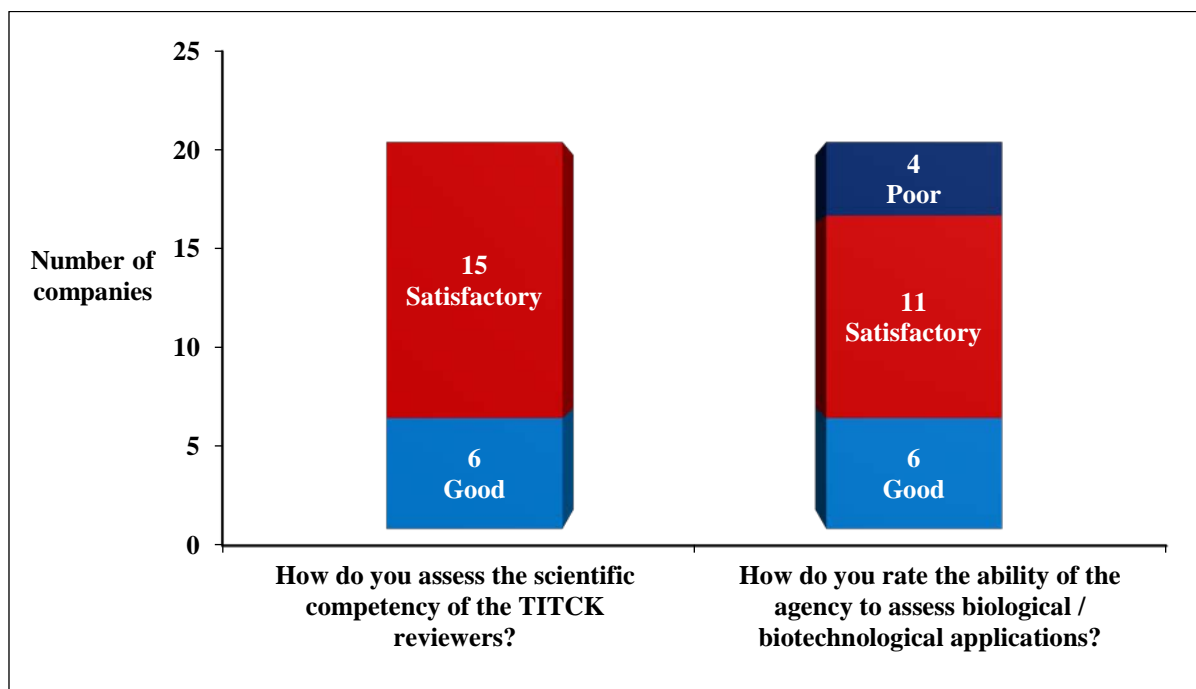
**Figure 5.7: Perception of the local GMP process by the Industry**



However, companies reported the average delay for NDA submissions to be twenty-two months since the GMP requirements were introduced and the range was identified to be between two and seventy-two months.

While twelve pharmaceutical companies responded that they had no information on how the nomination process of departmental heads and reviewers at TITCK is determined, only two believed that this process is carried out based on scientific abilities and merits. Moreover, the majority of companies evaluated the TITCK reviewers' scientific competencies and agency's abilities to review biological and biotechnological applications as satisfactory. However, no evidence was provided by companies to support their perception (Figure 5.8).

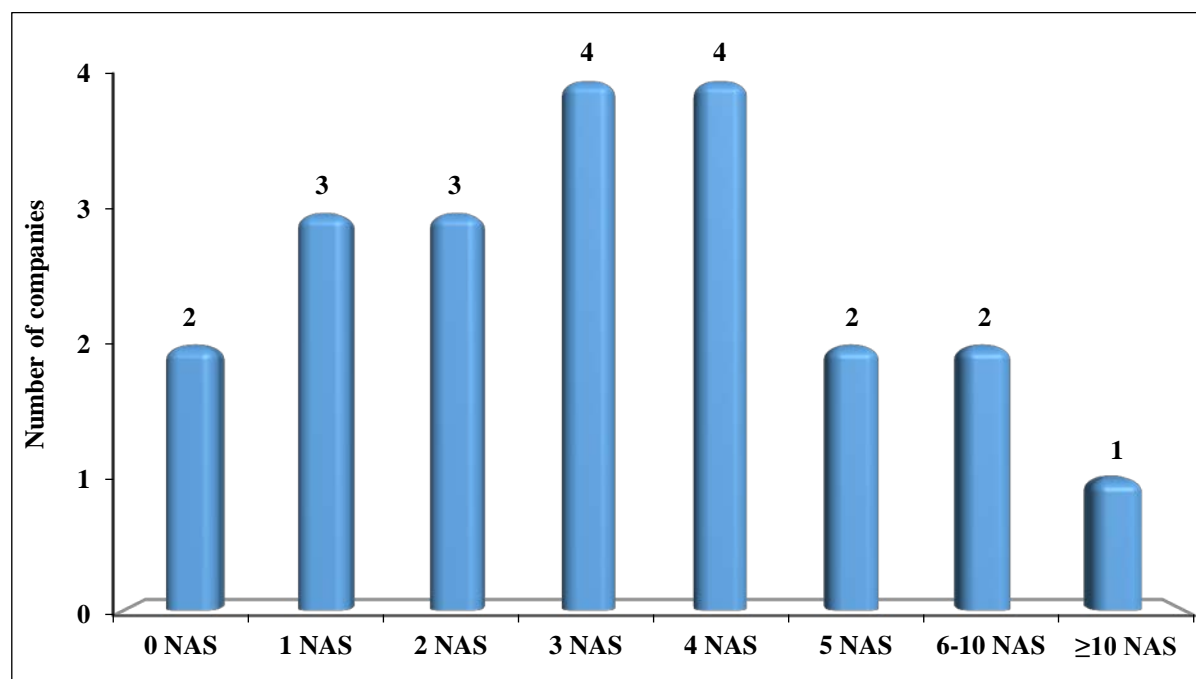
**Figure 5.8: Companies' assessment of the TITCK scientific competencies**



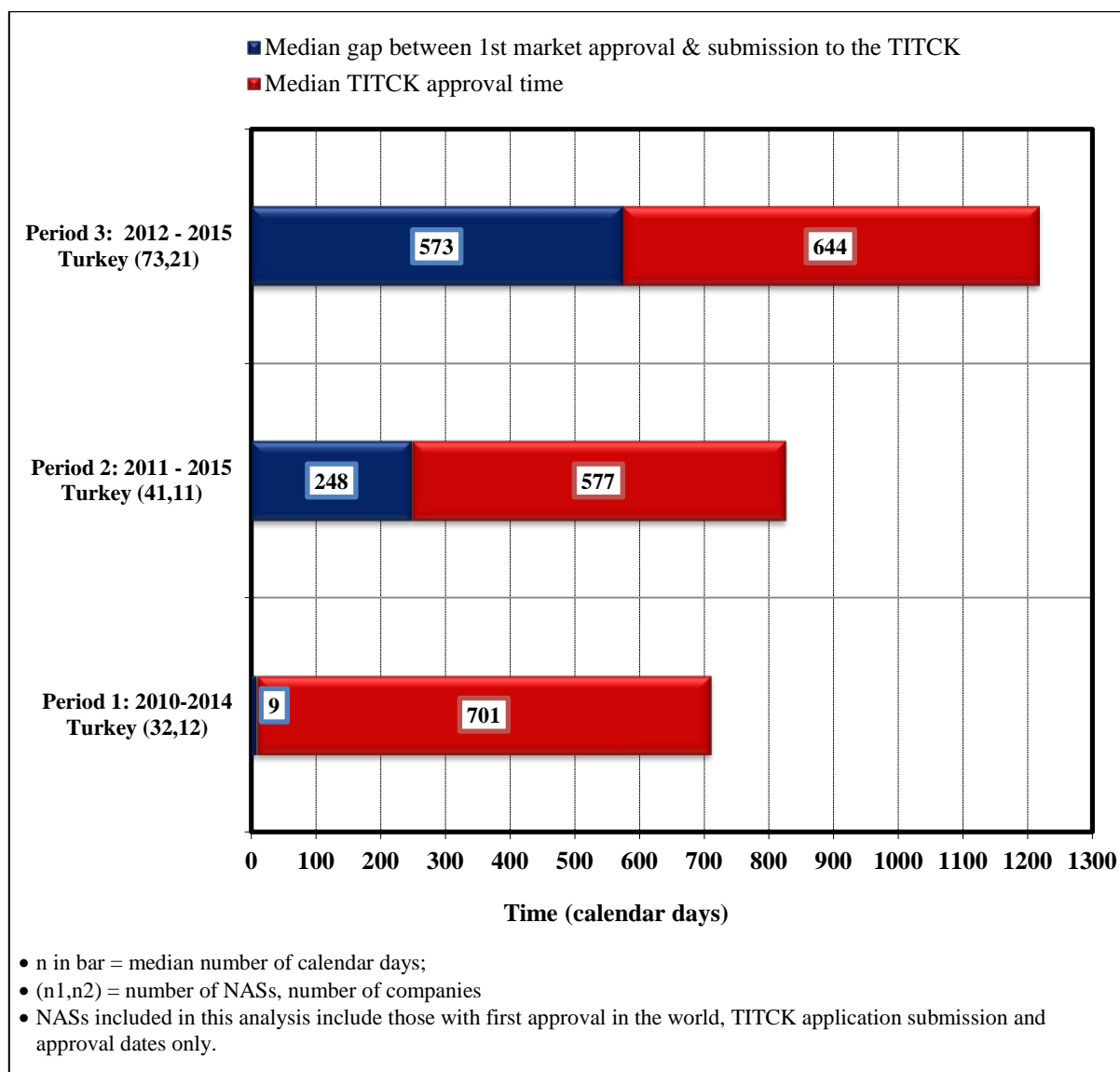
#### **Regulatory Metrics:**

This study identified that almost all companies have NAS applications currently pending approval at TITCK (Figure 5.9). Additionally, the median time to roll out to Turkey for New Active Substance (NASs) approved between 2012 and 2015 was determined (Figure 5.10).

**Figure 5.9: Number of NASs currently pending approval at TITCK**



**Figure 5.10: Approval timelines of NASs by TITCK (industry data)**

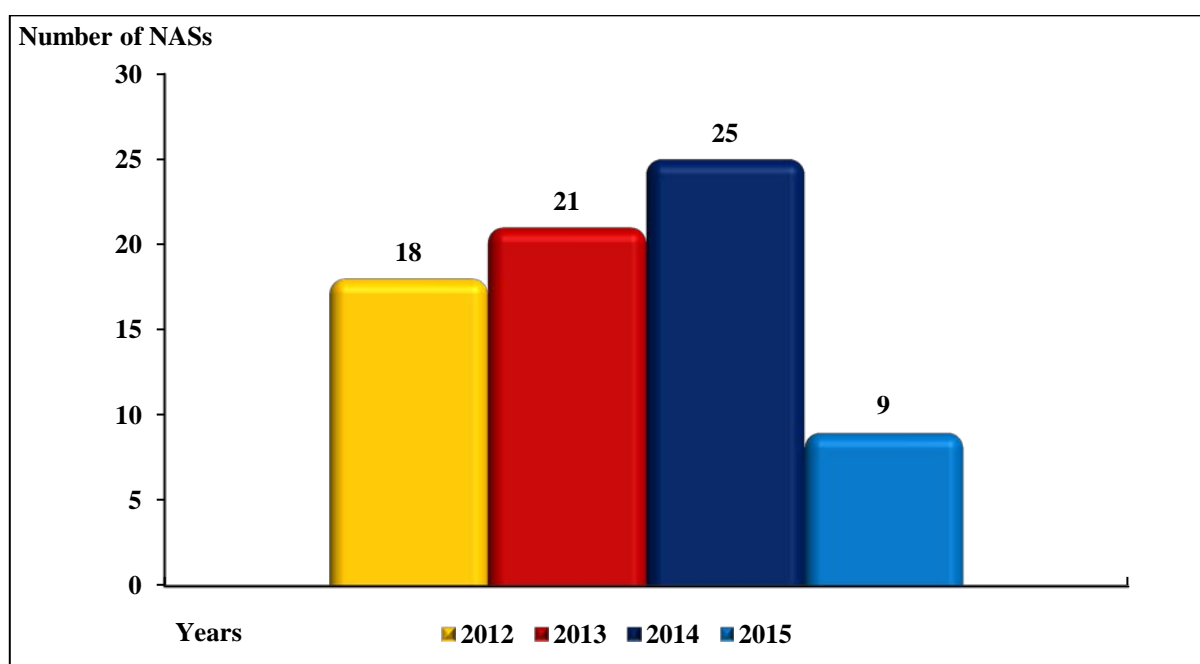


This analysis shows a composite of median interval duration for a NAS submission to TITCK after first approval anywhere in the world, followed by the median time of final TITCK approval for the same compound in Turkey. The methodology used in this analysis was based on data provided on the first approval date in the world, application submission and approval date by TITCK for NAS applications. These dates were used to calculate the duration of the gap between first market approval and TITCK submission, which was identified to be five hundred and seventy-three calendar days (nineteen months) for the period between 2012 to 2015 and approval time for NASs by the TITCK identified to be six hundred forty-four calendar days (twenty-one months). Data are shown for approval dates for three different periods: this study period from 2012 to 2015 for seventy-three NASs provided by twenty-one

companies from the industry study. Data for the first and second periods, obtained from previous studies, are the period between 2010 to 2014 and 2011 to 2015 respectively. These data identified that the duration of the gap between first market approval and TITCK submission for the second period was two hundred and forty-eight calendar days (eight months) compared with only eight calendar days for NAS approved in the first period from 2010 to 2014. This indicated an increasing delay and gap in the NAS applications to the TITCK after first approval anywhere in the world since 2010. The delay could be attributed to the introduction of the Turkish GMP regulation in 2010 where many companies were either hesitant or not able to submit their NAS applications due to the unclear GMP requirements, which was later on amended in 2012.

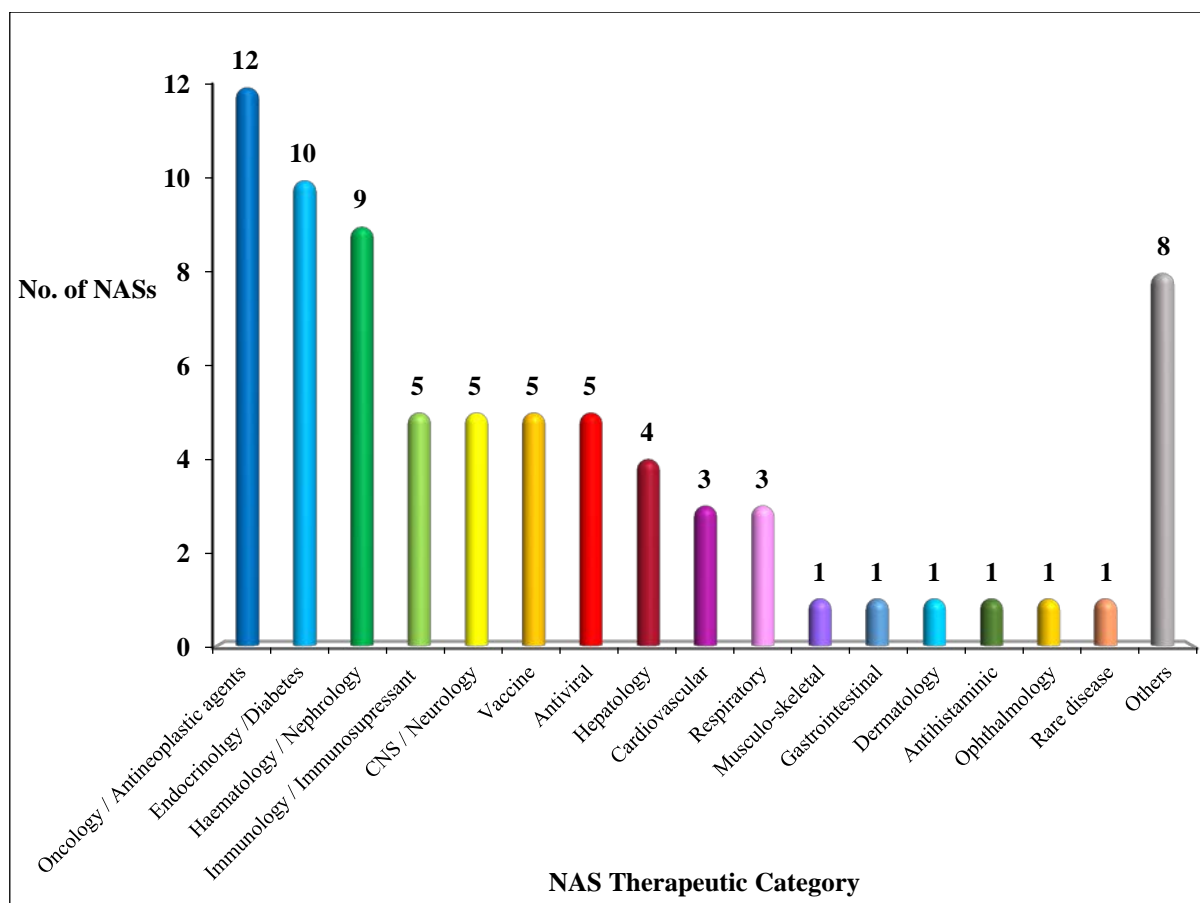
Additionally, the approval time for NASs by the TITCK was identified to be six hundred forty-four calendar days (twenty-one months) for this study, five hundred and seventy-seven calendar days (nineteen months) for the second period and seven hundred calendar days (twenty-three months) for the first period. Thus, the mean TITCK approval time remained approximately the same for the three periods ranging from nineteen to twenty-three months. The number of NASs approved by the TITCK showed an increasing trend from 2012 to 2015, where it increased to twenty-five NASs approved in 2014 compared to seventeen NASs approved in 2012 (Figure 5.11).

**Figure 5.11: Number of NASs approved by TITCK (industry data 2012-2015)**



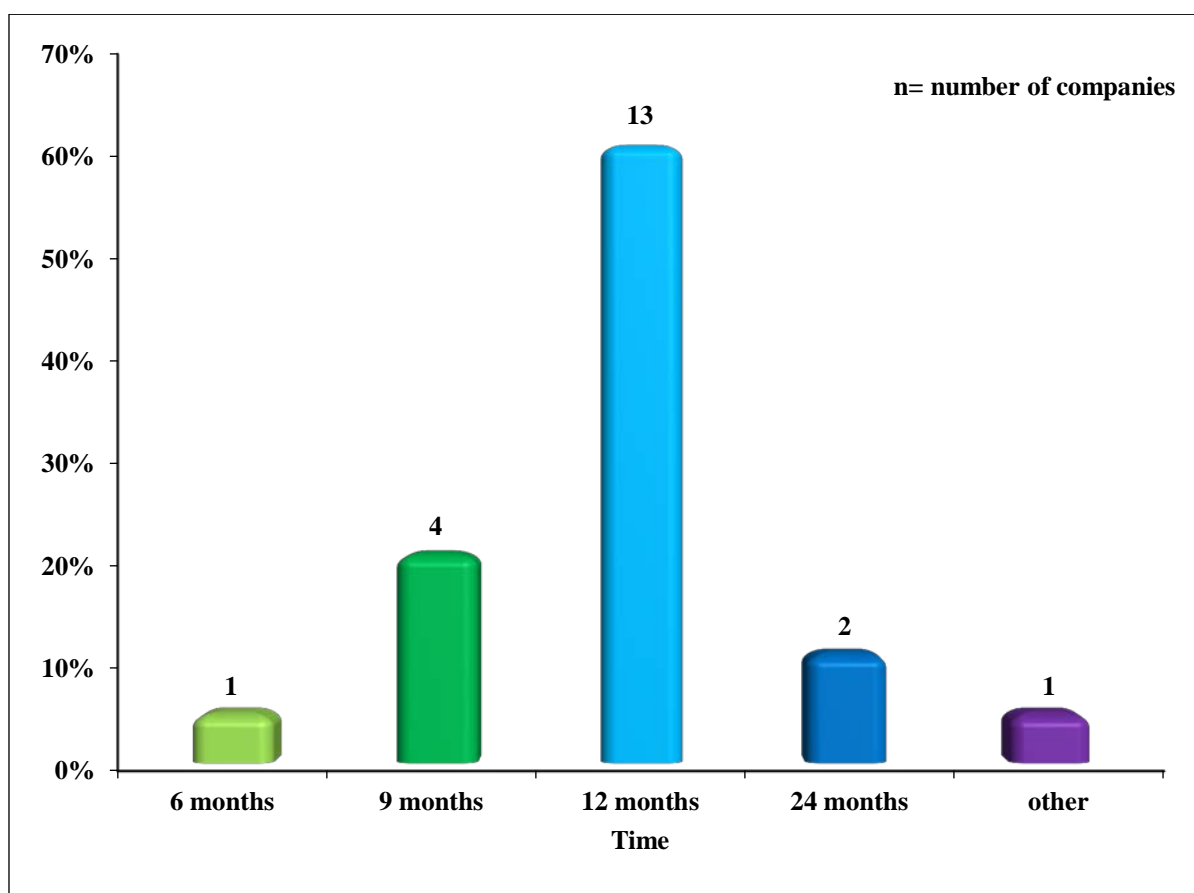
The therapeutic classification of approved NASs was identified for the same period of time, where the highest number of approvals was granted mostly to oncology and antineoplastic agents, followed by endocrinology and antidiabetic products (Figure 5.12).

**Figure 5.12: Therapeutic areas of NASs approved by the TITCK (2012 – 2015)**



The median time for NASs from the first approval anywhere in the world to TITCK approval time was identified to be one thousand two hundred and seventeen calendar days, which is approximately forty-one months (three and a half years). This means that patients in Turkey have access to new medicines as they become available in the Turkish market approximately three and a half years later compared to first approval of the product in the world. Thirteen companies (62%) agreed that the maximum time for the TITCK to complete the review process for a NAS application should be twelve months (Figure 5.13). This is approximately two hundred and forty working days compared with the two hundred and ten working days for target approval stated in the regulation.

**Figure 5.13: Companies' view on the maximum time for the regulatory review of NASs**



However, in practice the mean approval time in 2015 for NASs in Turkey is two hundred and seventy working days which is around twelve months based on the TITCK data which, does not include the clock stop for question and answer that on average is around ten months for each NAS application according to the data of the regulatory metrics of companies.

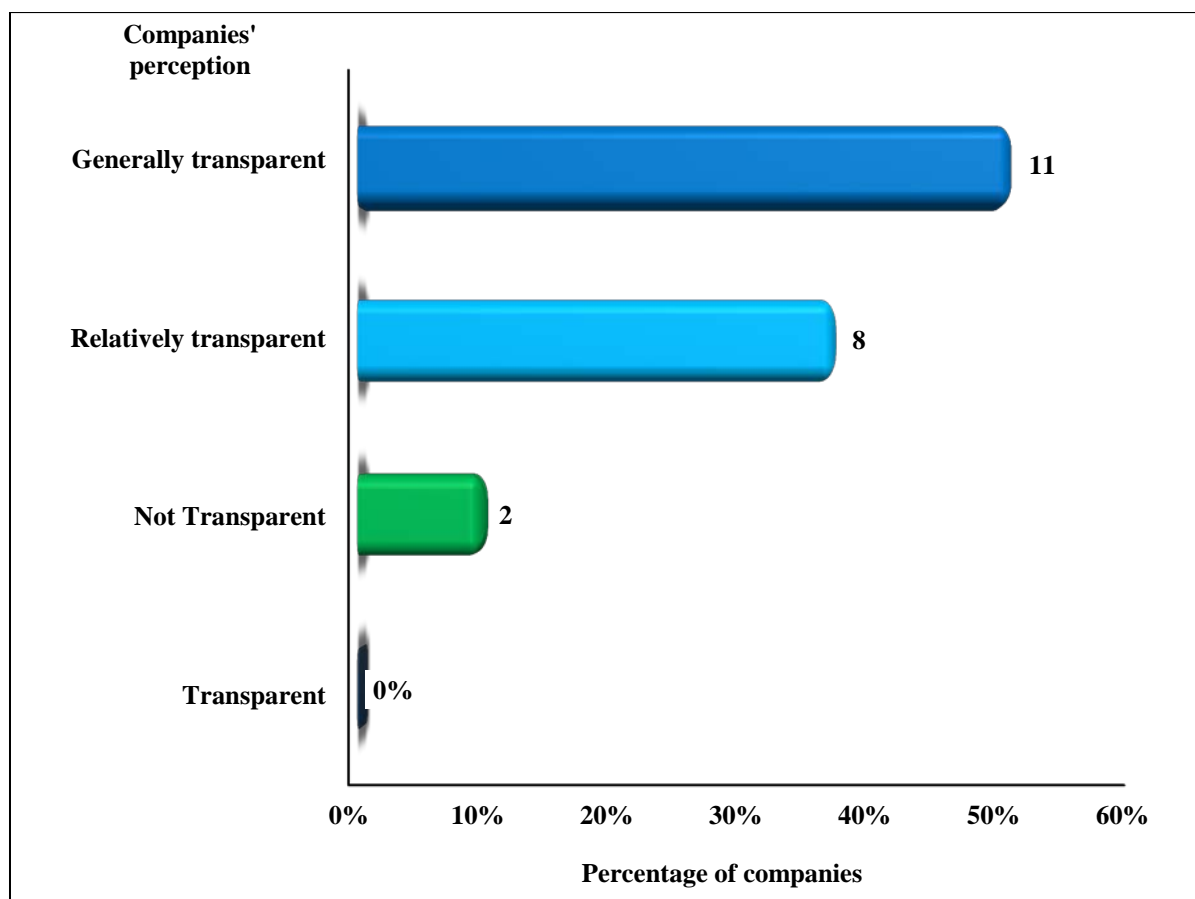
### **Part III: Regulatory Review Process**

Only five companies indicated that TITCK's practices were aligned with global Good Regulatory Practices (GReP), while nine stated that they were not aligned and seven were unsure. None of the companies indicated that the review process is transparent in that files cannot be tracked from submission to final approval by TITCK. Two companies stated that it is not transparent and half of the companies (n=11) indicated that the review process is generally transparent for the main milestones.



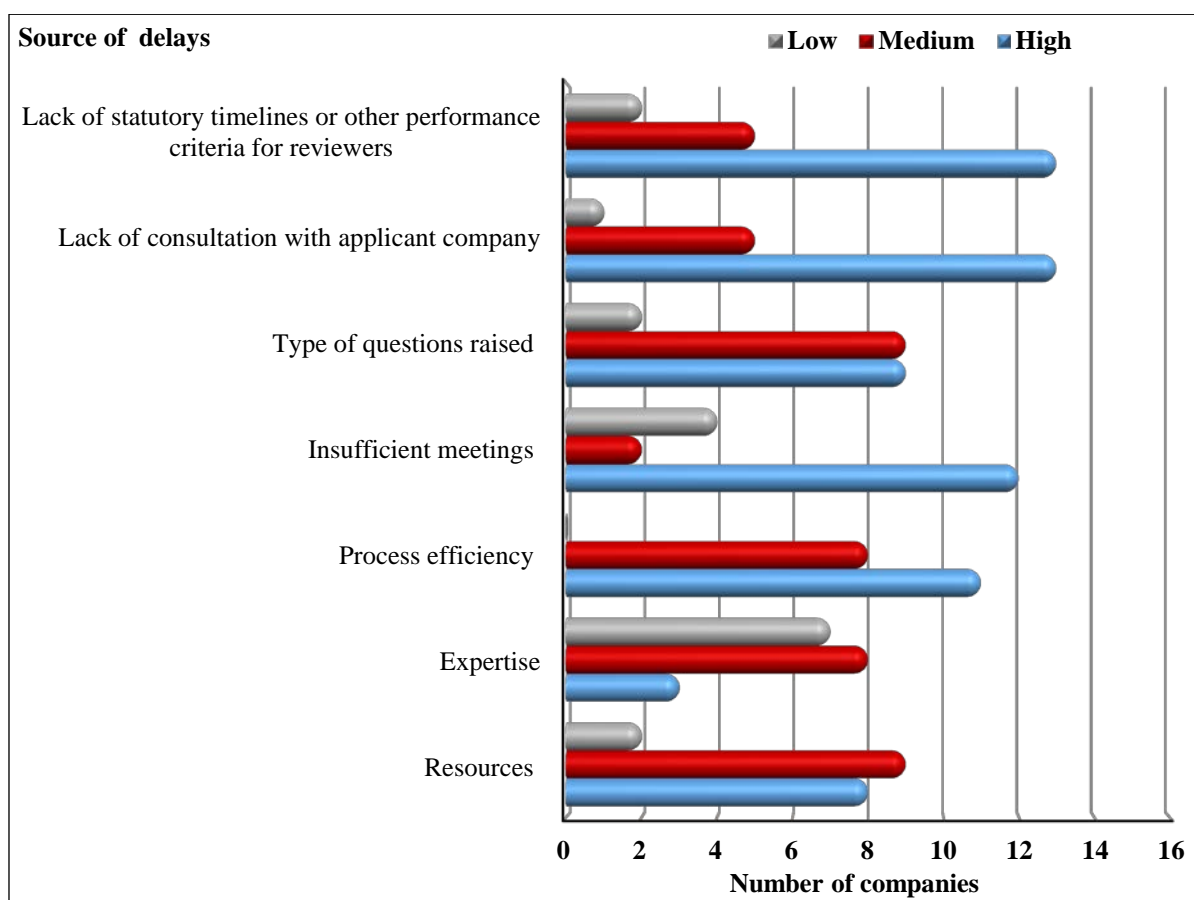
However, the decision-making process within each milestone is not transparent. Eight companies stated that the review process is relatively transparent as files can be tracked from TITCK's letters or through the question and answer phases (Figure 5.14).

**Figure 5.14: Industry perception of the TITCK transparency**



The majority of companies (n=16) declared that the review process is not predictable while only five agreed that it is predictable. Furthermore, only one company stated that they do not face any challenges in sequential submissions to the TITCK, while three indicated that they do and the remainder (n=17) stated that this depends on the submission. Since the registration review is a complex process influenced by several factors in Turkey, the target approval timeline of two hundred and ten working days is often missed and therefore prolonged. The TITCK's major sources of delay in approving new medicines were rated by companies according to their impact on the approval process as high, medium or low (Figure 5.15).

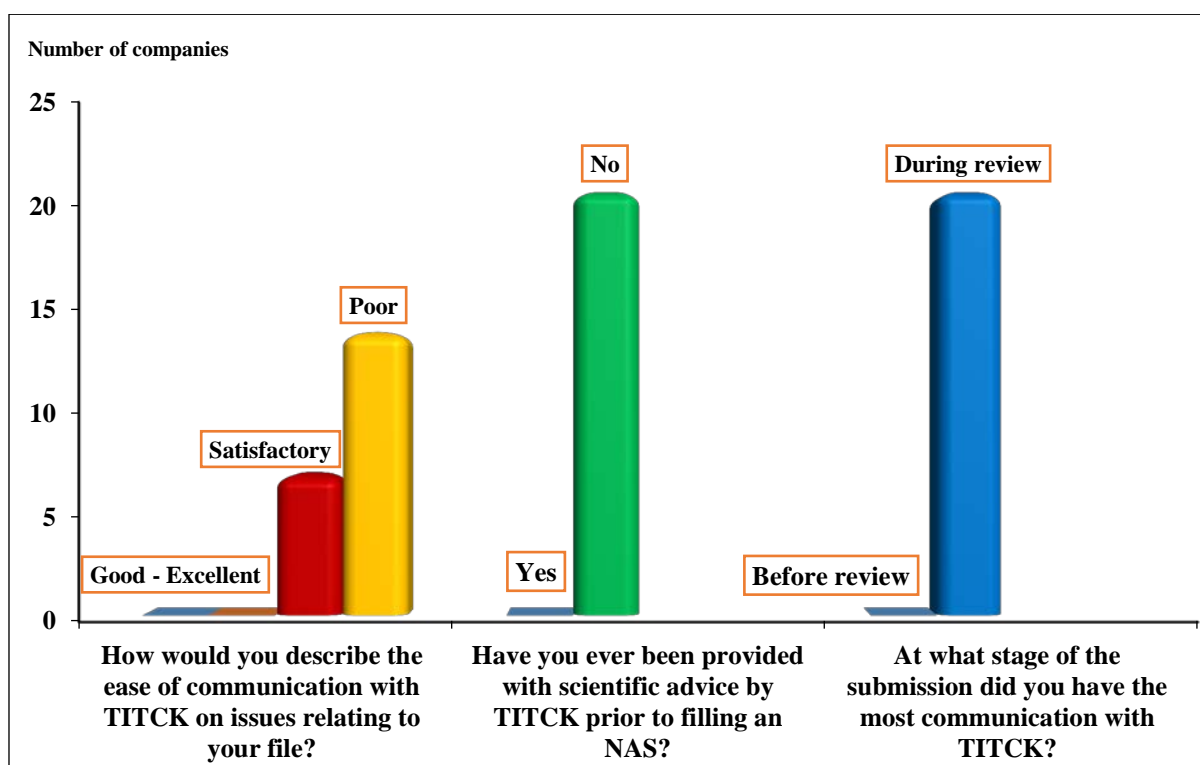
**Figure 5.15: TITCK's major sources of delay in approving new medicines**



The main sources of delay with the highest impact, as rated by the companies, were the lack of statutory timelines, performance criteria for reviewers and a consultation with the applicant company as well as insufficient agency meetings. This was followed by concerns about the efficiency of the review process, the types of questions raised during the review and the unavailability of staff resources and reviewers. Since the companies' perception of the TITCK review expertise was found to be either satisfactory or good, consequently the impact on the review and approval timelines was considered low.

A good review by an authority includes a comprehensive analysis of all clinical, non-clinical and quality aspects of new medicines to ensure the approval of their safety and efficacy. This also requires timely communication and consultation with applicants and reviewers as well as with other subject matter experts (Mussen, et al., 2007). In addition, the ability of a company to communicate easily with the regulatory authority during the review process is also important to track their application and enhance transparency. However, this study identified that fourteen companies (67%) described the ease of communication with TITCK on issues relating their files during the review process as poor (Figure 5.16).

**Figure 5.16: Companies' experiences with regard to TITCK communication**



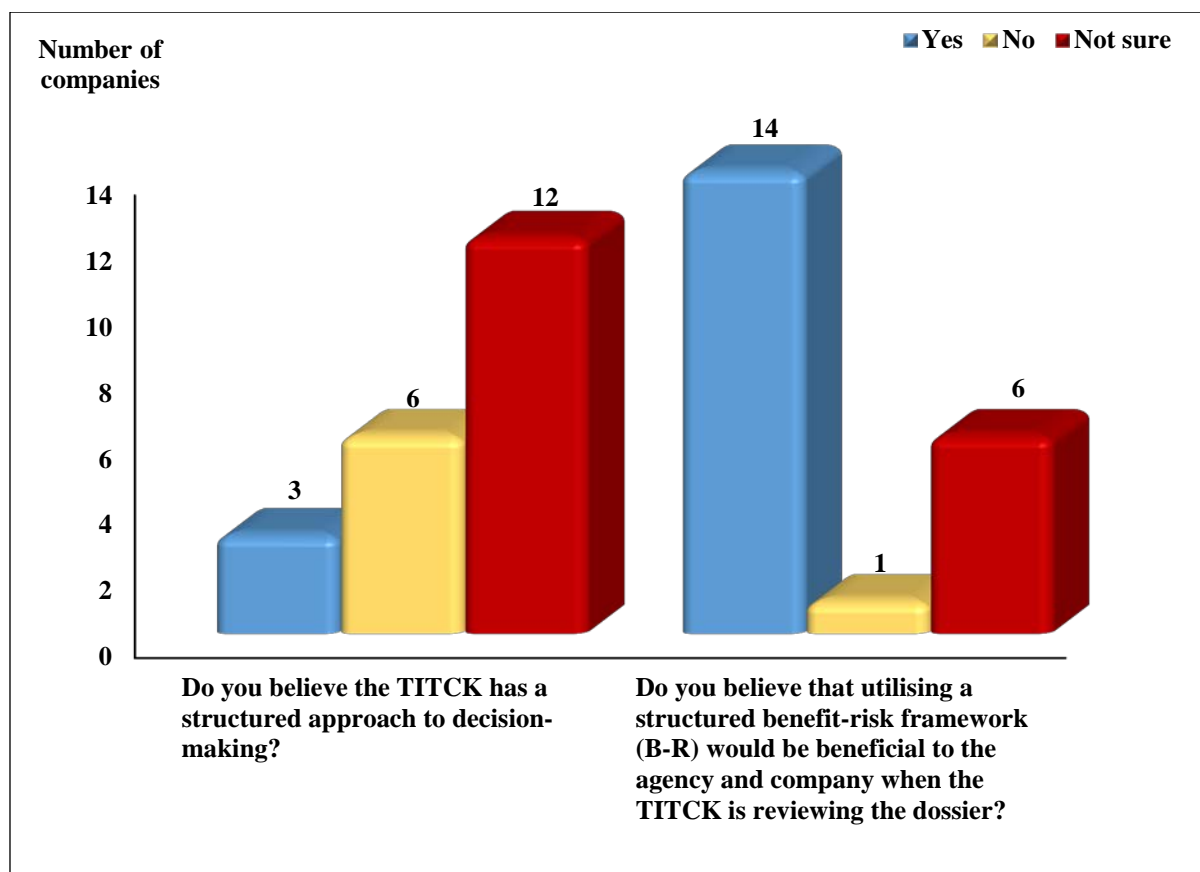
All companies indicated that they have never been provided with scientific advice by the TITCK prior to filing an NAS application and the only stage they have the most communication with TITCK was during the review mainly when questions arise. Most of the pharmaceutical companies have liaison offices in the capital city Ankara to facilitate the timely communication with the authorities such as the TITCK, MoH and SGK. Thus, thirteen out of the nineteen companies stated that they set meeting times and agendas with the TITCK through their official liaisons, while nine companies declared that they also book their meetings with the TITCK online.

One of the most important and challenging tasks of regulatory health authorities during the review of a new medicine is the timely conclusion of the assessment while safeguarding an appropriate evaluation of the benefits and harms. Therefore, recent studies have shown that regulatory health authorities are becoming interested in the implementation of different decision-making methods as well as a benefit-risk framework (Bujar, et al., 2016).

Six companies (29%) did not believe that the TITCK has a structured approach to decision-making and twelve companies (57%) were unsure, while fourteen (67%) agreed that utilising

a structured benefit-risk framework (B-R) would be beneficial when the TITCK is reviewing the dossier (Figure 5.17).

**Figure 5.17: Companies' view of the availability of a structured decision-making and benefit-risk framework at the TITCK**



Furthermore, companies evaluated the impact of the recent requirement by TITCK for a risk management plan for NASs with the majority of companies (n=19) stating that they found this requirement reasonable, whereas, two companies had no experience. Only three companies, who had previous experience with risk management plan submissions, indicated that this requirement had a negative impact on their review timelines.

## **Part IV. The Way Forward for TITCK**

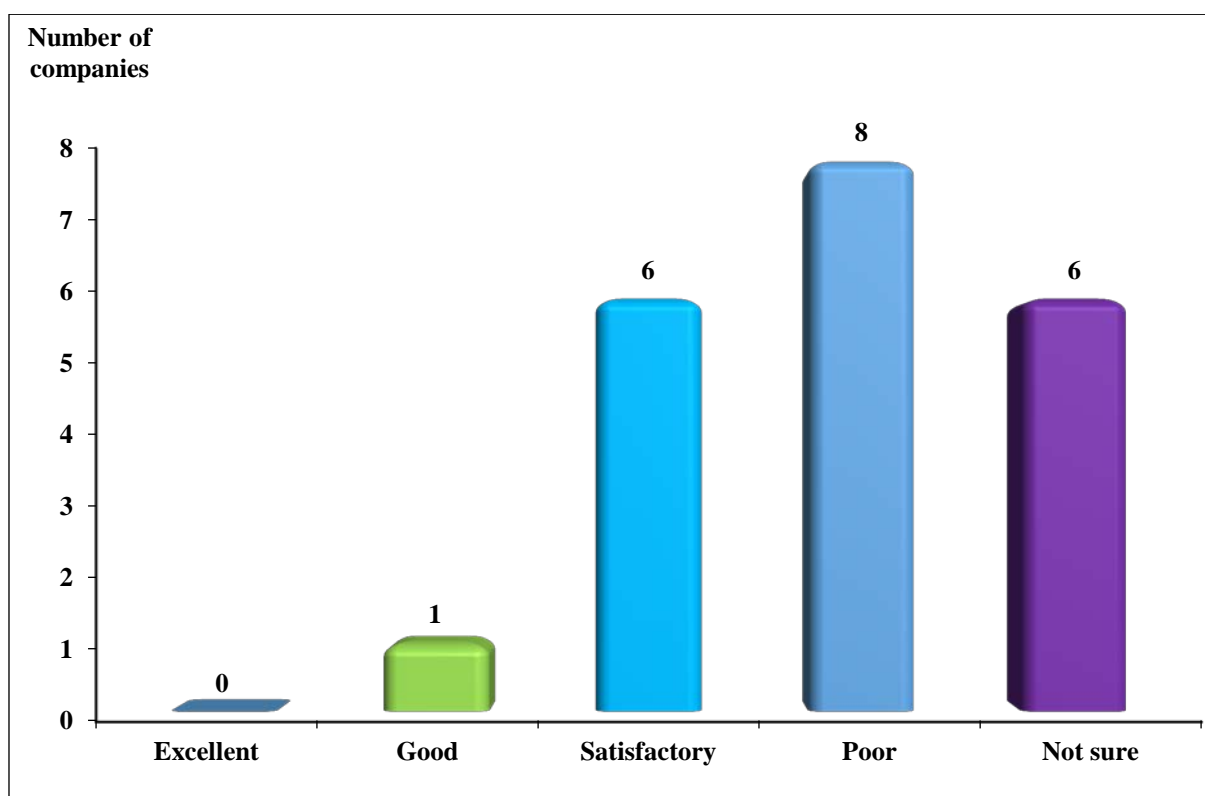
One of the main objectives of this study was to enable pharmaceutical companies to identify the main areas of improvement at the TITCK and the Turkish review process and accordingly provide a number of possible solutions and recommendations, which could help, address these issues (Table 5.7).

**Table 5.7: Areas of improvements in the review process as suggested by the industry**

Improvement areas	Examples of companies' quotes
<b>Scientific commissions and committees:</b>	<ul style="list-style-type: none"> <li>• <i>Commissions' regulatory review should be more structured and transparent.</i></li> <li>• <i>Applicants should be allowed to discuss issues directly with commissions.</i></li> <li>• <i>Commissions meeting must be regularly set.</i></li> <li>• <i>Increase the number of commission members and frequency of meetings.</i></li> <li>• <i>Assign a dedicated person from each commission for each application.</i></li> <li>• <i>Create review SOPs for commission members to standardise the evaluation.</i></li> </ul>
<b>Requirements</b>	<ul style="list-style-type: none"> <li>• <i>Regulations should be adapted as per global harmonised legislations.</i></li> <li>• <i>Harmonisation and update of regulations in line with the EU legislations.</i></li> </ul>
<b>Communication</b>	<ul style="list-style-type: none"> <li>• <i>Use of electronic correspondences (e-mails) to improve the review timelines.</i></li> <li>• <i>Show the status of each review step online on: <a href="http://www.ebs.titck.gov.tr">www.ebs.titck.gov.tr</a>.</i></li> <li>• <i>Enable companies to see and respond to questions online as they arise.</i></li> <li>• <i>Allow companies to communicate with TITCK on phone and record the call.</i></li> <li>• <i>Provide presentation opportunity for companies during registration review.</i></li> <li>• <i>Build an online tracking system to enable the follow up of applications.</i></li> </ul>
<b>Pre-submission meetings</b>	<ul style="list-style-type: none"> <li>• <i>TITCK should provide scientific advice and opinion before submission.</i></li> <li>• <i>Enable pre-submission meetings with companies as in EU countries.</i></li> </ul>
<b>GMP</b>	<ul style="list-style-type: none"> <li>• <i>Simplify the Turkish GMP requirement and inspection criteria.</i></li> <li>• <i>Allow parallel GMP submission and review for all submissions.</i></li> </ul>
<b>Transparency</b>	<ul style="list-style-type: none"> <li>• <i>TITCK could improve transparency and be open for discussion.</i></li> <li>• <i>Review process and milestones should be communicated to companies.</i></li> </ul>
<b>Timelines</b>	<ul style="list-style-type: none"> <li>• <i>TITCK should accelerate the review process.</i></li> <li>• <i>Define target timelines during review processes for each milestone.</i></li> </ul>
<b>Fast track</b>	<ul style="list-style-type: none"> <li>• <i>Prioritisation (fast track) criteria must be defined and clarified.</i></li> </ul>
<b>Good review practices</b>	<ul style="list-style-type: none"> <li>• <i>TITCK should implement a more standardised review approach.</i></li> <li>• <i>TITCK should be consistent in the decision-making process.</i></li> <li>• <i>Implement a structured review and use of SOPs for the review process.</i></li> </ul>

Nine of the responding companies were satisfied with the level of industry-TITCK communication/dialogue on regulatory issues affecting the sector, while more than half indicated that they were not satisfied. In addition, fourteen companies believed that the TITCK has a long-term strategy with respect to the regulatory environment, however; eight companies evaluated the TITCK's communication policy of its long-term strategy to be poor (Figure 5.18).

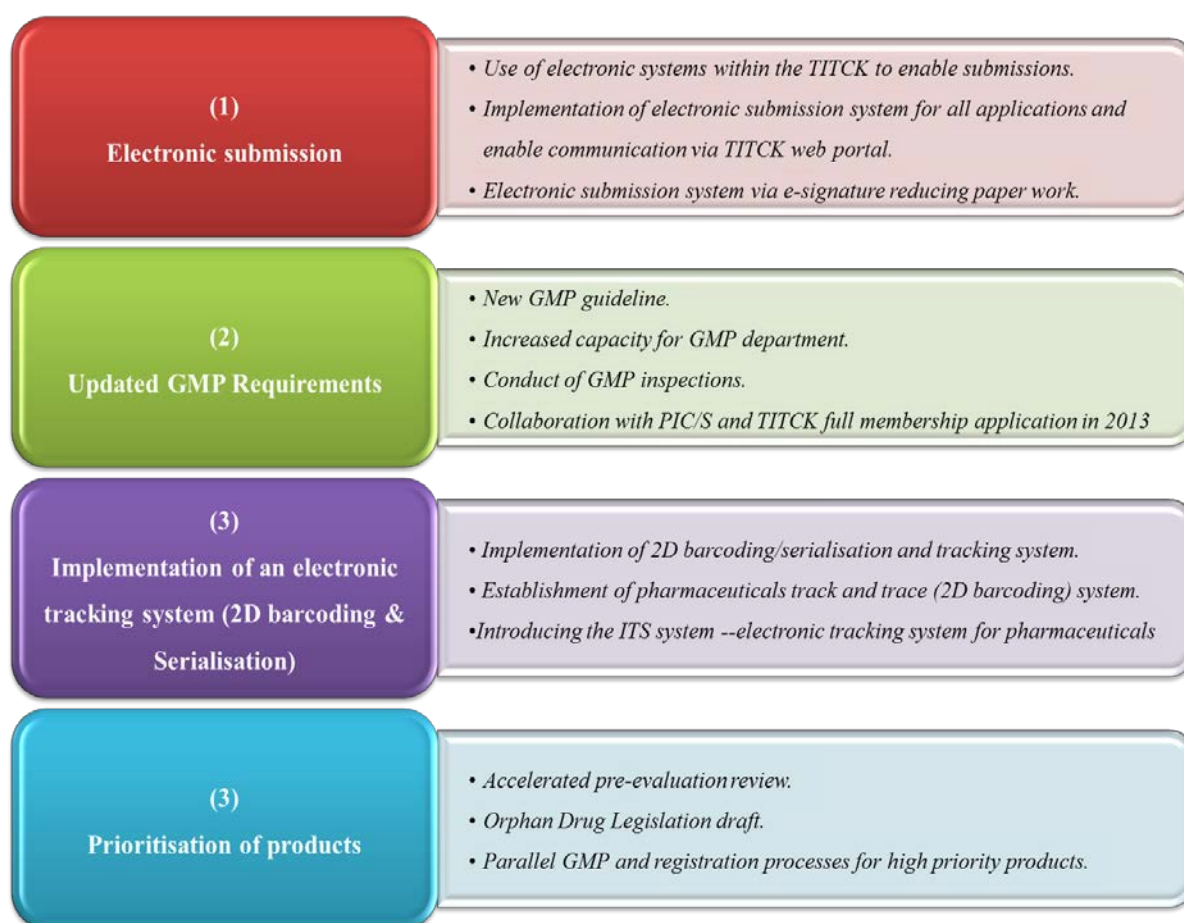
**Figure 5.18: TITCK's communication policy of its long-term strategy**



These findings suggest that there is room for improvement for TITCK regarding its communication policies with companies at all levels be it related to requirements, the review of applications or regulatory strategy and vision.

The last part of the questionnaire included open-ended questions regarding both positive and negative regulatory developments in the last few years. Accordingly, companies identified the introduction of the prioritisation guideline as one of the important positive developments (Figure 5.19). Furthermore, the implementation of the electronic signature for applications, the regulation on the rational use of medicines was indicated as the most significant positive developments at the TITCK since 2011. Companies also indicated the following to be among the positive developments at the TITC: the introduction of the electronic submission system for all applications via the TITCK web portal, the enforcement of the pharmaceutical tracking and tracing system (ITS) with the barcoding and serialisation process as well as the utilisation of e-mails as a communication and appointment setting vehicle and the accreditation of the analysis laboratories of the TITCK.

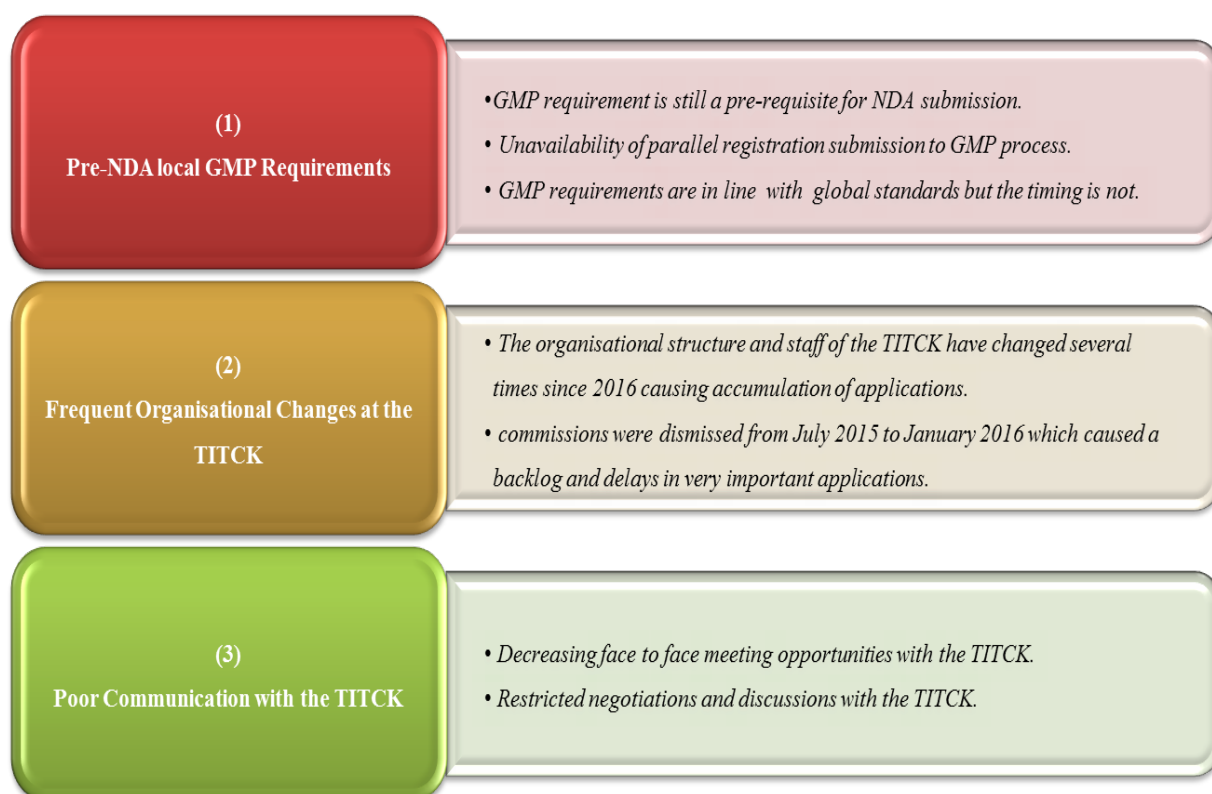
**Figure 5.19: The three most important positive developments at the TITCK since 2011**



Companies provided the three most important negative developments at the TITCK since 2011, which had a major impact on the review process. Thus, the local GMP requirement enforced in March 2010 was the most cited development by companies. The majority of companies indicated that they understand the benefit of conducting local GMP inspections by TITCK, which is perceived to be of high quality. However, the requirement to complete this process prior to an NAS application as a pre-requisite to submission rather than to have it conducted in parallel to the review process is a major challenge and source of delay to approval. The frequent organisational changes at the TITCK, which affected all functions and levels including the scientific committees within the agency, were identified as the next most important negative factor. Fourteen companies (67%) indicated that the fragile structure of the TITCK and the constant change of roles, department heads and committee members mainly in 2015 caused a significant backlog and delay in the review process and consequently in the approvals of critical NAS applications.

In addition, some companies stated that the eagerness to quickly implement changes within the TITCK infrastructure resulted in frequent database changes and transitions, which caused data loss on several occasions. The third most cited negative development was the poor TITCK communication policies, which, according to half of the companies, had deteriorated since 2011 and had become more challenging and restrictive. This led to a significant regression in the transparency of the TITCK review and decision-making processes as perceived by the industry (Figure 5.20).

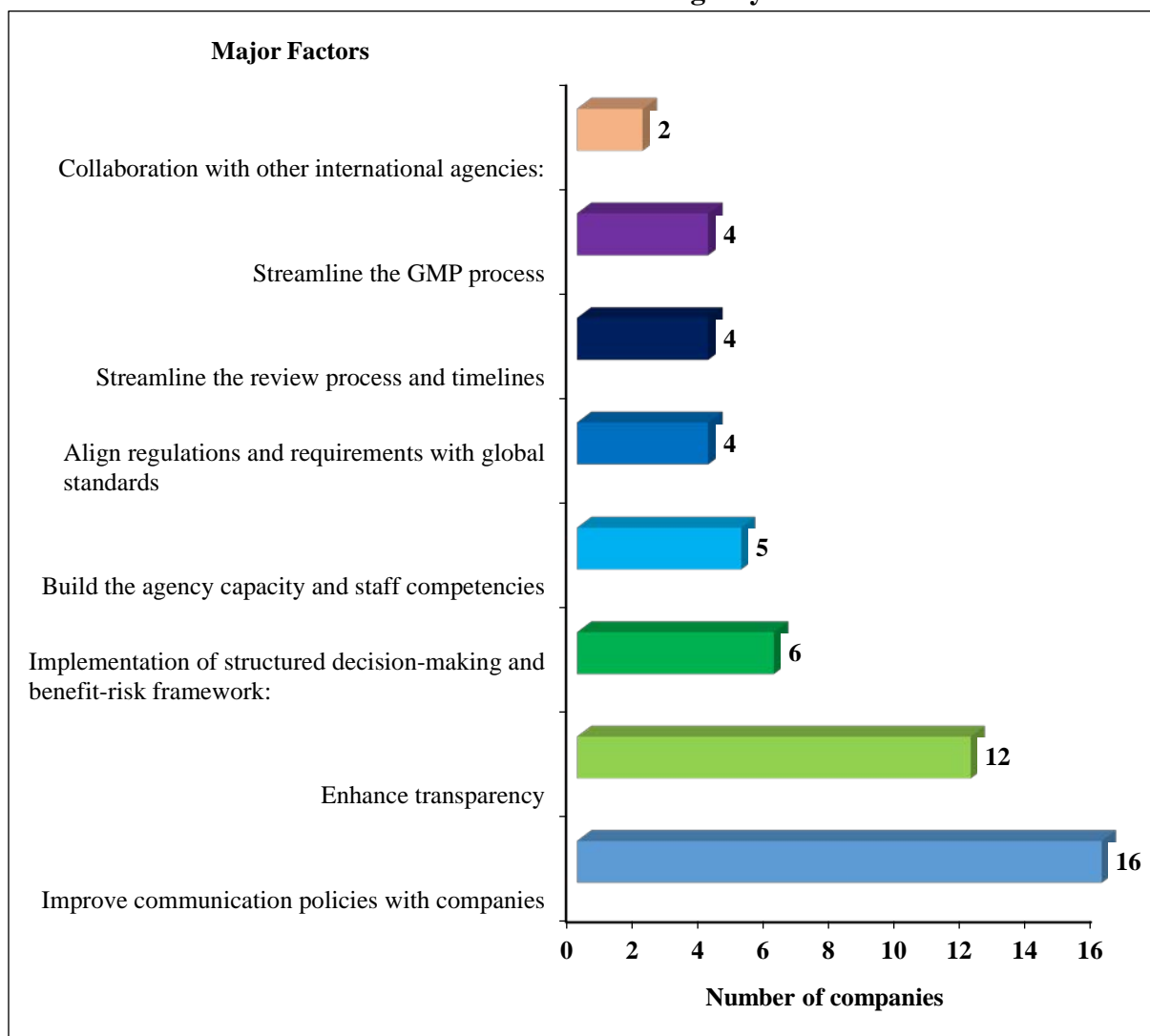
**Figure 5.20: The three most important negative developments at the TITCK since 2011**



Companies identified three major factors that could contribute towards an effective agency. These included the TITCK's improvements in the areas of communication, transparency, building structured decision-making into the review process and utilising a benefit-risk framework. The majority of companies (n=16) suggested that the communication policies of the TITCK with the industry should be improved in order to facilitate mutual collaboration. Several companies commented that the TITCK should be more open to discussions with companies in matters related to requirements, applications and review process. Therefore, the general recommendation from the companies was for the TITCK to have a more structured framework for effective communication and consultation (Figure 5.21).



**Figure 5.21: Companies' suggestions of three major factors that could contribute towards an effective agency**



The second most highlighted improvement recommendation from the industry was related to transparency. Twelve companies (57%) suggested that the TITCK should be more transparent with regard to the review process, submissions and approvals. One of the suggestions was for the TITCK to publish the submission and approval dates of new products when they are granted marketing authorisations and to publish the names and addresses of the manufacturing sites inspected by the TITCK. This would facilitate the sharing of experiences and enable companies to make the most accurate prediction about their own approvals. Furthermore, companies indicated the implementation of a structured decision-making process and a benefit-risk framework as the third most recommended improvement area for the TITCK. If this was implemented it would enhance the transparency, predictability and timeliness of the review process.

Finally, companies cited the three factors that they saw as barriers to making a new medicine available in a timely manner. Seventeen companies emphasized that the GMP accreditation process is a significant barrier for the timely access to new medicines. This is because the local GMP certificate process is a pre-requisite for a MAA except for highly prioritised products. With an insufficient number of inspectors and the large number of applications pertaining to accreditation of new sites as well as manufacturing site changes, the process is taking on average twenty-two months. A second barrier, the long TITCK evaluation and review process which mainly depends on external reviewers. Therefore, the workload of the external reviewers is constantly increasing and consequently companies have to wait a considerable time for the commission's decision.

Finally, the third factor was related again to the poor communication policy of the TITCK with the applicants. Thus having structured consultative meetings, mainly in the pre-submission phase, would reduce the number of questions during the review and therefore accelerate the approval. Other factors were those related to the pricing policy, additional requests from the TITCK which are outside the global requirements as well as indication restrictions. These occur due to the TITCK's assessment of indication based on economic and public finance criteria, which is supposed to take place during the reimbursement process with the SGK rather than the review process at the TITCK.

## **DISCUSSION**

Implementation of a good regulatory review process by health authorities has a major impact not only on the timely access of patients to their medicines but also on the growth and development of the pharmaceutical industry. Hence, a good regulatory environment often supports a sustainable investment environment where companies can receive authorisation approvals for their product and market these in a timely manner. Such an environment is characterised by three main principles which are: transparency, in the sense of sharing public policies and assessments with all stakeholders, predictability, which enables companies to anticipate outcomes and regulatory changes to manage their activities and investments in the most productive manner as well as establishing an open dialogue which reinforces communication between stakeholders and policymakers in the pharmaceutical sector (YASED, 2012). Therefore, evaluating the pharmaceutical industry's views about the regulatory review process and timelines of the TITCK in terms of transparency, predictability

and ease of communication and how these impact the marketing authorisation timelines of their products in Turkey was essential.

Within this study, the pharmaceutical companies in Turkey provided critical information on many aspects of the TITCK review practices, requirements together with positive and negative developments. These were evaluated in four main themes namely; communication and transparency, requirements, decision-making process as well as the agency structure and resources, which indicates the major challenges identified by the Turkish pharmaceutical industry.

## **Communication and Transparency**

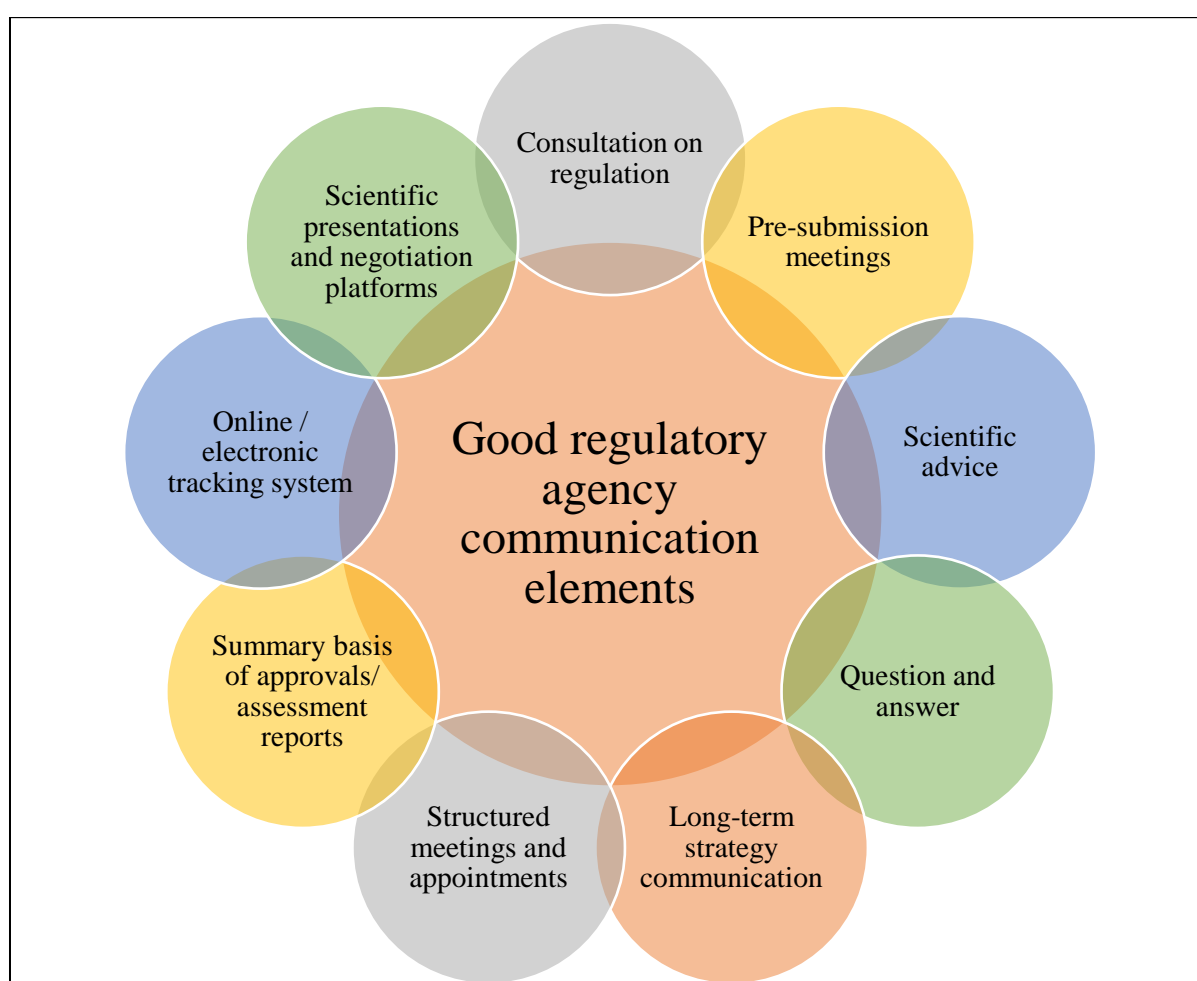
**Consultative process and scientific advice meetings:** this was evaluated by the industry where half of the companies stated that the TITCK consultative approach prior the issuance or major change of a regulatory requirement was satisfactory. However, most of the companies described the ease of communication with TITCK as poor before a regulatory submission or during the review process. The lack of a continuous consultation and constructive dialogue with the agency is perceived by the industry to be one of the major sources of delay for regulatory approval and thus creates a non-transparent and unpredictable environment, which ultimately cannot support a long-term investment strategy. Therefore, improving communication and implementing a structured framework for consultation by the TITCK with companies at all stages before the issuance of a regulation or during the review process is the most significant factor that could contribute towards an effective and high standard regulatory agency. Moreover, a continuous open dialogue can enhance the trust and reduce the number of questions raised during review. This will save the agency as well as the companies significant time and resources that will eventually be reflected in faster approvals and patients timely access to medicines.

In this context, the TITCK can take certain measures to improve its communication and consultative processes by building a structured communication policy that should include a number of key elements (Figure 5.22). These can enhance the interaction of the agency with companies and fulfil significant improvements in the system such as; the introduction of a flexible scheduling system for meetings with companies for critical and urgent cases, enabling applicants to present their arguments to internal and external reviewers during the review and

the question and answer stages to clarify concerns and create a scientific platform for negotiation and finally, setting standards for pre-submission and scientific advice meetings with companies.

It is well recognised by the industry that the TITCK currently has a good consultation process on regulations as they ensure that comments from all related parties are well received prior to issuing a major change or new regulation. However, a similar systematic approach is not implemented for pre-submission advice meetings.

**Figure 5.22: Aspects of good communication practices of a regulatory agency**



Since, the TITCK often provides administrative advice about the application dossier and on some occasions, they do provide scientific advice. These meetings are conducted officially by other regulatory agencies to maintain an open communication with the industry and ensure that resources are optimal and timely (EMA, 2014). Therefore, it is recommended that the TITCK structure the pre-submission meetings and describe these practices clearly in

guidelines in terms of scope, procedure, timelines and required fees. In addition, the TITCK could consider the use of scorecards as a vehicle to provide feedback and evaluations regarding application dossiers, which could provide a good assessment, and learning tool both for applicants and for agencies. Using a developed scorecard system can provide a standard and effective indicator of the regulatory performance in terms of the quality of the application and review process. This could equally facilitate the feedback at the end of each review both for regulatory authorities and companies (Salek, et al., 2012).

**Use of electronic communication vehicles:** During the last decade, the TITCK has significantly developed its electronic infrastructure and online systems. The implementation of a national electronic tracking and tracing system (serialisation and barcodes) for pharmaceuticals in 2010 is a good example. Accordingly, the TITCK mandated the implementation of a barcoding and serialisation system for each product in the market to optimise the rational use of medicines and minimise counterfeit products. Furthermore, since 2008 the introduction of an electronic submission via the TITCK web portal is well acknowledged as companies also receive a tracking number, which enables the follow-up of the file when questions are raised. However, there is room for improvement in tracking applications during the review process by companies, as the TITCK should establish an electronic tracking system to identify the stages of the file and enhance transparency as well as prompt more predictable standard timelines in the review process. In addition, the use of electronic online services and e-mail communications as web-based notifications can facilitate the timely communication between companies and the TITCK and therefore ensure the monitoring of the progress of applications, which can enable better understanding and planning when target times are exceeded.

**Question and answer:** the question and answer stages vary in practice among regulatory agencies as different countries may ask different types of questions related to the same application. This depends on their interest, expertise area and country need. It is also known that the CMC area is the area where most agencies like the TITCK have expertise whereas the clinical and non-clinical areas are not frequently challenged except when an outstanding safety concern is raised. In addition, while some regulatory agencies batch questions and send them at different points of the review to the applicant, other agencies send questions as soon as they are raised and therefore the review clock is stopped each time. Batching questions during the review process can contribute to the predictability of the process and often help

companies better plan their resources. The TITCK could optimise the question and answer process by batching questions at each milestone and setting clear deadlines for companies to respond. This way, approval timelines would suffer less from delayed questions and answers. Moreover, the TITCK could provide companies with an online notification of the questions raised and allow companies to respond initially online or electronically in order to accelerate the process and clarify certain issues immediately.

**Long-term strategy communication:** the TITCK publish on an annual basis a strategic plan that contains information about the plans and projects related to the previous year. However, for planning and forecast purposes, these reports could include future plans as well as long-term strategies to be implemented by the agency in Turkey. The TITCK may also consider including budget and resource data and thus request companies to provide them with an estimate of major NAS applications that they are likely to submit in advance. Sharing the regulatory vision and strategic future plans of the agency with its stakeholders and vice versa would ensure that they are well prepared and would enhance predictability.

## **Requirements**

In general, the Turkish pharmaceutical requirements for NDA applications are detailed and aligned with global ICH standards and hence as highlighted in this study, these requirements are partially aligned with those of the EU and are clearly listed. However, they are not fully enforced and subject to various interpretations. Furthermore, companies expressed their satisfaction with the improvements in the regulations area especially in relation to the issuance of the prioritisation guideline in 2016 and the introduction of the accelerated registration review process. However, it is important to emphasize that the TITCK will still need to make additional efforts to harmonise the marketing authorisation requirements with global requirements while updating the current ones in line with the EU directives. It is well recognised that the harmonisation of requirements facilitates the sharing of best practices and decision-making outcomes between regulatory authorities (nationally, regionally and internationally) and enables the optimum use of resources and efforts during the review process. It also contributes to building effective regulatory systems and leveraging solid collaborative networks based on trust and scientific expertise between authorities (Al-Rubai, et al., 2015). For instance, the Turkish GMP accreditation process, the scientific evaluation and approval of indications, the recognition of orphan drug designations and regulatory framework as well as the pricing procedure are the main aspects of the review process, which

were highlighted by the industry to be areas that urgently need to be aligned with international regulations and standards.

### **Decision-Making Process**

More regulatory agencies are aware of the need to improve transparency by providing more information to stakeholders about the review and decision-making processes and outcomes. However, only a few agencies implement the main elements of transparency such as the provision of scientific advice and information related to the technical staff to be contacted during review and publishing the summary basis for their approvals. The summary basis of approval is a report where regulatory authorities detail the assessment outcome and mechanism of the decision-making process that was considered in approving a new medicine (Habibi & Lexchin, 2014). Currently only four countries; Australia, Canada, the EU and the USA are publishing these summary basis of approvals and providing assessment reports to companies. However, several other countries are in the process of reviewing their methods, criteria and the timelines and considering making available summary basis of approval to stakeholders. With this in mind, the TITCK may wish to consider publishing approval summaries to the public similar to the public assessment report (PAR) in order to verify the decision on the application. This would enhance the TITCK transparency since the PAR in the EU for example was developed to communicate a usable, transparent and detailed body of information regarding the approval of a new medicine (Papathanasiou, et al., 2016). Furthermore, the TITCK could have access to the assessment reports of other countries to obtain more insight of other authorities' assessment and experience. This could be directly requested from companies and may contribute to accelerate the TITCK review process by putting some reliance on products reviewed or approved by other major authorities as recommended for consideration by the WHO (WHO, 2016).

Standardisation of the review system helps to improve and facilitate the registration process as well as maintaining the supply of safe and effective medicines within a reasonable period (Al-Rubai, et al., 2015). In addition, this would entail an assessment and approval procedure based on scientific evidence and use of structured decision-making and benefit-risk frameworks. One of the most important uses of Benefit-Risk assessment pertains to the approval of new medicines or new safety or clinical data by regulatory authorities in a more scientific and less complicated method, which would save time and effort and promote transparency (Mussen, et al., 2007). This will also contribute to a better coordination of the regulatory activities and

tasks across departments and reviewers and prevent delays in approvals (Li-Ling, et al., 2013). In relation to this, the TITCK should consider devoting more effort to improving the quality of their decision-making process and ensure its consistency by implementing and enforcing detailed guidelines, internal standard procedures (SOPs), requirements and target timelines for each milestone of the review process. For this purpose, the TITCK may wish to implement some of the available methodologies for benefit-risk assessment frameworks that can be either descriptive or quantitative to increase transparency as these consist of a clear guide for good decision-making practices (PROTECT, 2017).

### **Agency Structure and Resources**

One of the key concerns, highlighted by the companies was the constant change in the organisational structure of the TITCK as well as the change of staff, roles and responsibilities within the agency. Since these frequent changes often create a chaotic, fragile and unpredictable environment within the agency (mainly in 2015 and 2016) and cause significant backlogs and delays in the approval of new drug applications. Moreover, the reorganisation and introduction of systematic changes engendered the loss of several databases and critical reviewers' outcomes and information related to applications, which affected the consistency of assessments during the different transitions.

Additionally, as the majority of companies indicated, the nomination process of departmental heads and reviewers at TITCK as well as the assignment of the regulatory tasks for internal and external reviewers are unknown. This often creates the perception that agency nominations and assignments are not based on scientific abilities and merits and therefore may trigger the questioning of the assessment decisions and outcomes. Furthermore, the TITCK usually refers to external reviewers in order to ensure the involvement of scientific expertise in the review process. However, it was also identified that the pharmaceutical companies are unaware of how external reviewers and commission meetings take place or who the reviewers and contacts for their applications are and the scientific commission meetings to evaluate applications are clearly insufficient to meet the increasing demands for new product registration and approval. Therefore, it is suggested that the TITCK firstly maintain, if possible, a more stable structure of the agency, which is made known to the industry, and improve the communication and transparency between its different departments as well as between the agency and external stakeholders. It is also recommended to increase the frequency of commission meetings and establish specific committees with more frequent



meetings to handle urgent cases and specialized matters such the registration of life-saving products and evaluation of orphan drugs. Furthermore, the TITCK could reduce the registration review process inconsistencies across departments and the different commissions by implementing good review and decision-making practices with SOPs and assessment templates as well as minimising system complexities such as enabling the parallel review of GMP and separating the pricing process from the registration review to maintain the scientific evaluation.

Finally, it is recommended that the agency improve resource management by investing in staff training to ensure they are well organised and equipped with the required competencies, as well as trained and empowered in sufficient numbers within the agency to achieve the ultimate target of patients' access to medicines. This can be achieved by leveraging training, seminars and workshops to improve the experience of TITCK staff and collaborating more with industry associations, academia and international institutes to benefit from the overall available local knowledge as well as from the global experience of the pharmaceutical sciences and decision-making processes. In this way, the registration review process would be expedited resulting in faster approvals and enhanced patients' timely access to medicines.

## SUMMARY

- The pharmaceutical companies who participated in this study provided critical information on the regulatory review process and timelines of the TITCK.
- In general, companies were satisfied with the introduction of the electronic submission as well as with the tracking and tracing system. However, they emphasised that there are still opportunities for improvement at the TITCK in using more electronic and online services to expedite and facilitate communication with companies and enable follow-up of the application review.
- The majority of companies emphasised the communication challenge they face with the TITCK and therefore they indicated that poor communication with the agency at the different stages of the NDA application have major negative impacts on the review process and timelines as well as on transparency. Accordingly, they have suggested a number of improvements in this area and further collaboration with the industry.
- The participant companies were satisfied with the level of competencies and review abilities of the TITCK staff. However, they reported that the number of commissions and staff, mainly for those involved in the GMP and review process, should increase.
- The study confirmed that most of the pharmaceutical companies suffer from significant delays in obtaining marketing authorisation approval for their products and therefore access of patients to their products is prolonged compared with other developed countries. This is mainly due to several factors such as long GMP processes; increased number of questions asked by the TITCK outside of global requirements, constant changes in the TITCK organisational structure and commission members, pricing procedure and long laboratory analysis steps.
- Companies agreed that the implementation of a structured systematic decision-making approach and the use of a benefit-risk framework would be a possible way forward for the TITCK as it will result in an increased transparency, predictability and consistency within the registration process. In addition, it could enhance the scientific communication between the TITCK and the companies and promote improved communication with the stakeholders.

## **CHAPTER 6**

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# **PATIENTS' AWARENESS OF THE REGULATORY ENVIRONMENT AND ITS IMPACT ON THEIR ACCESS TO MEDICINES**

## **INTRODUCTION**

Patients' access to medicines is a major concern both for regulators as well as for the pharmaceutical industry. Currently it is estimated that two billion people worldwide still cannot access the medicines they need for their treatment mainly due to the increasing cost of healthcare expenditures (Access to Medicine Foundation, 2015). However, allocating the required resources for healthcare services and innovative medicines remains a common dilemma in many regions in the world particularly in low-income countries. The challenges in medicines' access are being constantly addressed by global health organisations, governments and all other related stakeholders including the pharmaceutical industry in order to improve access to healthcare and medicines (EFPIA, 2010). This becomes crucial, especially for life threatening diseases, where access to innovative medicines makes an important difference in patients' lives. Access to healthcare in Turkey has undergone dramatic changes in the past decade as a positive outcome of the economic growth and the "Health Transformation Programme" which was initiated in Turkey in 2002 (Akadagi, 2008). While, the reforms resulted in major developments in the pharmaceutical regulatory environment, which improved public access to health services, a number of measures were undertaken by the government to control the increasing healthcare budget, mainly pharmaceuticals to enable a sustainable financing source for a wider healthcare coverage in Turkey. (Tarmur, 2011). Furthermore, restricting healthcare expenditures will have a negative impact on patients' access to high quality healthcare and innovative medicines. Thus, there could be a different perception of public and patients of the recent developments in the pharmaceutical environment and as to whether they are in line with those worldwide. Yet, so far, no available data was able to illustrate the impact of such developments on patients' access to healthcare and the quality of available medication treatments. One of the key areas requiring investigation is to identify and assess the awareness of Turkish patients to those changes in the pharmaceutical regulatory environment and its impact on their access to innovative medicines in Turkey.

## **OBJECTIVES**

The objectives of this study were to:

- Identify public awareness and knowledge of the regulatory environment in Turkey.
- Evaluate the impact of the regulatory and reimbursement processes on patients' access to innovative medicines.

- Assess the patients' perspective of their role in the decision-making process for the approval and reimbursement of medicines.
- Identify patients' views of the barriers to accessing medicines and the possible solutions.

## **METHODS**

### **Study Design**

A comprehensive paper-based questionnaire was designed following discussion with patients and physicians regarding patients' knowledge and concerns about the regulatory environment. This questionnaire was then piloted by distributing to a group of patients to determine its acceptability and its content validation. It was designed to be complementary to the two other studies, which were to examine both the pharmaceutical companies' perspective as well as the TITCK perspective in relation to the regulatory environment in Turkey. The study was designed as a cross-sectional study, aimed at collecting data during a specific period of one month and included a total number of thirty questions to ensure a statistical standardisation and facilitate objective analysis and comparison. The questionnaire was designed in three parts;

1. General demographic details; i.e. age, gender, educational background,
2. Knowledge of the regulatory environment including the review and reimbursement processes in Turkey.
3. Key challenges and possible solutions regarding patients' access to medicines.

The study timeline was planned to be three months from the time of the first patient enrolment to final outcome report. The approximate time for patients to complete the questionnaire was estimated to be ten to fifteen minutes. The schematic design of the study is summarised in Figure 6.1. Each text box in the diagram represents a key milestone and contains study-specific information and the required activity for each step.

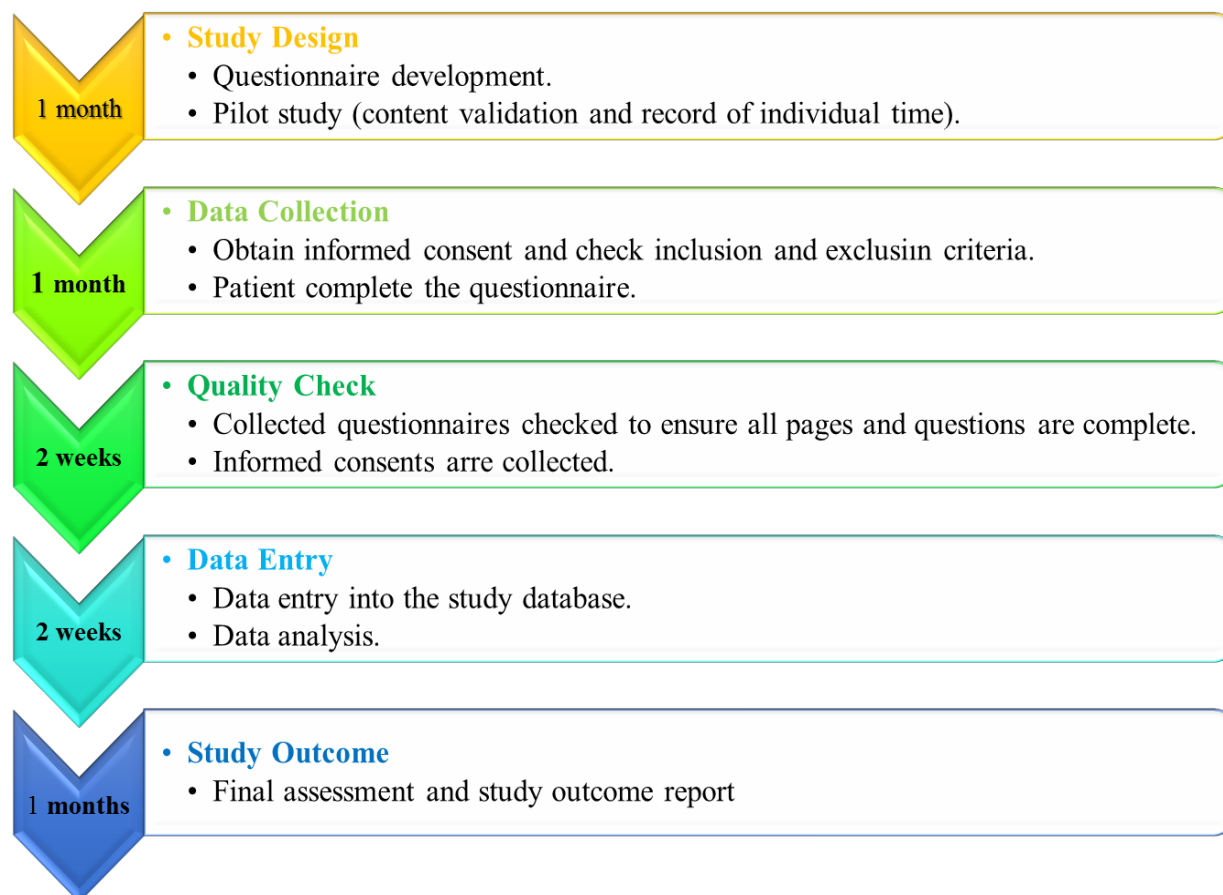
### **Development of the Questionnaire**

#### **Pilot study**

A pilot phase of one month for this study was designed with the aim of content validation to identify areas of improvements in the questionnaire in terms of wording, terminology, deletion and/or addition of questions to ensure that questions were clear and easy to understand. The questionnaire was translated from English to Turkish and back translated as

well as proof read to ensure quality of the translation. Thus, it was presented to patients in Turkish and the time required to complete the questionnaire was individually recorded.

**Figure 6.1: Schematic design of the questionnaire study**



Upon completion of the questionnaire, all participants were asked to provide input on the questions stated in Table 6.1. The pilot study was conducted with thirteen patients and five doctors as semi structured face-to-face interviews. Patients were selected with similar inclusion and exclusion criteria to the main study.

**Table 6.1: Pilot phase questions for content validation**

▪ In general how did you find the questionnaire?
▪ How do you evaluate the language of the questionnaire?
▪ Are there any questions which you found difficult to answer, and if so, which ones? Please state briefly why you think they were difficult?
▪ Are there any repetitive questions in the questionnaire?
▪ Are there any questions you think are not relevant?
▪ Are there any other questions you would like to add?

## Study Participants

### Main study

The questionnaire was designed to be distributed to outpatients who were under treatment with medicines in the following therapeutic areas: oncology, cardiovascular disease, diabetes, rheumatoid arthritis, central nervous system and hormonal disorders. The study took place in Istanbul, the largest city in Turkey with a population of approximately 14 million (January 2015) since it has the most representative demographic population in terms of ethnic groups, minorities, religion, cultural and educational background. Furthermore, the study population was targeted to cover equal representation of patients from the different demographic groups and the following factors were considered:

- Equal number of questionnaires to be distributed to both male and female participants.
- Questionnaires to be distributed to adults from various ages ( $\geq 18$ ).
- Equal number of questionnaires to be distributed to patients with different demographic and social groups (employed versus retired), and different educational backgrounds.

Participating in this study was voluntary. Patients were not compensated nor did they receive any payment for their participation. Yet, in order to be eligible to participate individuals had to meet all of the inclusion criteria (Table 6.2) and were asked first to read the patient information sheet (Figure 6.3) and accordingly sign and date an informed consent which includes a confidentiality declaration (Niles, 2006) (Figure 6.4).

**Table 6.2: Inclusion and exclusion criteria**

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"><li>• Adults aged 18 years old and above.</li><li>• Both genders, male or female.</li><li>• Currently under chronic disease treatment and / or have received treatments in Turkey.</li><li>• In good general mental and health status and capable to read, understand and complete the questionnaire.</li><li>• Provide a signed informed consent form.</li></ul>	<ul style="list-style-type: none"><li>• Those below 18 years old.</li><li>• Those not on medication treatment.</li><li>• Those not covered under the social security or any reimbursement system.</li><li>• Those with any medical condition that would prevent their participation in the study.</li></ul>

### Data Collection and Processing

The study was conducted in accordance with the local research requirements in Turkey. The validated paper copies of the questionnaire were distributed to patients' associations, clinics, pharmacies and family medicine clinics and were collected within one month.

Figure 6.2: Patient questionnaire

Patient Questionnaire	
Part I: General Questions	
1.	What is your illness /disease (s).....
2.	For how long you have been taking your medicines
3.	Do you know what medicines are you taking? <input type="checkbox"/> Yes <input type="checkbox"/> No
4.	If yes, can you name your medicines:.....
5.	Do you attempt to get information about these medicines (s) such as active substance, mode of action, usage, etc...? <input type="checkbox"/> Always <input type="checkbox"/> Sometimes <input type="checkbox"/> Rarely <input type="checkbox"/> Never
6.	Where do you get information about your medicines? (Please tick (X) all that apply) <input type="checkbox"/> My doctor <input type="checkbox"/> Pharmacist <input type="checkbox"/> Nurse <input type="checkbox"/> Insert leaflet <input type="checkbox"/> Internet <input type="checkbox"/> Other sources.....
7.	How useful is the information you receive regarding your medicine (s)? <input type="checkbox"/> Very useful <input type="checkbox"/> Useful <input type="checkbox"/> Not useful
8.	Do you get sufficient information about the benefits and harms of the medicines that you are taking? <input type="checkbox"/> Yes <input type="checkbox"/> No
9.	Do you always take your medicines as directed? <input type="checkbox"/> Always <input type="checkbox"/> Sometimes <input type="checkbox"/> Rarely
10.	If you have an adverse reaction from your medicine, do you think you should report it? <input type="checkbox"/> Yes <input type="checkbox"/> No
11.	If yes, to whom do you report it? (Please tick (X) all that apply) <input type="checkbox"/> To my doctor <input type="checkbox"/> To the pharmacist <input type="checkbox"/> To the Turkish Pharmacovigilance Centre as stated in the leaflet
Part II: Knowledge on Regulatory environment & access to innovative medicines	
12.	Do medicines in Turkey need to be approved by the government? <input type="checkbox"/> Yes <input type="checkbox"/> No
13.	Are you aware about how the government approves the marketing of medicines in Turkey? <input type="checkbox"/> Yes <input type="checkbox"/> No
14.	In your opinion, do you think that there are novel alternative medicines for your disease available in other counties? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> I don't know
15.	If yes, where do you think they are available in (Please tick (X) all that apply) <input type="checkbox"/> EU <input type="checkbox"/> USA <input type="checkbox"/> other, please name:.....

Emel Mashaki, 01.08.2015

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**16. When do you think new medicines become available in Turkey**

- ☐ Later than developed countries such as the USA & EU  
☐ Similar to developed countries  
☐ Earlier than developed countries  
☐ I don't know

**17. How would you describe the Turkish government's standards to approve new medicines compared to those implemented internationally? (e.g. EU, US)**

- ☐ Higher standards    ☐ Similar standards    ☐ Lower standards    ☐ I don't know

**18. How long do you think it takes the government to approve a new medicine?**

- ☐ <6 months    ☐ 12 months    ☐ 24 months or longer    ☐ I don't know

**19. Who pays for the medicines in Turkey within the social security system?**

- ☐ Government pays most  
☐ Patient pays most  
☐ 50% patient and 50% government  
☐ Other, please state:.....  
☐ I don't know.

**20. Are you satisfied with the current system of the government paying for medicines?**

- ☐ Not Satisfied    ☐ Satisfied    ☐ Highly Satisfied    ☐ Not sure

**Part III: Key issues in access to innovative medicines**

**21. How would you rate your access to medicines in Turkey?**

- ☐ Excellent  
☐ Good  
☐ Satisfactory  
☐ Poor

**22. Do you think that the government provides enough information about new marketed medicines?**

- ☐ Yes    ☐ No    ☐ I don't know

**23. What do you think are the major challenges facing the government in providing new marketed medicines (Please tick (X) all that apply)**

**Challenges**

- ☐ Lack of government resources  
☐ Lack of scientific expertise at government  
☐ Cost of new medicines is high  
☐ Pharmaceutical companies pricing policies  
☐ The patients' needs not taken into account  
☐ Other, please name:.....  
☐ I have no information

**24. How do you see the current role of patients in the decision-making process of the government for approving new medicines by the government in Turkey?**

- ☐ Excellent, patients have an active role

- ☐ Satisfactory, patients sometimes have a role
- ☐ Poor, patients rarely play a role
- ☐ Patients have no role at all, as it is all decided by government

**25. How do you see the current role of patients in the decision-making process of the government for paying for new medicines by the government in Turkey?**

- ☐ Excellent, patients have an active role
- ☐ Satisfactory, patients sometimes have a role
- ☐ Poor, patients rarely play a role
- ☐ Patients have no role at all, as it is all decided by government

**26. Do you think as a patient you should have a role in informing which medicines need to be approved by the government?**

- ☐ Yes                      ☐ No

If yes, please explain in what way:.....  
 .....  
 .....

**27. Do you think as a patient you should have a role in informing which medicines need to be paid for by the government?**

- ☐ Yes                      ☐ No

If yes, please explain in what way:.....  
 .....  
 .....

**28. Please describe the three most important improvements in obtaining the medicines you need that you have experienced as a patient in Turkey in the last years?**

1. ....
2. ....
3. ....

**29. Can you describe the three most important barriers you face in obtaining the medicines you need and the possible solutions?**

Barriers	Possible solutions
1.	1.
2.	2.
3.	3.

30. Do you have any further comments or details you would like to share in this questionnaire?

.....

.....

.....

**Thank You for completing this questionnaire,**

-----

**Please kindly complete, sign and date the below box**

<b>Age:</b>	<b>Gender:</b>	<input type="checkbox"/> Male	<input type="checkbox"/> Female
<b>Education;</b>	<input type="checkbox"/> below high school	<input type="checkbox"/> High school	<input type="checkbox"/> University <input type="checkbox"/> Postgraduate
<b>Profession;</b>	<input type="checkbox"/> Retired	<input type="checkbox"/> Working	<input type="checkbox"/> other
<b>Date:</b>	<b>Place:</b>		

Please return by e-mail to Emel Mashaki [Mashakie@cf.ac.UK](mailto:Mashakie@cf.ac.UK) Centre for Innovation in Regulatory Science no later than 21<sup>st</sup> of September 2015.

Figure 6.3: Patient information sheet

<p align="center"><b>“EVALUATION OF THE REGULATORY REVIEW PROCESS AND TIMELINES IN TURKEY AND ITS IMPACT ON PATIENTS’ ACCESS TO INNOVATIVE MEDICINES” PUBLIC PERSPECTIVE QUESTIONNAIRE STUDY</b></p>	
<p><b>Participant Information Sheet</b></p>	
<p><b>Dear Participant</b></p>	<p><b>Date:</b></p>
<p>You are being invited to participate in this questionnaire study which is part of a PhD research project in association with Cardiff University in the UK. The title of the study is: <i>Evaluation of the regulatory review process and timelines in Turkey and its impact on patients’ access to innovative medicines</i>.</p>	
<p><b>Purpose of the study:</b></p>	
<p>The aim of the study is to evaluate the Turkish regulatory environment and the current situation of Turkey’s healthcare access to medicines. Moreover, the study aims to understand the perception of patients in relation to recent regulatory changes and the impact of such changes on patients’ access to innovative treatments. The study is being conducted in collaboration with the Centre of Innovation for Regulatory Science (CIRS) in the UK. This questionnaire is designed to be complementary to two other projects involving pharmaceutical companies operating in Turkey and the Turkish Pharmaceuticals and Medical Device Agency (TITCK).</p>	
<p><b>Why you were selected?</b></p>	
<p>You were selected as a possible participant from 350 other participating patients because you are an adult out-patient who is currently under medication treatment and/or have an experience with regard to your access to medicines in Turkey.</p>	
<p><b>What are the possible benefits and risks of participating?</b></p>	
<p>Participating in this questionnaire is voluntarily. There are no known disadvantages or costs whether you participate or not in this study. You may not benefit directly from this study but the information obtained will make a scientific contribution to the healthcare system in Turkey. The outcome report from this study will provide benefits to the public and enhance the role of patients in the decision-making process to approve and ensure access to innovative medicines.</p>	
<p>You and your answers will not be identified, and no one will know whether or not you participated in the study. Once the study is completed, data might be published but no individual</p>	
<p align="right">Page 1 of 7</p>	

information will be disclosed and the information you provide will be treated and kept strictly confidential. A final report of the study can be mailed to you, should you require it.

### **What do you need to do?**

If you choose to participate in this project, you are kindly asked to complete the questionnaire which will take only about 10 – 15 minutes. You are free to withdraw from the study or not to answer any particular question for any reason. This study is anonymous so please do not write your name on the questionnaire. Please make sure to read carefully the informed consent attached and sign it before you start completing the questionnaire. Please answer all questions as honestly as possible - there are no correct or wrong answers. Please return the completed questionnaire and the signed consent form by e-mail or as paper copy to your association, your health care professional or your clinic who initially provided you with this copy.

### **Who to contact for questions or additional information?**

If you need any additional information or have questions, please contact us at the number listed below. If you would like a summary copy of the outcome report please state your request at the end of the questionnaire.

Thank you for participating

Sincerely,

Emel Mashaki

### **Contact details**

Name: Emel Mashaki Institution Name: University of Cardiff Address: Istanbul – Turkey Phone Number: +90 532 296 88 85 e-mail: <a href="mailto:Mashakie@cf.ac.UK">Mashakie@cf.ac.UK</a>	Name: Professor Stuart Walker Institution Name: CIRS & the University of Cardiff Address: London – UK Phone Number: +44 20 8395 54 74 e-mail: <a href="mailto:swalker@cirsci.org">swalker@cirsci.org</a>
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**Figure 6.4: Informed consent**

Patient Consent Form		
<b>Consent Form number:</b> TR-02 version 6.0:.....		
<b>Title of Project:</b> Evaluation of the regulatory review process and timelines in turkey and its impact on patients' access to innovative medicines - patient perspective questionnaire study.		
<b>Name of researcher:</b> Emel Mashaki Ceyhan		
<input type="checkbox"/> I confirm that I have read the information sheet dated 19 July 2015 version 6.0 for the above study. I have had the opportunity to consider the information provided, ask questions and have had these answered satisfactorily.		
<input type="checkbox"/> I understand that my participation is voluntary and I am free to withdraw at any time from the study or not to answer any particular question for any reason.		
<input type="checkbox"/> I understand that the information collected about me will be used to support this study and may be shared anonymously to be complementary to two other projects involving pharmaceutical companies operating in Turkey and the Turkish Pharmaceuticals and Medical Device Agency (TITCK).		
<input type="checkbox"/> I understand that a final report of the study will be generated from the data collected.		
<input type="checkbox"/> I agree to take part in the above study.		
Name / Family Name of Participant	Date	Signature

Emel Mashaki, 01.08.2015

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## **Hypotheses**

The Turkish healthcare system has undergone significant change since the implementation of the Health Reform Programme in 2003 to enhance access to healthcare in all aspects. For example; through the different social security schemes provided by the government, the health insurance coverage of the Turkish population increased to 87% compared to 64% in 2003 (OECD, 2015). As a result, patients in Turkey have increased access today to the various healthcare services including medicines. Furthermore, Turkish patients have a considerable amount of interest in general health issues and treatments and it is identified that on average each patient visits physicians eight times a year, which is more frequently than in other peer countries (OECD, 2014). However, patients' awareness about the pharmaceutical regulatory environment as well as the decision-making processes of the regulatory bodies seems not to get the same level of attention in Turkey. Thus, the general perception is that the role of patients or patients' organisations in informing which medicines need to be approved or paid for by the government is not as active compared to other countries (Noordman, et al., 2010).

This study examined the following hypotheses,

1. Patients have considerable interest in their treatment and medicines.
2. Patients have little knowledge and understanding of the regulatory review and reimbursement processes.
3. The perception of patients is that the Turkish healthcare system is not comparable to other developed countries.
4. Patients in Turkey are not satisfied with their access to innovative medicines.
5. Patients have little interest in being directly involved in decision-making with respect to the regulatory review and reimbursement processes.

## **RESULTS:**

This study was designed to identify the awareness of Turkish patients in relation to the pharmaceutical regulatory environment, the approval, reimbursement and decision-making processes regarding new medicines and the impact of such changes on patients' access to medicines.

## Pilot Study

The questionnaire was piloted among thirteen patients who were adults under active chronic disease treatment for more than five years and four doctors of different specialties (Table 6.3).

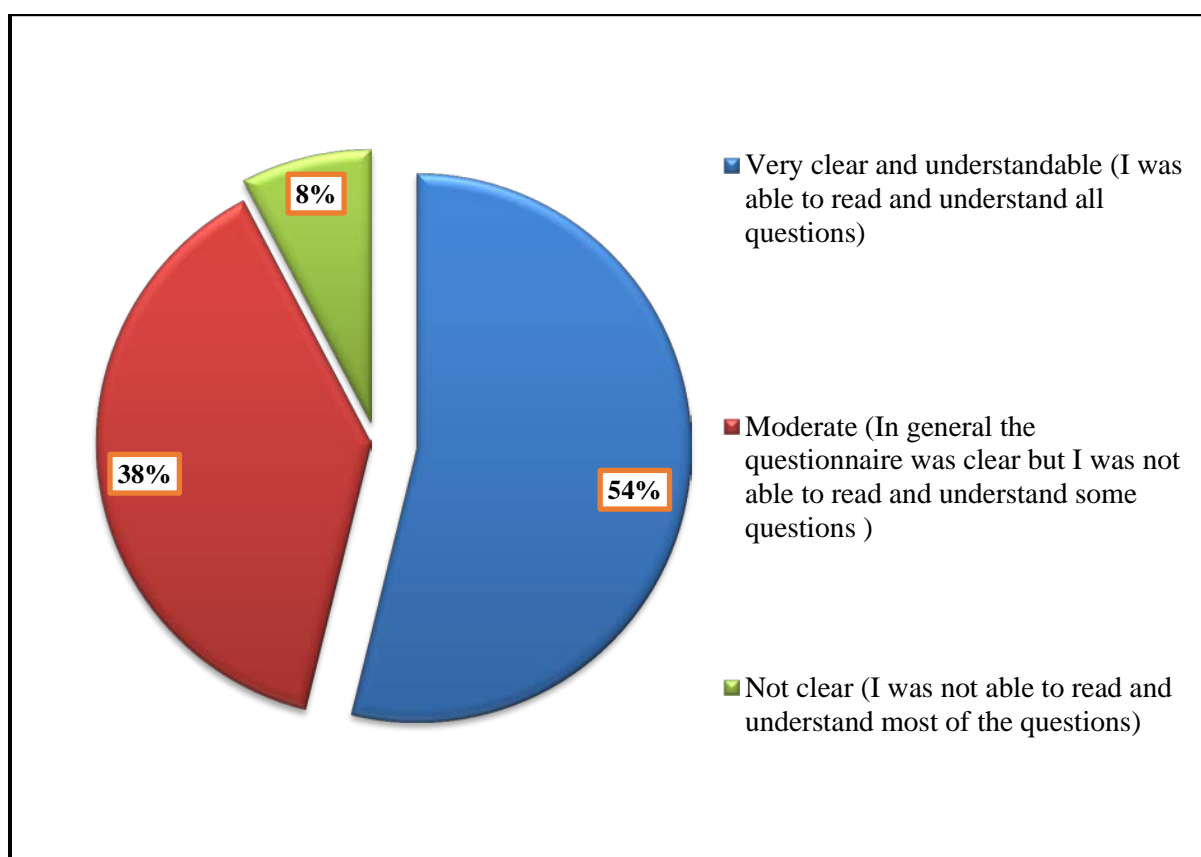
**Table 6.3: Participants' demographic and therapeutic area distribution for pilot study**

Demographic Characteristics	Doctors (n=4)	Patients (n=13)
<b>Gender</b>		
Male	50%	46%
Female	50%	54%
<b>Age</b>		
Median	44	65
Mean	45	62
<b>Education</b>		
Primary School	N/A	0%
High School	N/A	46%
Graduate	N/A	38%
Postgraduate	100%	15%
<b>Therapeutic Area / Disease</b>		
Endocrinology / Diabetes	25%	38%
Cardiovascular	25%	31%
Central Nervous System	N/A	15%
Oncology / Cancer	25%	15%
Family Medicine	25%	N/A

The inputs and recommendations provided by the patients and physicians in the pilot phase were then gathered and analysed collectively. As a result, in general patients found the questionnaire relatively easy to read and understand (Figure 6.5) and appreciated their enrolment in the content validation of such a questionnaire where they have stated that it increased their awareness in relation to the regulatory environment in Turkey. Accordingly, some patients suggested adding a specific question to evaluate the role of patients in the regulatory review and reimbursement processes of medicines in Turkey.



**Figure 6.5: Patients' evaluation of the questionnaires' language**



Additionally, 38% (n=5) of the patients stated they had difficulty in understanding some words and terminologies used in the questionnaire such as; *reimbursement*, *regulatory review*, *registration approval* and suggested that these words to be simplified. Patients were hesitant to answer the question related to the improvements in health care system in Turkey since 2012 and thus suggested that this question should not be limited to a specific period.

The inputs received from the physicians who participated in the pilot phase were very much aligned with the patients' comments and thus emphasised the importance of reviewing the questionnaire again to simplify the wording and ensure that it is patient friendly and easy to read and understand. In the light of the above, the questionnaire was modified and updated to incorporate all the received comments and suggestions, where some questions from the questionnaire were deleted, some were merged and others were added and modified as per the inputs to ensure the readiness of the questionnaire for the main study (Table 6.4).

**Table 6.4: Questionnaire modifications as a result of the pilot study**

Question		Change
Pilot Study	Main Study	
One page cover letter	Two pages ‘Patient Information Sheet’	Added with more details for patients
N/A	Question 9: <i>Do you always take your medicines as directed?</i>	Question added
Q.12: ... <i>registered</i> by the government?	Q.12: ... <i>approved</i> by the government?	Word simplified
Q.13: ... <i>how government’s registration process of medicines</i>	Q.13: <i>how government approves the marketing of medicines</i>	Sentence simplified
Q.14: ... <i>novel</i> alternative medicines	Q.14: <i>innovative</i> medicines	Word simplified
Q.16: <i>Are you aware of how medicines are reimbursed ...</i>	N/A	Question deleted and merged with question 17
Q.23: Five multiple choices	Q.23: Seven multiple choices	Choices added: <input type="checkbox"/> <b>Other, please name</b> <input type="checkbox"/> <b>I have no information</b>
N/A	Q.26 and Q.27 ‘... <i>role of patients in informing which medicines need to be approved / paid by...</i>	Question 26 and 27 added
Q.28: ... <i>three most important enhancements since 2012 in obtaining...</i>	Q.28: ... <i>three most important improvements in obtaining..</i>	Question modified
N/A	Q.30: <i>Do you have any further comments...</i>	Question added

## Main Study

### Characteristics of study participants

A total number of three hundred and fifty questionnaires were distributed as paper copies to outpatients in ten clinics and twelve pharmacies in Istanbul. Additionally, face-to-face interviews were conducted with twenty-two patients while asking them to complete the questionnaire. Adult patients of both genders, on chronic disease treatment for more than five years were selected to participate voluntarily to conduct a face-to-face interview and were encouraged to share their inputs and experiences regarding the study. By the end of the study period, two hundred and ten patients completed the questionnaire and thus a response rate of 60% was achieved among which 10% was interviewed face to face. Moreover, the results demonstrated a balanced representation of patient population in terms of demographic characteristics and background as shown in Table 6.5. Seventy four percent of patients

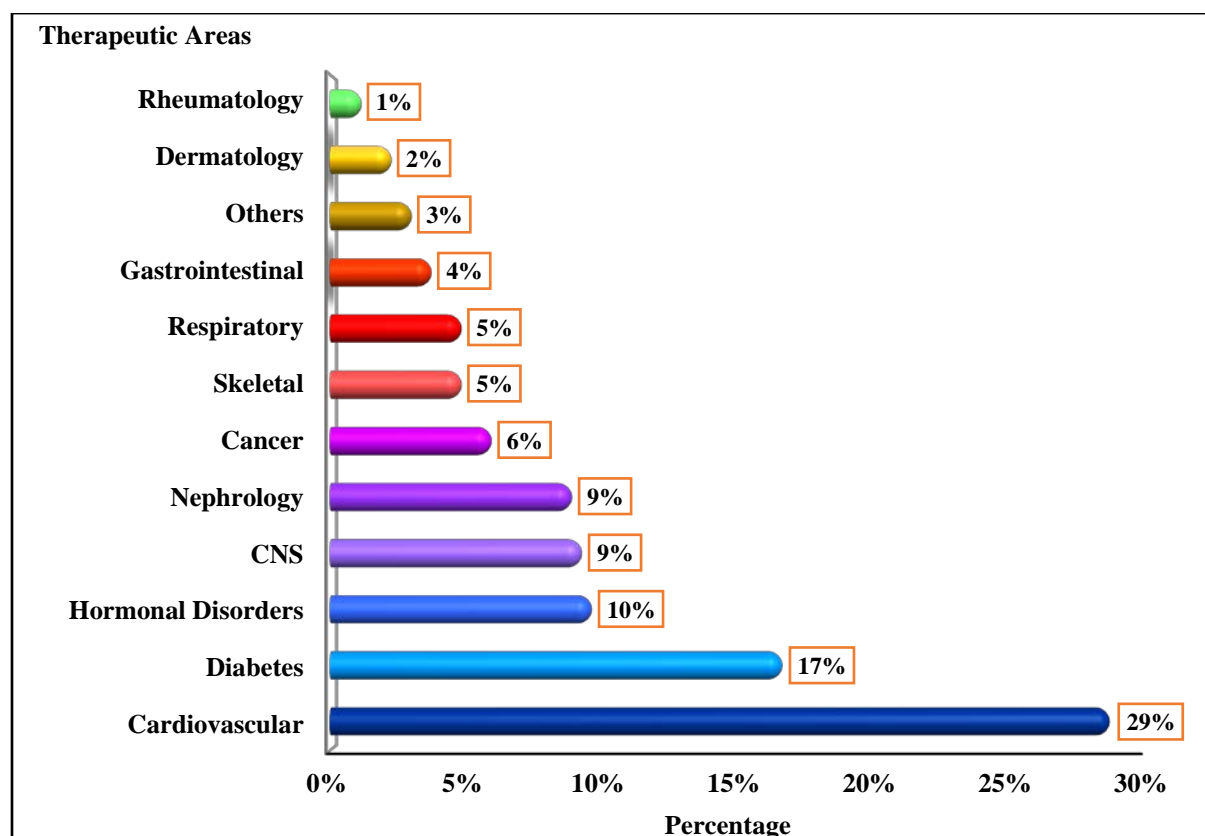
(n=155) were on medication for various chronic diseases from six disease areas namely (80%): cardiovascular, diabetes, hormonal disorder, CNS, nephrology and cancer (Figure 6.6).

**Table 6.5: Characteristics of study patients**

Demographic Characteristics (n = 210)	Background and Status (n = 210)
<ul style="list-style-type: none"> <li>• <b>Gender</b> <ul style="list-style-type: none"> <li>Male 51%</li> <li>Female 49%</li> </ul> </li> <li>• <b>Age</b> <ul style="list-style-type: none"> <li>Median 54 years</li> <li>Mean 56 years</li> </ul> </li> <li>• <b>Age Range*</b> <ul style="list-style-type: none"> <li>Early Adulthood (18-39) 55 %</li> <li>Adulthood / Middle Age (40-64) 19 %</li> <li>Maturity (<math>\geq 65</math>) 26 %</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• <b>Education</b> <ul style="list-style-type: none"> <li>Primary School 25 %</li> <li>High School 31 %</li> <li>Graduate 37 %</li> <li>Postgraduate 8 %</li> </ul> </li> <li>• <b>Working status</b> <ul style="list-style-type: none"> <li>Retired 50 %</li> <li>Working 34 %</li> <li>Other, (<i>part time, freelance, etc...</i>) 16 %</li> </ul> </li> </ul>

\*Stages of Social-Emotional Development (Erikson, 2015)

**Figure 6.6: Percentage of patients relevant to their therapeutic areas treatment**



Out of the two hundred and ten participants, 77% (n=162) of the patients had a single disease while the rest of the patients had multiple diseases for which they were receiving various medications. Results showed that 55% (n=115) of patients were on chronic disease treatment for three to ten years and 20% (n=42) for more than ten years.

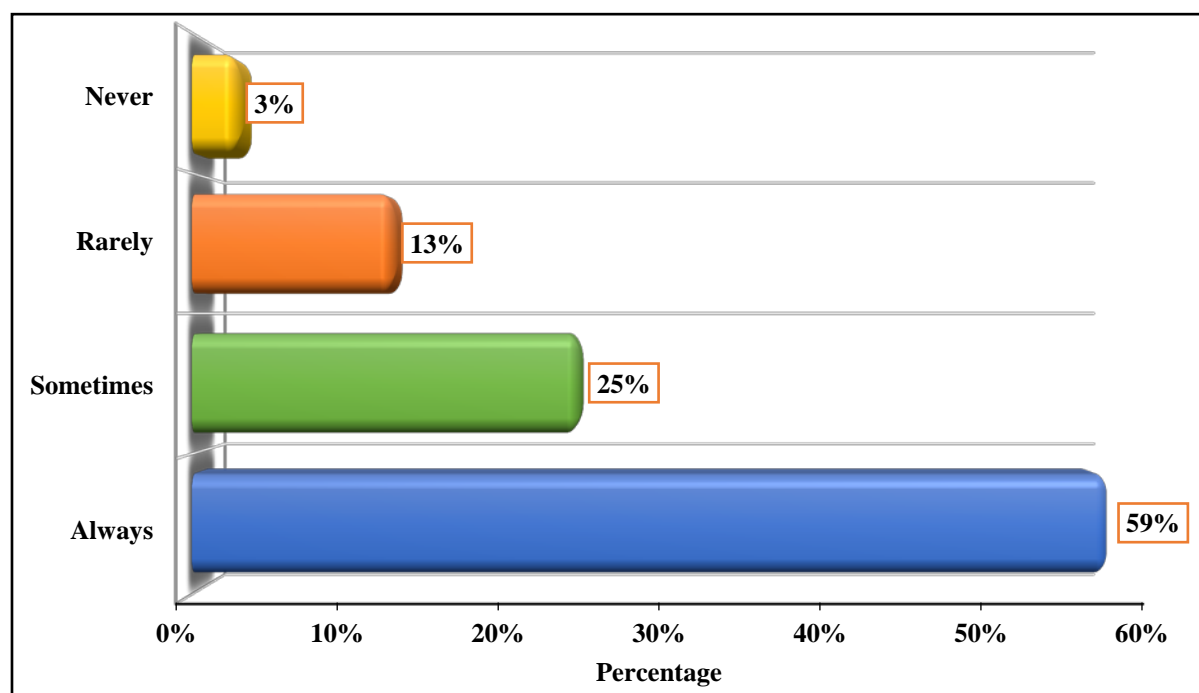
The key results of the main study are presented in four parts:

1. Patients' awareness and knowledge of their medicines.
2. Patients' perception and knowledge of the regulatory and reimbursement environment and access to medicines.
3. Role of patients in the regulatory review and reimbursement processes.
4. Challenges and possible solutions to improve access to medicines.

### **Part 1: Patients' awareness and knowledge of their medicines.**

This study identified that 98% (n=206) of patients on chronic disease treatment were able to define their medical condition in general and knew about their medicines they take. In addition, 59% (n=124) of patients indicated that they always attempt to learn about their medicines from the various available sources (Figure 6.7) with 70% (n=124) of patients believe they get sufficient useful information from these sources about their medicines' benefits and harms.

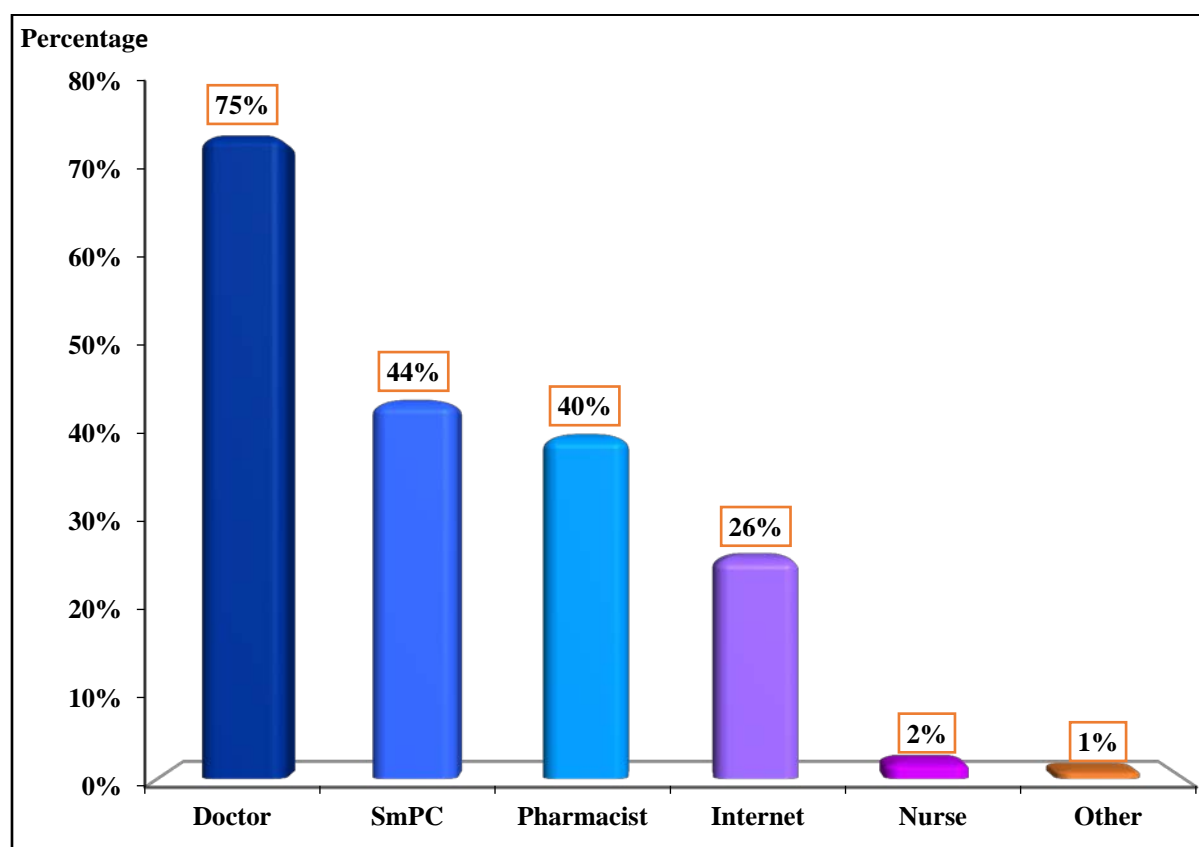
**Figure 6.7: Patients' attempt to obtain information about their medicines**



Accordingly, patients generally rely on their doctors to obtain information about their medicines. Pharmacists and the summary of the product characteristics (SmPC) are the secondary sources. Furthermore, 41% (n=86) of the patients stated that they rely on one source to get information about their medicines, while 59% (n=124) stated that they rely on several sources to learn more about their medicines, such as the summary of the product characteristics (SmPC), internet and pharmacists (Figure 6.8).

While 67% (n=140) of patients declared that they get sufficient information about the benefits and harms of their medicines, 62% (n=130) of patients stated that the information they obtain about their medicines is very useful. Additionally, 85% (n=179) of patients indicated that they do recognise the importance of treatment compliance and therefore expressed that they are compliant in taking their treatments as directed.

**Figure 6.8: Sources of patients to obtain information about their medicines**

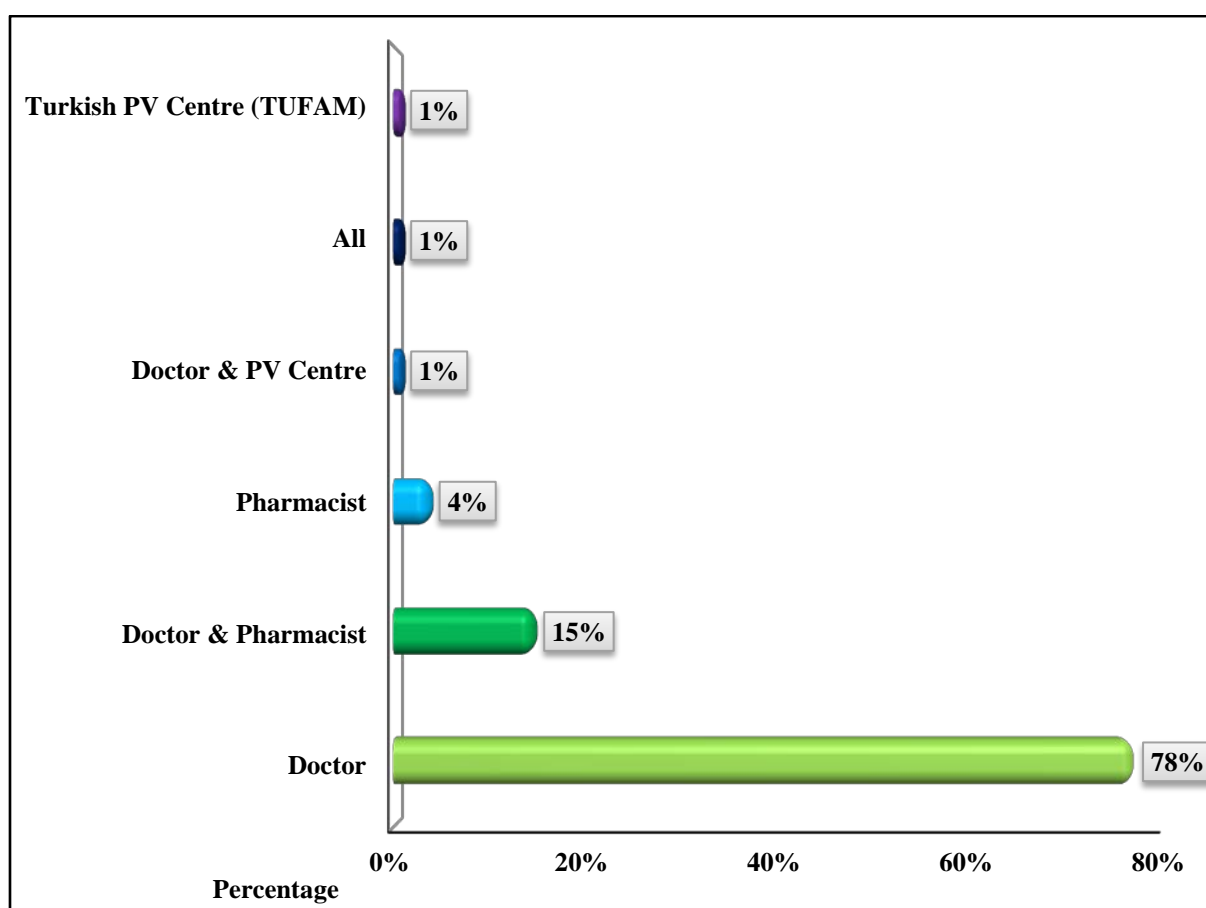


### Reporting of adverse events

Pharmacovigilance and patient safety are important healthcare issues in all countries, regardless of the development criteria. There are very limited data, staff notes, or research

related to the reporting of adverse events by patients in Turkey. The culture and awareness of patients in reporting adverse events and pharmacovigilance cases was also evaluated in this study. Surprisingly, a high proportion of patients (91% (n=191) stated that they are keen to report adverse events with 78% (n=164) reporting directly to their physicians (Figure 6.9).

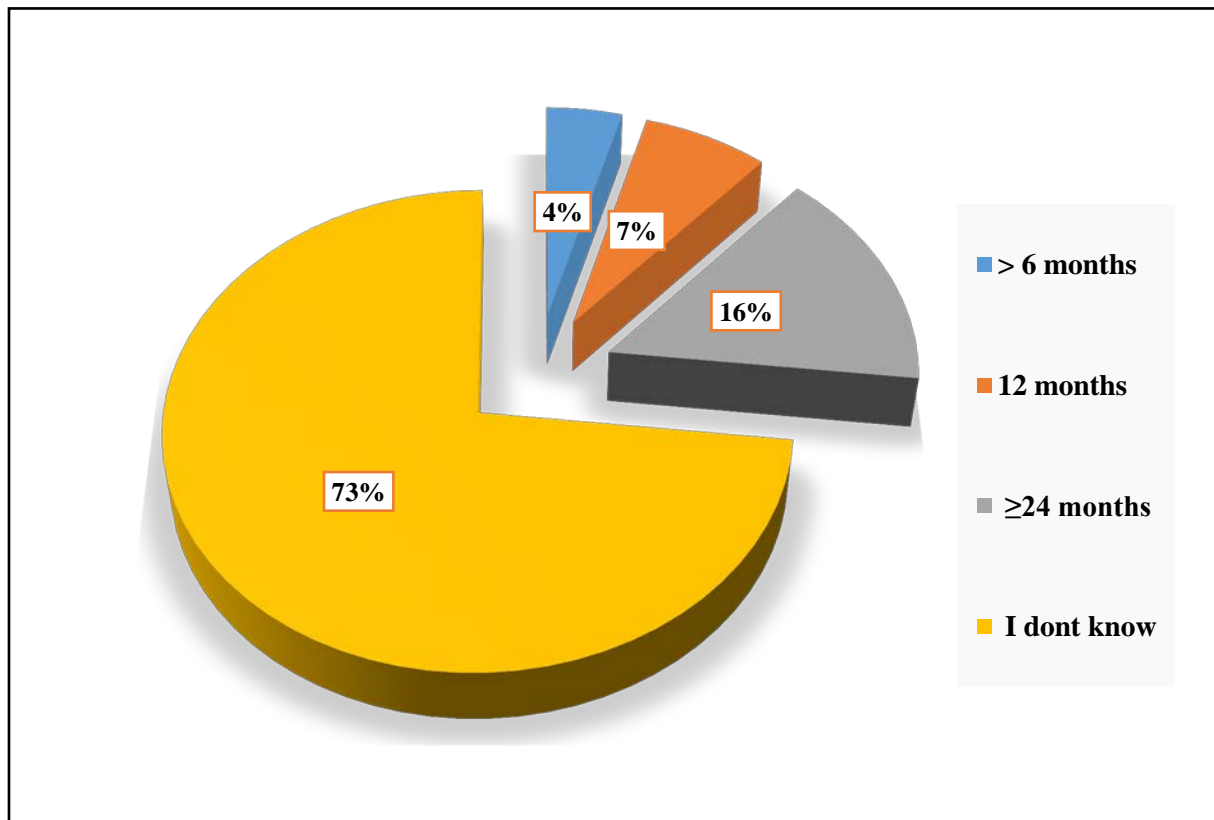
**Figure 6.9: Reporting of adverse events by patients**



## **Part 2: Patients' perception and knowledge of the regulatory and reimbursement environment and access to medicines.**

This study identified that the majority of patients demonstrated a good knowledge of the pharmaceutical regulatory environment and the registration review and reimbursement processes. Although 84% (n=177) of patients knew that medicines had to be approved by the government, yet 81% (n=170) of patients stated that they are not aware of the details of the regulatory review process with the overall majority (73%, n=153) unaware of how long it takes the government to approve a new medicine (Figure 6.10).

**Figure 6.10: Patients' knowledge of the government's timelines to approve a new medicine**

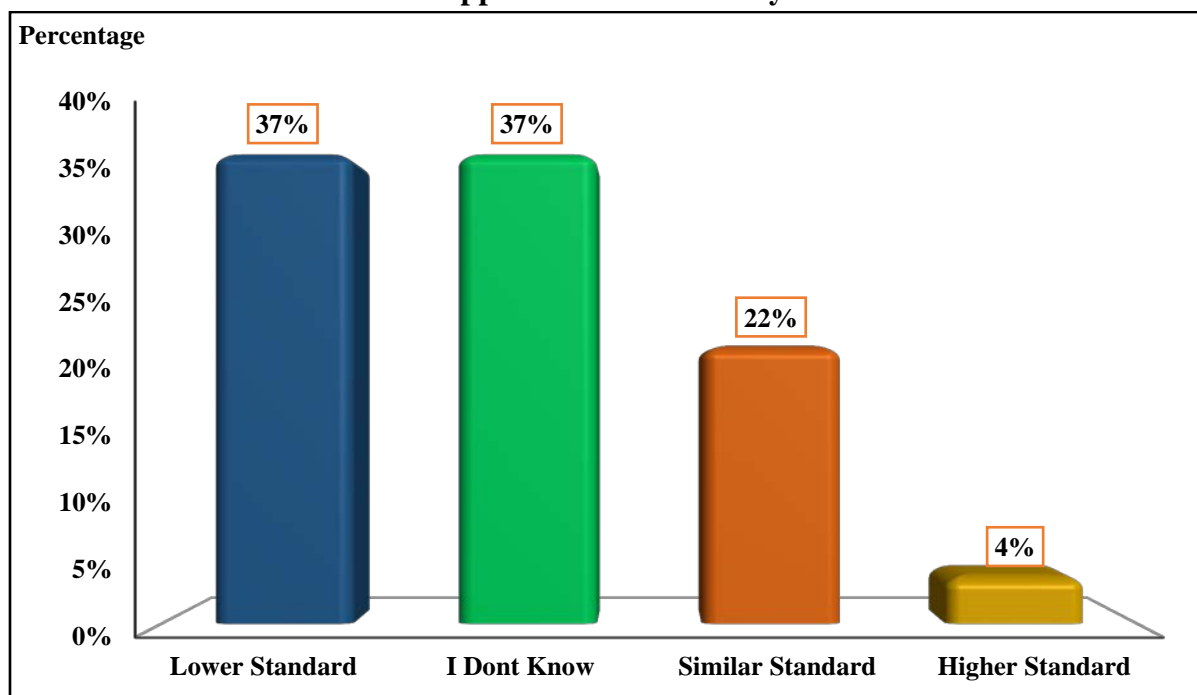


Twenty-three patients (11%) believed that the government took between up to twelve months to approve a new medicine, whereas 16% (n=34) thought that it was more than two years. This coincides with the industry experience of between two to three years (Figure 5.13).

### **Standard of Approval**

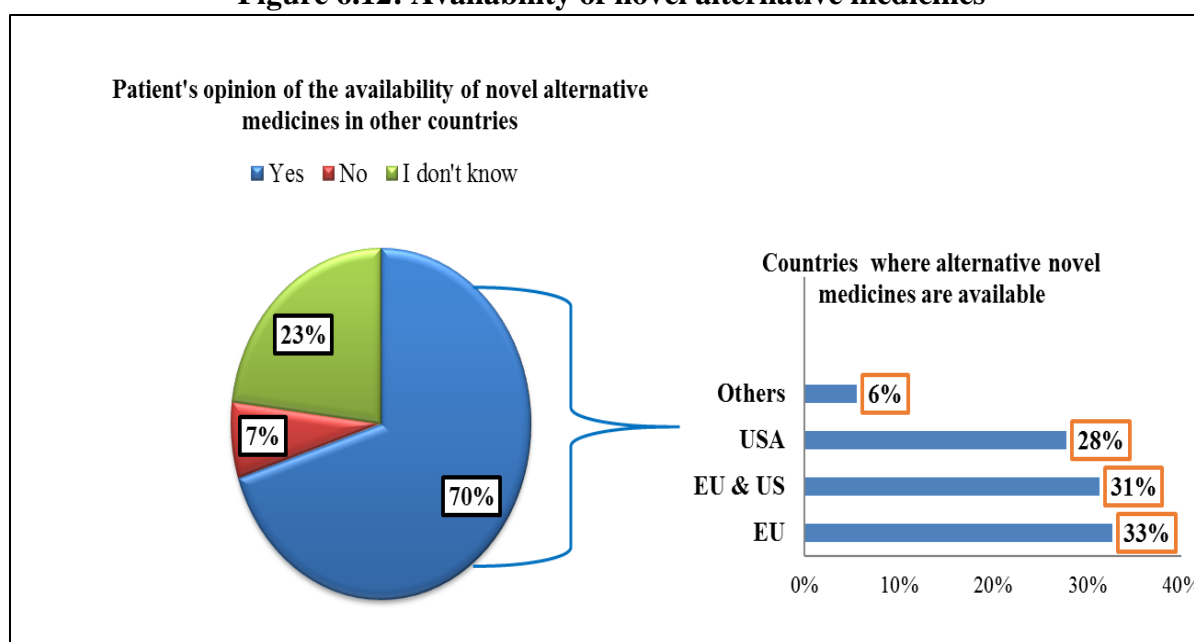
The standard of the regulatory approval process and access to medicines is critical for the health of a nation. As agreed at the European Council in December 2004, accession negotiations for Turkey as a candidate country was launched on October 3, 2005 and therefore similar to many other regulated industries in Turkey, the pharmaceutical requirements and standards have undergone a number of developments to establish an alignment with those of the European Union and enhance the standards of requirements and process (Ministry for EU Affairs, 2016). However, 37% (n=70) of patients believed that the Turkish approval process to be of a lower standard compared to United States and Europe, whereas 25% (n=52) thought that it was of a similar or a higher standard (Figure 6.11).

**Figure 6.11: Patients' perception of government's standards compared to medicines approved internationally**



A significant proportion of patients (60% n=126) thought that new medicines only become available in Turkey after other developed countries, whereas, 70% (n=147) were under the impression that there are novel alternative medicines for their disease available in other developed countries mainly in the USA (49%) and the EU (44%) (Figure 6.12).

**Figure 6.12: Availability of novel alternative medicines**

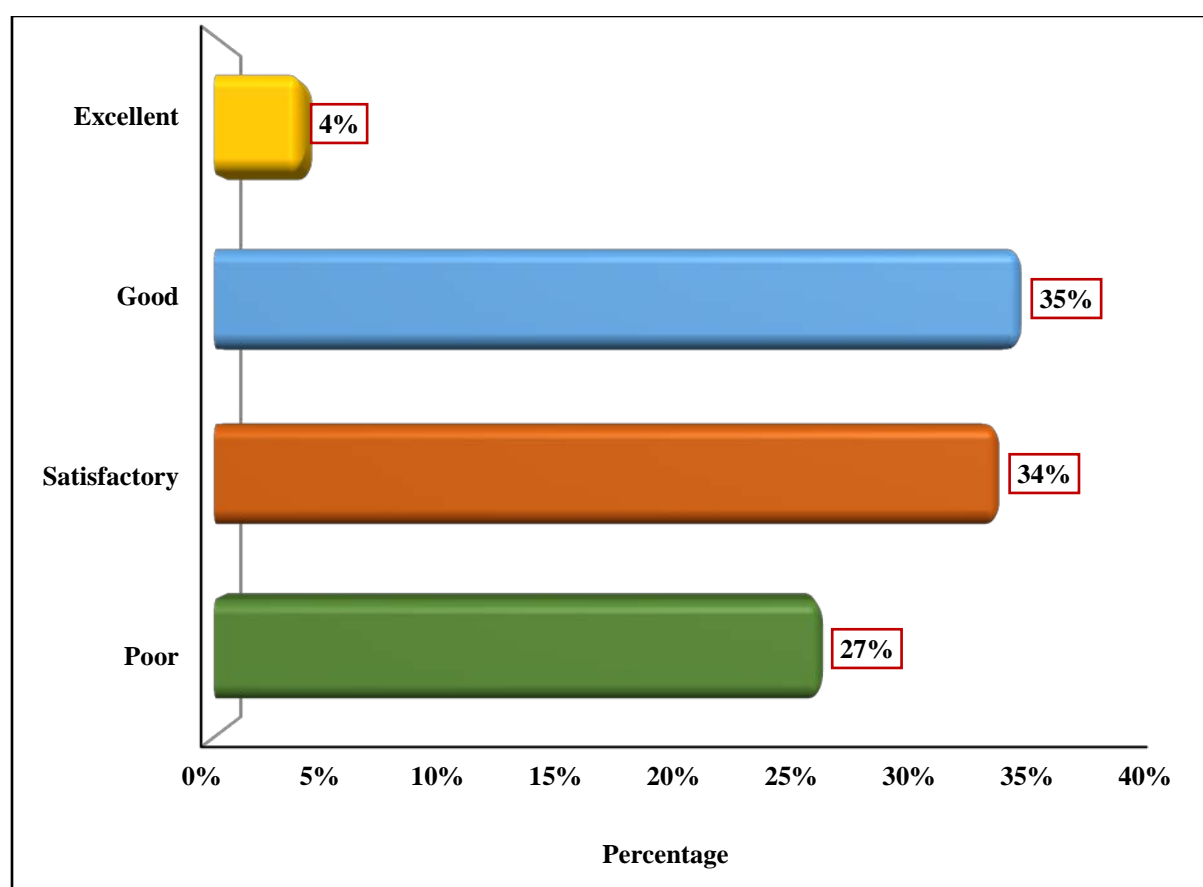




## Reimbursement and Access to Medicines

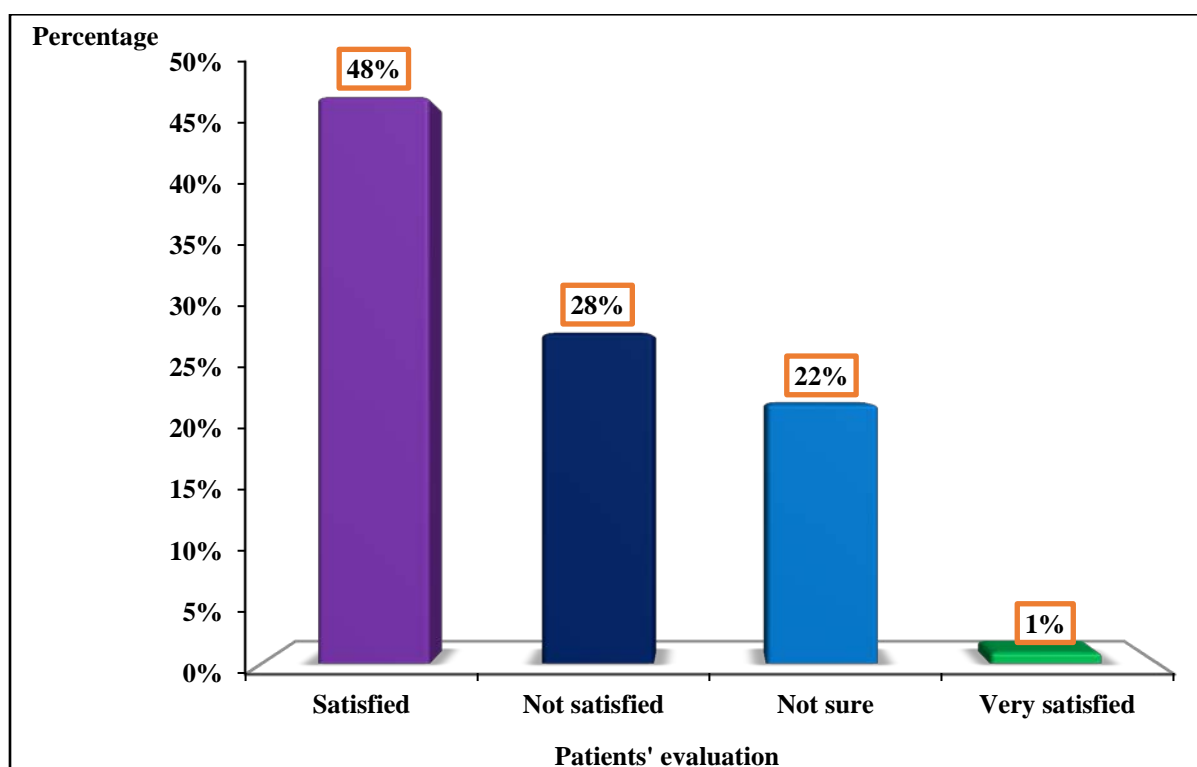
Although a key step in patients' access to medicines is having the product registered and licensed by regulatory authorities, nevertheless, with the current economic climate and controls on healthcare expenditure, reimbursement is becoming the determining milestone of access to medicines. The results indicate that 39% (n=82) of patients rated their access to medicines as excellent or good whereas 34% (n=71) stated that they were satisfied with the availability of their medicines, while 27% (n=57) rated their access as poor (Figure 6.13).

**Figure 6.13: Patients' assessment of their access to medicines**



This study demonstrated that patients in Turkey knew more about the reimbursement system compared to the review process, where the majority of patients 75% (n=157) recognised that the government is the main payer, even though insufficient information is provided about new medicines. Almost half (49%) of the patients involved in this study stated that they were satisfied or very satisfied with the reimbursement system with 34% (n=72) describing access to new medicines as adequate in Turkey. However, 28% (n=59) stated that they were not satisfied and 22% (n=46) indicated that they were unsure (Figure 6.14).

**Figure 6.14: Patients' evaluation of the reimbursement system**



### **Part 3: Role of patients in the regulatory review and reimbursement processes.**

Currently the role and responsibility of patients and patients' advocacy groups in the decision-making process of approving new medicines is becoming a high priority for all stakeholders including the pharmaceutical industry, the regulatory authorities and health technology assessment agencies (HTA) as well as payers. However, this study demonstrated that 71% (n=149) of patients stated that they do not have any role in the decision-making process for approving new medicines while 72% (n=151) stated that they do not have any role in the reimbursement process. Therefore, most of them indicated that they needed to be more involved in reimbursement 60% (n=126) as well as in the approval process 58% (n=122).

### **Part 4: Challenges and Possible Solutions to Improve Access to Medicines**

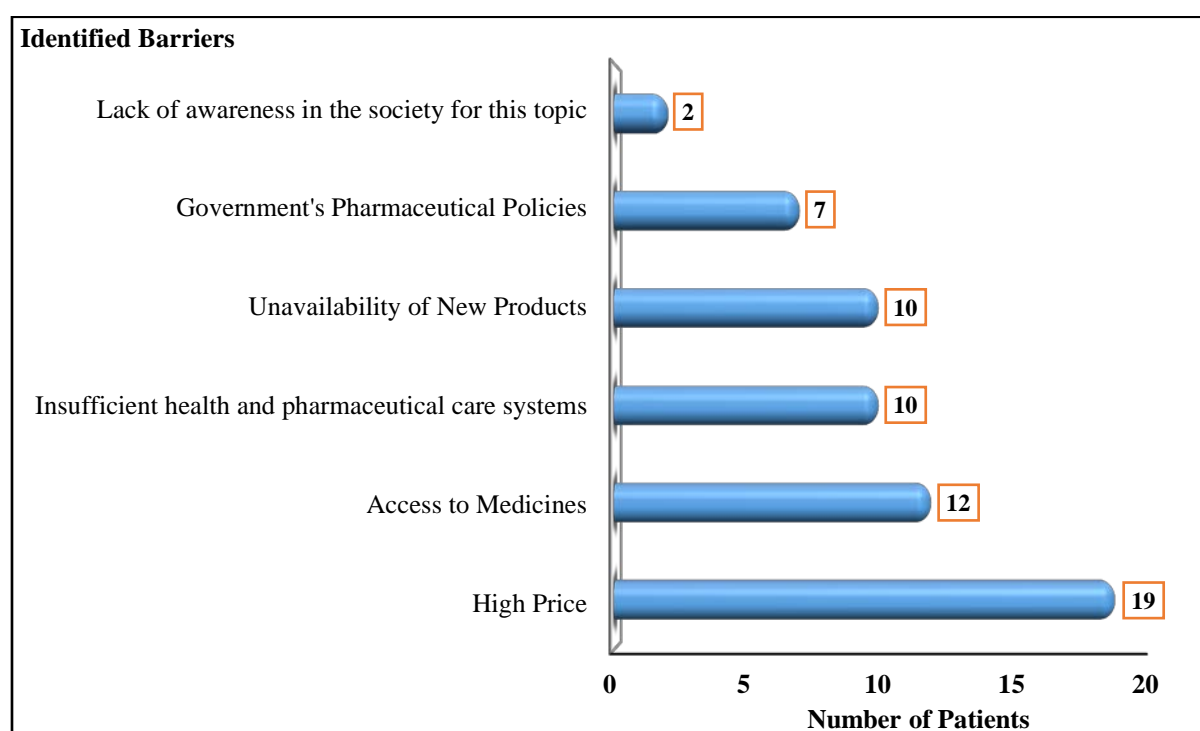
Currently the key issues concerning access to medicines relate either to the challenges facing the regulatory authorities or the barriers experienced by patients. As a result of this study the following major challenges facing the government were identified by the patients namely; the cost of new medicines is high, there is a lack of government resources and scientific expertise which were recognised as the top three issues (Table 6.6).

**Table 6.6: Major challenges facing the government in providing new-marketed medicines**

Challenge	Percentage (n = 210)
• Cost of new medicines is high	23% (n=48)
• Lack of government resources	19% (n=40)
• Lack of scientific expertise in government	18% (n=38)
• Pharmaceutical companies pricing policies	14% (n=29)
• Have no information	17% (n=36)
• The patients' needs not taken into account	10% (n=21)

Within this study only sixty patients out of two hundred and ten (29%) were able to list the most important barriers they face in obtaining the medicines they need. The top four barriers were; *the high price of medicines, their access to treatment, the lack of an appropriate healthcare system infrastructure and the unavailability of new products* (Figure 6.15).

**Figure 6.15: Barriers to medicines' access as identified by patients**



Similarly, patients were also able to offer some solutions to address these concerns, which were then grouped into four principal categories (Figure 6.16). The majority of the proposed solutions reported by patients were related to improving the health and pharmaceutical care systems (n=27), implementing better pricing and regulatory policies to enable timely access to new marketed medicines (n=18), as well as considering the patients' needs and supporting their roles in the decision making process of approving and reimbursement of new medicines (n=7).

**Figure 6.16: Principal solutions and patients' statements**

Government's Pharmaceutical Policies	Public Involvement	Improve Access	Increase Awareness
<i>"There should be more collaboration between the academic experts and government to enhance pharmaceutical policies and shorten the registration" process",</i>	<i>"Encourage involvement through patients' questionnaires and online forms",</i>	<i>"The government has been successful to transform the primary health care services; similar effort must be carried out to enhance patients' timely access to medicines with lower costs",</i>	<i>"Doctors and pharmacists must contribute to raise the awareness of patients regarding access to medicines"</i>

## DISCUSSION:

Turkey with its large population and good educational level is a developed country and among first world countries (OECD, 2015). Its economy is developed and ranked as the world's 16<sup>th</sup> among the G20 countries in 2015. Therefore, it was concluded from this study that patients in Turkey are as comparable to other developed countries in the world and they increasingly want to be more involved in the registration and reimbursement processes.

The study aimed to evaluate patients' perspective of the Turkish healthcare system and the regulatory review process; and thus assessed how comparable the results are to other medium size countries in terms of a scientific review. Additionally, the study aimed to evaluate the level of involvement and the role of patients in the decision making process of new medicines in Turkey. While it is crucial to evaluate the healthcare system services from the patients' perspective to achieve the optimal outcome of treatments, patients' active participation in the selection and use of their treatments has also been increasingly encouraged recently by all health organisations (WHO, 2002). Recent studies have demonstrated that making the patient a part of the process will also increase the patient's compliance to the treatment (Maxwell, 2009) as well as enhances the strategic development of medicines (Hoos, et al., 2015).

The study examined five hypotheses and thus the findings correlating to each hypothesis are discussed below.

**Hypothesis 1: Patients have considerable interest in their treatment and medicines.**

The results of this study identified patients' current knowledge of their medicines as well as their compliance with their treatment regimens. The study showed a positive correlation between the patients' knowledge and the duration of their medication. This was mainly identified among relatively educated (patients with high school or university degree) and patients with polypharmacy. Furthermore, their level of interest about their treatments and medicines correlates to their keenness to ensure treatment compliance and learn more about their medicines such as their use, benefits, harms and adverse events.

The culture of reporting adverse events is an important aspect of modern patient safety and is vital to improve the healthcare quality (Verbakel, et al., 2014). Thus, a culture is described as the cumulative result of an entire set of common behaviours, experiences, beliefs, and values that reflects how things are done in a certain environment and therefore an assessment of the current culture to identify the behaviours, practices as well as to identify the areas for improvement, is an important step to establish a specific culture in the healthcare system (Scott, et al., 2003). The results identified that the culture of patients in Turkey is to rely more on their physicians in obtaining relevant information about their medicines and reporting adverse events. Therefore, to overcome the under-reporting problem of pharmacovigilance in Turkey, it is suggested that it is important to encourage a reporting culture mainly among physicians to enhance the reporting of adverse events to the Turkish Pharmacovigilance Centre within the TITCK and ensure that all important adverse events reported by patients are also reported to the authorities in a timely manner. Furthermore, physicians and pharmacists play a crucial role in guiding, consulting and educating patients about their medicines and other health related issues and processes. Therefore, these results support the hypothesis.

**Hypothesis 2: Patients have little knowledge and understanding of the regulatory review and reimbursement processes.**

This study has demonstrated the importance of the patients' awareness, knowledge and role with regards to the decision-making process of registration review and reimbursement procedures in Turkey. Most patients in Turkey indicated that they know that the government must approve medicines before they are marketed. However, both the process of registration review and reimbursement are not familiar to patients and thus they seem to have little interest

in understanding these processes. Therefore, the public interest and level of patients' awareness of the pharmaceutical regulatory environment in Turkey can be enhanced if the sources of such information and benefits are better explained to patients as well as appropriate tools being created to ensure their active involvement. From these results, this hypothesis was confirmed and therefore accepted.

**Hypothesis 3: The perception of patients is that the Turkish healthcare system is not comparable to other developed countries.**

The perception of patients is that there is a correlation between the efficiency of healthcare system and their access to innovative medicines in Turkey. As a result, patients in Turkey do not believe that they have comparable access to innovative medicines compared to other 1<sup>st</sup> world countries. Most patients in Turkey are under the impression that alternative novel treatments are available in other countries and that the regulatory review processes and timelines are of a lower standard compared to other developed countries. The study therefore identified that patients are unaware about early access and TITCK named patient supply programmes. These aim to ensure the timely access of patients who are in critical need of life-saving medicines, prior to their registration approval in Turkey, which enables access to medicines within a similar timeframe to the developed countries. Moreover, early access to innovative medicines programmes constituted approximately 7% of the allocated pharmaceutical budget (SGK 2015) of the SGK, which is the main reimbursement body in Turkey. Therefore, it is suggested that both the TITCK and the SGK need to develop an increasing public awareness in relation to regulatory review and access processes in comparison with other countries globally. This would educate patients about early access programmes, which would ensure the timely access to innovative medicines for patients in critical need. This hypothesis was therefore accepted.

**Hypothesis 4: Patients in Turkey are not satisfied with their access to innovative medicines.**

When patients were asked to describe the three most important recent improvements in obtaining the medicines they need, they indicated *access to medicines, improved health and pharmaceutical care as well as price*. This was despite the major challenges they perceived facing the government namely; *the cost of innovative medicines is still too high as well as lack of government resources and scientific expertise*. Thus, the “Health Transformation Program” which was initiated in Turkey in 2003 has generated a number of developments in the healthcare services and was mainly appreciated by patients in several areas including

timely access to medicines. Patients indicated that they do recognise the governments' efforts in enhancing the healthcare services and patients' access to medicines through pharmacies and hospitals. Therefore, this hypothesis was not accepted.

**Hypothesis 5: Patients have little interest in being directly involved in decision-making with respect to the regulatory review and reimbursement processes.**

The role of patients in the decision-making process of approving and reimbursing new medicines by the government should be encouraged since currently patients do not have any active involvement in Turkey. Patients suggested that to ensure that their needs are met in a timely way, that patients' associations become more involved in decision-making regarding new medicines and that there is a considerable public representation in the process. This is in line with the many international calls from regulators, pharmaceutical industry representative as well as academia to engage patients in the pharmaceutical research and development, regulatory decision-making and healthcare access (Anderson & McCleary, 2015).

Patients' interest was mainly concerned with decision-making regarding access to medicines and reimbursement rather than the registration review process, since the general perception of patients was that the registration process of medicines is a technical procedure that requires more scientific expertise than the reimbursement. Face-to-face interviews with patients also identified that they think that they should be more involved in the reimbursement process since it is all about quality of life and thus namely through patient organisations, patients can share their own experiences with regards to their access to medicines and their use. Therefore, patient organisations have significant potential role to play in the reimbursement process. Studies showed that large and professional organisations seem to play an active role in this respect; they enable better accessibility of medicines for patients, negotiate to expand the coverage of the reimbursement for a larger group of patients as well as they lobby regarding a variety of medicines and better reimbursement conditions (Verbakel, et al., 2014). Within this study, it is concluded that the use of patient questionnaires online or via physicians, pharmacists and/or patients' organisations together with the use of social media could raise the awareness of patients to regulatory changes and reimbursement procedures, which could enable more active participation from the public. These results confirmed that this hypothesis was not accepted as patients in Turkey have considerable interest in the decision-making process of medicines.

## SUMMARY

- This study has demonstrated the importance of patients' awareness, knowledge and their role with regard to the regulatory review and reimbursement procedures in Turkey.
- When patients were asked to describe the three most important improvements in obtaining their medicines, they indicated that it was access to medicines, improved health and pharmaceutical care as well as price. This was despite the major challenges they perceived facing the government namely, the cost of innovative medicines being too high as well as lack of government resources and scientific expertise.
- Patients were willing to offer four principal solutions to address these concerns such as more collaboration between academic experts and government to enhance pharmaceutical policies and shorten the registration process, encourage involvement through patients' questionnaires and online forms, more effort by the government to enhance patients' timely access to medicines with lower costs and encourage healthcare professionals to raise the awareness of patients regarding access to medicines.
- The role of patients in the decision-making process of approving and reimbursing new medicines by the government should be encouraged. Patients suggested that to ensure that their needs are met in a timely way that patients' associations become more involved in decision-making by ensuring a fair representation in the process. It is concluded that the use of patient questionnaires online or via doctors and pharmacists together with the use of social media could raise the awareness of patients to regulatory changes and access procedures.



## **CHAPTER 7**

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# **ASSESSMENT OF STAKEHOLDERS' KEY ISSUES AND A PROPOSED NEW MODEL FOR THE TURKISH REVIEW PROCESS**

## INTRODUCTION

Decision-making for approving a new medicine, from a health authority perspective, is a complex scientific process, which requires careful assessment of all the potential benefits and harms. Thus the success criteria for a regulatory authority to ensure the timely access of patients to new medicines is based on quality, safety and efficacy standards as well as a low risk of withdrawals from the market due to therapeutic failures, quality concerns or serious adverse events. In broader terms, the mission of a regulatory health authority is to protect and promote public health (Salek, et al., 2012).

As a regulatory health authority, the TITCK has a significant role in fulfilling its responsibilities to the public, the pharmaceutical industry and other relevant governmental authorities as well as to its staff and reviewers. These include the responsibility for maintaining an efficient good review system to enable the approval of high quality and safe medicines in a timely manner, ensuring patients' access to their medicines while safeguarding the phamaco-economic impact on the healthcare budget and eliciting adequate transparency with the public and industry for the rationale behind the approval or rejection of medicines. This is not an easy task mainly because of the increasing number of NAS applications to the TITCK and the eagerness of pharmaceutical companies to complete the registration requirements to gain access to the market in the shortest possible time. However, the outcome from the TITCK and pharmaceutical industry studies demonstrated that the TITCK is facing a number of challenges in granting the timely approval of new medicines. Overall, the TITCK has a good review system, yet, there are some major barriers, which relate mainly to the structure and organisation, insufficient infrastructure, staffing issues, lack of a communication policy or a structured approach to decision-making as well as the challenges related to requirements and alignment with global standards. Therefore, it was essential to evaluate the regulatory review system and the key milestones individually to identify the type and impact of these barriers and consequently assess the ability of the TITCK to implement a successful standardised and efficient regulatory review system.

The purpose of this research was to evaluate the regulatory environment and its impact on patients' access to medicines in Turkey. The study began with an evaluation of the regulatory review process and approval timelines at the TITCK to understand the key milestones, review dynamics, internal procedures and quality measures. This was then followed with a comparative study between the TITCK and four regulatory agencies in Australia, Canada,

Saudi Arabia and Singapore, to explore the similarities and differences in the regulatory review process and good review practices between the TITCK and agencies. Similarly, the pharmaceutical companies' experiences of the review process and the trends in new medicines approval timelines over the period from 2012 to 2015 were analysed. Finally, since the ultimate recipients of medicines are the patients, a study was designed to assess the knowledge and role of patients in decision-making for approving and reimbursing new medicines. This was a major study conducted for the first time in Turkey, which demonstrated that despite patients having little knowledge about the review process of medicines, yet they were generally aware of the challenges in medicines' access and the agency's capacity issues.

Having identified the areas of concern from all relevant stakeholders, it is now possible to explore the opportunities to improve the Turkish review system. Therefore, this chapter examines the four studies to identify the common areas of concern between these stakeholders and brings together the related outcomes to provide recommendations for a new improved model for the TITCK if it aims to become a more efficient and effective regulatory agency in line with other mature health authorities and meet public expectations. Improving the TITCK's capacity and ability as an agency will enhance the quality of the review process in terms of quality decisions and timelines, whilst streamlining the processes and improving the communication policies, which will enable faster access to new medicines with a better sustainable environment for the industry for investment and development. By optimising its resources and improving the review process, the TITCK may also enjoy substantial cost savings as well as fundamental developments, which could lead the agency to become a reference for regulatory excellence in the region.

## **OBJECTIVES**

The main objectives of this chapter were to:

- Identify the key issues of concern facing the TITCK as they endeavour to become an international recognised authority.
- Evaluate the main outcomes recognised by relevant stakeholders including the pharmaceutical industry and patients with regards to the regulatory review process.
- Compare similarities and differences among the different stakeholders with a view to making new medicines available in an efficient and timely manner.
- Propose a new improved model for the Turkish regulatory review based on the key issues identified by different stakeholders.

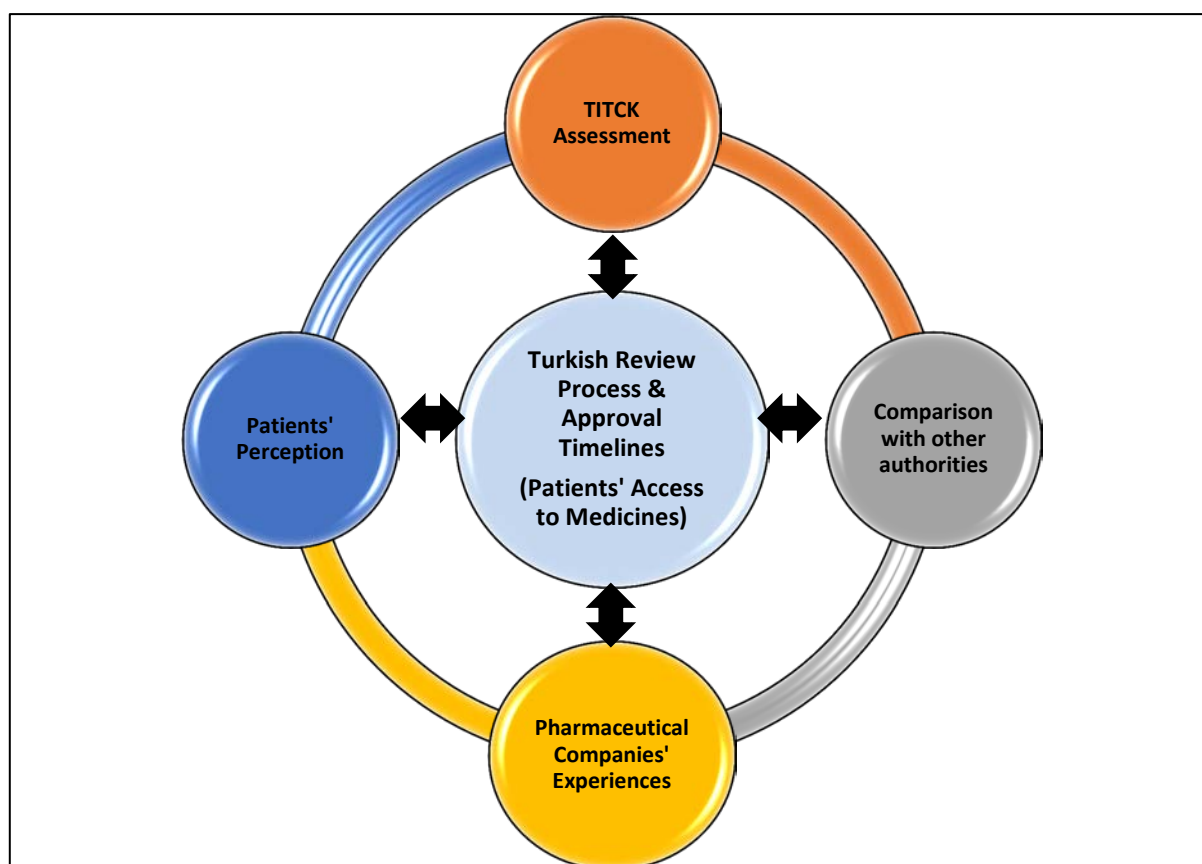
## METHODS

Stakeholders' perspectives and suggestions for improving the regulatory review in Turkey were assessed from the outcomes of four major studies namely;

1. An evaluation of the TITCK regulatory review process and timelines,
2. An assessment of current TITCK regulatory review processes and timelines in comparison with other international, mid-sized regulatory health authorities,
3. An evaluation of the experiences and views of pharmaceutical companies with respect to the Turkish registration review process,
4. Finally an assessment of the awareness of Turkish patients concerning the pharmaceutical regulatory environment and its impact on patients' access to innovative medicines.

A comparative analysis between these four studies (Figure 7.1) highlights the challenges faced by these stakeholders as a prelude to making the necessary recommendations. These facilitated the proposal of the new model.

**Figure 7.1: The contribution of the four studies to enhance patients' access to medicines**



## RESULTS AND DISCUSSION

The results of this comparative analysis are presented in three main parts:

- Part I: Organisational structure of the TITCK and the regulatory environment.
- Part II: Turkish regulatory review process.
- Part III: Turkish regulatory review times and access of patients to new medicines.

### **Part I: TITCK organisational structure and the regulatory environment**

The TITCK was established as a separate agency within the administrative structure of the Ministry of Health to regulate the pharmaceutical and medical device industry in Turkey. This follows the approach taken by Australia, Canada, Saudi Arabia and Singapore; the local law and regulations define the role and responsibilities of the TITCK, which are well known by the pharmaceutical industry. In addition, this study identified that the majority of Turkish patients were also aware of the government's responsibility to approve new medicines.

The organisational structure of the TITCK is publicly available on the agency's official website. At present, they have a total staff of over one thousand with more than 25% having a medical background as either physicians or pharmacists. This is comparable to other mid-sized regulatory agencies such as Canada, Saudi Arabia and Singapore. One hundred and forty-seven of the TITCK staff members are assigned as reviewers for marketing authorisation applications and product licences. In addition, nineteen committees of six different types within the TITCK carry out various scientific assessments. For this, external experts are selected from a list of one hundred and twenty for the assessment of scientific data. An examination of the organisational structure demonstrated that the TITCK considers itself scientifically competent and capable to conduct its own full review process (Type 3A assessment model) where in general the quality, safety and efficacy assessments are carried out in parallel, which is line with other mature agencies. Nevertheless, the resources and abilities of TITCK were perceived differently by the pharmaceutical industry with the majority of the participating companies indicating that the number of commissions and experts involved in the review process was insufficient for the increasing number of NAS applications submitted. This was considered a major area, which would have a significant impact as the industry think that the TITCK is under resourced. Moreover, the pharmaceutical companies believed that the current TITCK reviewers' scientific competencies and agency's abilities to review biological and biotechnological applications were satisfactory or good. Yet

the changeable structure of the TITCK and its staff as well as the insufficient number of reviewers and expert committees were the main cause indicated by the industry to delay approvals. In addition, patients were under the impression that the lack of government resources and scientific expertise were the major challenges facing the regulatory authorities in ensuring their timely access to medicines.

According to pharmaceutical regulations in Turkey, a marketing authorisation approval by the TITCK is required for any pharmaceutical product prior to marketing in the country. A number of regulatory guidelines are issued and made available by the TITCK to guide the pharmaceutical industry and support their applications. Therefore, all pharmaceutical companies are fully aware of the application and approval requirements for any new medicine. This also seemed to be well recognised by the public since most of the patients indicated that new medicines had to be approved by the government prior to marketing although, not surprisingly, they were unaware of the details of the regulatory review process.

Similar to other countries, the requirements for new drug applications in Turkey are fully aligned with the ICH. Thus, the application dossier must be prepared according to the CTD with quality, safety and efficacy modules covering both the active drug substance and the finished product. Nevertheless, the pharmaceutical industry's perception is that, in general, local requirements for NDA applications are subject to various interpretations although they are clearly listed. They believe that these requirements are only partially aligned with international standards such as the EU and that sometimes, additional data requested by the TITCK are not always aligned with international regulatory requirements especially those related to CMC. Furthermore, companies expressed their satisfaction with the improvements in the regulatory area especially in relation to prioritisation and accelerated registration review, which were recently issued. However, they emphasised that the TITCK still needs to focus more on harmonising requirements such as; the Turkish GMP process, the scientific evaluation and approval of indications, product quality control and laboratory analysis; post marketing variation requirements, orphan drug requirements and the pricing procedure. Furthermore, it was a surprising finding that the majority of patients were under the impression that the Turkish pharmaceutical approval process and requirements to be of a lower standard compared to international and developed countries like the US and the EU (Table 7.1).

**Table 7.1: The TITCK and pharmaceutical regulatory requirements**

Requirement	TITCK	Industry perception	Public perception	Other agencies
<b>Agency Structure, Role &amp; Requirements</b>				
Agency's role in regulating the pharmaceutical environment and approving new medicines.	Known	Known	Known	Known
Alignment of requirements and standards with ICH/ EU & International standards	Aligned	Partially aligned	Not aligned	Aligned
Agency reviewers & commissions are sufficient	Sufficient	Insufficient	Not known	Not identified
Agency's abilities & capacities are adequate	Adequate	Adequate	Inadequate *	Adequate
Clear roles and responsibilities for reviewers	Defined	Not defined **	Not available	Defined

\* *Lack of scientific expertise at government* is one of the challenges highlighted by patients in approving new medicines.

\*\* *Majority of companies indicated that the TITCK structure, roles and responsibilities are not stable.*

## Part II: Turkish Regulatory Review Process

This study explored the Turkish review and assessment model, where the TITCK conduct a full review assessment (Type 3A) for all new active substance applications. While, any new marketing authorisation application can be submitted to the TITCK at the same time as any submission in the world, evidence of approval in the country of origin, EU or USA must be submitted prior to the final approval. This is similar to other regulatory agencies like Canada, Australia, Saudi Arabia and Singapore who also perform full review for some applications, but do not necessarily require authorisation by another reference agency. Some regulatory agencies such as Singapore and Australia utilise a risk stratification approach and conduct an abridged review where the product has previously been approved. This enables a faster approval and an improved management of limited resources.

The majority of the pharmaceutical companies indicated that the TITCK's review practices were not aligned with global GReP. However, the comparative study with other agencies demonstrated that the TITCK do have most of the quality measures of the regulatory review process in place, namely an internal quality policy, GReP system, SOPs for assessors, assessment templates, a dedicated quality assurance department and a scientific committee. However, an official GReP framework for the TITCK is not codified. In addition, pharmaceutical companies believed that the review process is not transparent as applications

cannot be tracked easily during the review process except through direct communication and/or question and answer. They also thought that the review process was not predictable and they also did not know whether the TITCK had a structured approach to decision-making (Table 7.2). These were among the improvement initiatives that seemed to be missing from the TITCK study when compared with other agencies. Finally, the majority of patients perceived that the review process is of a lower standard compared to international authorities and that the key elements for a high standard review model were inadequate including the lack of scientific expertise and standardisation of the decision-making process.

It also appeared that the TITCK does not have a peer review system, which is considered by some authorities as beneficial. For example in the EU reports from the rapporteur and co-rapporteur for a NAS are subsequently peer reviewed by the CHMP committee before the final decision is issued. Furthermore, the pricing process in the TITCK is carried out in parallel following the clinical and safety assessment while the details of the Risk Management Plan (RMP), labelling and technological evaluation are assessed in parallel. This again is a positive approach even though in Europe pricing and reimbursement are reviewed separately following the regulatory review. However, the pricing process is perceived by the industry as a delaying step to timely market medicines, even though it can be reviewed in parallel.

**Table 7.2 TITCK review and Decision-Making process**

Process Elements	TITCK	Industry Perception	Public Perception	Other agencies
Implementation of a standard review model to approve medicines.	Agreed	Agreed	Agreed	Agreed
Standard processes for review procedures; SOPs, assessment templates.	Partially implemented	Not implemented	Not available	Implemented
Agency scientific expertise and abilities.	Accepted	Not accepted	Not accepted	Accepted
Implementation of Good Review Practices (GReP).	Informally Implemented	Not implemented	Not known	Implemented
Review process transparency. Ability to track progress of application internally and externally.	Transparent	Generally transparent	Not available	Transparent
Predictability of the review process.	Predictable	Not predictable	Not known	Predictable
Utilisation of a structured-decision making process.	Structured	Not structured	Not known	Structured
Structured Benefit-Risk approach	Not available	Not available	Not known	Available (except for SA)



### **Part III: Turkish Regulatory Review Time and Patients' Access to Medicines**

The regulatory approval time for a pharmaceutical product is the time calculated from the date of submission to the date of approval by the regulatory agency, which includes agency and company time (Bujar, et al., 2016). The approval timelines of new medicines differs from country to country and from product to product. Nevertheless, many countries define in their regulations the target approval times to ensure the completion of the review process within a reasonable time frame provided that all required data are available and adequate. For example, the overall target approval time for a new medicine in the European centralised review procedure is defined as two hundred and ten working days (two hundred and ninety-four calendar days) excluding the clock stops during questions and additional requests to the applicant (Wade, 2010).

According to the regulations in Turkey, the overall approval timeline is set to be two hundred and ten working days for new drug applications. Furthermore, the prioritised accelerated review is defined as one hundred and eighty working days and for highly prioritised products, the target approval time is one hundred and fifty working days. In contrast, the TITCK mean approval times for the years 2013, 2014 and 2015 exceeded the agency's overall target time, which indicated that there is room for improved timeliness, consistency and process predictability in the system. The study demonstrated that the TITCK has longer approval timelines compared with other major health authorities such as the EMA and the FDA and the PMDA (Bujar, et al., 2016).

Although the approval times at the SFDA, TGA and HSA from 2011-2013 exceeded agency target times, yet it would appear that the approval timelines in Turkey are still longer by two to three months compared to these countries. This was in line with the data for NAS approval timelines obtained from the pharmaceutical industry as well, where the median time for the TITCK approval was identified to be twenty-one months. This highlighted the fact that patients have access to new medicines as they become available in the Turkish market approximately three and a half years later compared to first approval of the product in the world. This also coincides with the general patients' perception of the government's timelines to approve a new medicine, which was more than two years. Thus, a significant proportion of patients thought that new and alternative medicines only become available in Turkey after

other developed countries (Table 7.3). Surprisingly, both the industry and patients have a common perception that the maximum target approval timeline for the TITCK should be twelve months.

Target timelines for key milestones of the review process such as queuing, clinical assessment and expert committees' timelines, are not defined in the regulation or in the agency's internal SOPs. Thus, part of the delay in approval could be attributed to the time taken by the company to respond to agency's questions. As industry experience also shows the question and answer phases can take fifteen months with an average of ten to fifteen questions received for each NAS application and an average of two to four months to answer each question. Therefore, setting deadlines for the question and answer phase should improve approval timelines. It is also suggested that the TITCK batch their questions and encourage companies to keep a systematic record of the number of questions received and response times.

**Table 7.3: Availability of medicines and target timelines of TITCK**

Process Elements	TITCK	Industry perception	Public perception	Other agencies
The agency set target approval timelines for the review and approval of an application.	Available	Available	Not known	Available
Target approval times are defined for each review milestone and scientific assessment of committees.	Not available	Not available	Not known	Available
Question and answer response deadlines defined.	Not defined	Not defined	Not known	Defined*
Target approval times are met by the agency within reasonable limits.	Not achieved	Not achieved	Not known	Achieved
New medicines become available at the same time of other developed countries.	Not agreed	Not agreed	Not agreed	Agreed (except SA)

\* There is a 90 days' time limit (clock stop) for sponsors to reply to questions from SFDA. However, until now SFDA still accept responses even if it exceeds the time limit

## **TITCK Workshop and Focus Group**

Reviewing the outcomes of the four studies and conducting analyses of all the common areas of concern led to a final step by key experts at the TITCK to make recommendations for an improved review system. This was achieved by conducting a two-day workshop with focus group discussions by the senior management of the TITCK in Ankara. The aim was to review the challenges and opportunities for the TITCK to improve their review system and ultimately become an international centre of regulatory excellence in the region. The workshop was organised in collaboration with the Centre for Innovation in Regulatory science (CIRS) and TITCK where the participants included the president, vice president and thirty-three staff members from different departments as well as external academic reviewers. Following the workshop, a full report was made available (Appendix IV).

The objectives of the workshop were to:

- Provide an independent assessment of the TITCK in comparison with other medium sized international regulatory agencies.
- Understand the key issues of concern from the pharmaceutical industry and patients regarding the pharmaceutical regulatory environment and possible solutions.
- Explain the importance of quality decision-making and a systematic structured approach to the benefit risk assessment of medicines.
- Determine the challenges and opportunities for TITCK to become a Recognised Centre of Regulatory Excellence.

The president of the TITCK, who spoke of the major developments achieved recently in Turkey through the Healthcare Transformation Program (HTP) since 2002, opened the workshop. During this time, several initiatives took place to examine the healthcare system from different perspectives and an international point of view, which helped significantly in improving the healthcare system. Therefore, he indicated that a similar approach could be valuable for the evaluation of the pharmaceutical regulatory review process in Turkey. He concluded that the TITCK is recognising the challenges they face regarding their review system and particularly in meeting target approval times for new medicines. Therefore, he emphasised that the agency is aiming to implement a number of improvements within the process including a systematic approach to monitor individual milestones. This is to fulfil the

TITCK’s vision to become a leading reference regulatory agency; this requires commitment, high quality work and partnership with national and international stakeholders.

The workshop included five sessions where the objectives, methods and key outcomes of the four main studies were presented. Furthermore, there were two sessions explaining the structured approach for the benefit risk assessment of medicines and quality decision-making in medicines development and the regulatory review. These provided a comprehensive background to the structured approach for the Benefit Risk (B-R) assessment of medicines, which is key to improving decision-making in drug development and the regulatory review. The current B-R Frameworks implemented by other regulatory agencies were evaluated and examples of how these contributed to the improvement of the decision making process were presented.

The penultimate session was about Quality Decision Making (QDM) in medicines development and the regulatory review. Thus, the importance of QDM and the development of a decision making tool as well as the practicality and applicability of QDM practices in the regulatory environment, were emphasised. Finally, the last session of the workshop included a focus group with round table discussions aimed at identifying the key issues to be addressed by the agency. During this session, participants were organised into five separate groups and were asked to provide feedback to three questions in the light of the information they had been given (Table 7.4). Accordingly, the feedback established the basis for the key recommendations for an improved review model.

**Table 7.4: The three key questions for the TITCK round table discussion**

Q1.	Please list the most important key issues that you believe as an agency should be addressed?
Q2.	What is the area you would like the agency to address in order to improve and become an “International Centre of Regulatory Excellence”?
Q3.	What would you like to change and improve in the regulatory review process of the TITCK?

### Areas to be addressed and recommendations for the TITCK

In the focus group discussions, the participants identified the most important key issues that TITCK should consider in order to become a “Centre of Regulatory Excellence” (Figure 7.2).

**Figure 7.2: Key issues for consideration by the TITCK**



**TITCK organisation and capacity:** it was suggested that the TITCK should increase the number of scientifically qualified staff/personnel in the organisation and ensure a stable structure as much as possible with clear roles and responsibilities to be made known to stakeholders.

**Training and staff competencies:** participants recommended that TITCK create a formal and standard process for training within the agency to ensure a high calibre of reviewers as well as

enabling consistency and quality of assessment. Thus, the following should be considered to further improve the training process:

- Establish formal induction training for all new employees.
- Deliver focused training that is specific to the different scientific areas in order to increase the expertise of the staff and reviewers within their own areas of responsibility.
- Increase the partnership with the other regulatory agencies, encourage secondments, and job shadowing as well as the participation of TITCK staff in international training abroad.
- Ensure a standard process to transfer and share the best practices from those staff participating in international training.
- Follow a structured approach for “on the job” and “in house” training for staff and ensure they are also monitored and evaluated in terms of knowledge understanding.
- Leverage a transparent policy for staff training.
- Establish a **“Regulatory Science Academy”** within the TITCK in collaboration with universities and/or the pharmaceutical industry where specific regulatory scientific topics and Good Regulatory Practice training can be delivered to both internal and external reviewers.

**Transparency and communication with all stakeholders:** The agency should enhance the transparency and consistency of its decision-making process and improve its communication policy with its stakeholders. Thus, the following recommendations were provided:

- Consider making available summary basis of approval for stakeholders and assessment reports for applicants to justify how and why the agency took certain decisions.
- Implement a structured framework for pre-submission scientific advice/consultation meetings for the industry in order to minimise rejections, optimise the approval process and enhance communication with applicants before and during submission.
- Increase the number of scientific commissions to meet the increasing number of applications.

- Establish a formal process for tracking all the review process milestones and target timelines.
- Develop regulations and SOPs for standardisation/ alignment with international standards.
- Increase the cross-functional coordination within the agency and streamline processes.
- Implement a structured approach for the decision-making process and build quality systems to ensure consistency and business continuity.
- Assign specific staff or departments for external communication to improve consultation with applicants.

**Agency infrastructure and quality management system:** it was suggested that the TITCK should improve its physical and electronic infrastructure including information technology and quality management system by:

- Supporting the full adaptation to the (e-CTD) and enhance the review process and timelines through electronic tracking systems leading to faster communication with applicants.
- Increasing its quality management systems and ensure a standard policy for quality.
- Ensuring the efficiency and appropriate training of internal reviewers by preparing SOPs for the key tasks and clearly defining roles and responsibilities.

Furthermore, participants identified two main areas where the agency should focus in the near future in order to progress its mission to become a recognised reference regulatory agency; **Good Review Practices (GReP)** and the standardisation of **the decision-making process**. Thus, the majority of participants indicated that the TITCK should prioritise the adoption of a structured formal approach for GReP and decision-making process and ensure that it is fully implemented and monitored.

For this purpose reviewing and importing the best practices from other regulatory agencies could be beneficial. In conclusion, having identified the key issues from the four studies and the TITCK focus group, Figure 7.3 summarises the recommendations to be considered in the improved review model.

**Figure 7.3: Recommendations to be considered in the improved review model**



## IMPLICATIONS FOR AN IMPROVED REVIEW MODEL

In the light of the outcomes of the studies, a number of key recommendations were made by the pharmaceutical companies, patients and the agency's senior management to address the challenges in the review process and access to medicines. These were mainly in the following areas:

- Strengthening the structure and organisational capacity of the TITCK,
- Alignment of the regulatory review process and requirements with international standards,
- Implementation of a structured approach for Good Review Practices and Benefit-Risk assessment to become mandatory,
- Monitoring the review milestones and establishing key performance indicators to achieve target approvals,
- And enhancing transparency of the decision-making process.



## **Structure and organisational capacity of the TITCK**

It is recommended that the TITCK devote some effort to improving its organisational capacity and reviewing its capabilities by establishing a clear professional role for reviewers and experts and defining the responsibilities of the administrative tasks. This could optimise its limited scientific expertise for the assessment of new medicines and establish performance criteria for reviewers. By building a more stable structure, it could mitigate the turn over and changing roles of staff based on scientific merit as well as addressing the retention of expertise. Based on the solution proposed by patients and the recommendations from the agency's focus group; it was suggested to increase the collaboration between the academic experts and the regulatory health authorities to enhance pharmaceutical policies and shorten registration by increasing the review capacity of the agency through training opportunities. The agency staff recommended that a *“Regulatory Science Academy”* should be established and be capable of delivering regulatory affairs training modules and conducting research programs in collaboration with universities and industry to continuously improve the regulatory review system.

Another recommendation was related to the placements and secondments of the TITCK staff in other agencies, which would enhance the quality, and competencies of the staff. As the TITCK president stated in his opening presentation, the number of committees as well as committee members already has increased and should continue in response to the number of applications. Moreover, the number of internal reviewers with Ph.D.s has increased and this facilitated their active participation and membership within committees. This was again positive, nevertheless, the working principles and timelines of the committees should be reviewed by setting clear SOPs to define the roles and enhance collaboration with internal assessors. As a result, an optimum working environment for all scientific committees can be ensured while providing them with the internal technical support they need.

## **Review model**

In the last decade, the TITCK had continuously improved the registration procedure and increased its staff level of expertise enabling it to conduct a full assessment and accept NAS applications in parallel with other mature health authorities such as the EMA and the FDA. However, it is suggested that the TITCK adopt different regulatory review pathways such as the verification model for products already approved by reference agencies or an abridged review model in the case of NAS applications, where the TITCK can conduct its own

assessment while placing some reliance on other agencies' decision and approval thereby saving time and resources. Singapore, for example, conducts a verification review for all types of medicines, which are previously authorised by at least two reference agencies (EMA, US FDA, Health Canada and MHRA) (Hashan, et al., 2016), except for biological and biotechnology products and an abridged review if approved by one reference agency.

Moreover, in terms of the assessment and review process, it seems that the TITCK may need to invest more effort to enhance the standardisation and predictability of the review process by utilising SOPs, detailed assessment templates and feedback forms. In addition, the agency would need to formally mandate the full implementation of all the elements of Good Review Practices and a structured approach for decision-making using a benefit-risk framework. These will contribute to the scientific quality level of the decision-making process as well as enhance consistency, efficiency, clarity, and transparency. Furthermore, the TITCK could consider publishing the summary basis of approvals (PARs for stakeholders) and assessment reports to be provided to the applicants. In addition, the TITCK could explore the possibility of conducting shared or joint reviews with other comparable regulatory authorities.

### **Communication policy**

The outcome of these studies emphasised the importance of an effective open communication between the industry and the authority. Several examples were shared of some agencies where the key milestones of the assessment process are made available to the industry including key agency contacts for each application, which could facilitate dialogue during the review process. Moreover, it is recommended that the TITCK should have an official communication policy with all its stakeholders whereby all types of communication steps and vehicles are officially described and implemented in a structured way. These would include the following:

- Share periodically the TITCK long-term vision and strategic plans.
- Establish a structured formal process for consultation with stakeholders prior to the issuance of a new regulation or a change in local pharmaceutical requirements.
- Develop standard procedures for scientific advice and pre-submission meetings with applicants before and during the review process.
- Enhance the use of electronic communication tools to accelerate the exchange of information with applicants and the tracking of responses.

- Enable applicants to directly communicate with assigned contacts for each application and facilitate scientific presentations to committees when required.
- Publish the summary basis of approvals to be shared with stakeholders while communicating assessment reports to applicants to justify the rationale behind the decision outcomes.

### **Approval timelines**

The lack of resources, mainly human expertise in the TITCK contributes as well to the delays even though there is an effective collaboration and sharing of information between the TITCK and its external academic reviewers. Recruiting external experts can aid the TITCK with the shortage of human expertise, but there is a concern that this will influence the review quality. Additionally, delays in approval may also be related to the structure and working procedures of the committees. Therefore, as mentioned previously the TITCK should consider delegating the review and assessment of some variations or extensions to internal assessors in order to reduce the number of dossiers assessed by committees and enhance the committees' scientific review thus allowing them to focus on new product applications and major clinical or quality variations. Although currently the TITCK has a manual system for tracking applications: they are planning to convert this into an electronic internal system, which will enable the monitoring of milestone timelines. Therefore, it is recommended that the agency define target times for each review milestone in addition to the overall target timeline and this information should be available to stakeholders. Thus, establishing an electronic tracking system with target timelines would enhance the efficiency and continuity of the review process while enabling the TITCK to monitor the timelines between milestones as well as to observe the time between first-in-world approval and approval in Turkey. Therefore, the TITCK should evaluate the resources required and the expected number of applications reviewed in order to meet the target times. This can be achieved by introducing a more collaborative systematic approach between the TITCK and the industry. Thus, pharmaceutical companies should notify the TITCK in advance of the expected number of major regulatory submissions including NAS applications at the time of their annual budget/resource planning. This could facilitate both the planning for the review process as well as enhance the transparency and communication prior to applications. Additionally, the agency should batch the questions raised during the review process and set reasonable deadlines for companies to respond. Similarly, this would enable companies to better plan their resources and maximise their efforts to reduce the clock stop period during the review. The findings from this study also

suggest that the TITCK could consider collaborating with other regulatory health authorities as well as increasing the amount of available resources to meet the target timelines. The TITCK have continued to put initiatives in place to improve the quality and timeliness of the review, which may explain the increase of its review performance in 2015 and the number of approvals granted within the same year. One area the agency has been concentrating on was the improvement of the electronic infrastructure and use of electronic systems to receive and record applications, track products, communicate with companies, handle some question, and answer cases.

### **Aligning requirements and pricing**

The TITCK has been investing and updating guidelines and regulations to support the industry and facilitate the standardisation in many regulatory areas such as new drug applications, prioritisation, labelling, risk management plans, GMP process and clinical research applications. Such activities further improve consistency and predictability of the review, but have also influenced the overall approval time either in a positive or negative way as seen in the last decade. Therefore, it is important for the TITCK to consider strengthening and aligning its national regulatory requirements with global standards and the EU to ensure the timely approval and use of medicines. For example, the TITCK is involved in the initial pricing process of medicines, which is based on reference pricing and is conducted in parallel to the registration review. However, a separate body (SGK) in Turkey determines the final reimbursed price. Whereas in Australia and Canada, the pricing mechanism for medicines depends on a Health Technology Assessment and is determined by a review body independently of the registration review process (Bonner, 2010). This has three main advantages, firstly the pricing process is conducted independently of the review process, therefore the budget impact is not influencing the scientific assessment of the agency, secondly, the product approval is not impacted by pricing delays and thirdly the pricing decision is based on cost effectiveness data of the product rather than comparative pricing.

Another important aspect that needs to be highlighted is the local GMP requirement as a pre-requisite to a new medicine application. This process is found to be acceptable by the majority of pharmaceutical companies, only if it could be in parallel to the registration review process. However, currently it is not. Therefore, it is critical to consider a thorough analysis of the impact of the GMP step with regards to new medicines approval. In response to feedback from the pharmaceutical industry, the TITCK has recently carried out work to streamline the

GMP process. They focused on this area and the quality has improved significantly over the last five-years. The number of GMP inspectors and assessors increased from ten to forty. Nevertheless, the main critical challenge remains in having the GMP process as a pre-requisite for the marketing authorisation applications as well as the fact that the TITCK still rely only on local GMP approvals. Therefore, it is crucial to streamline the process to allow the conduct and review of the GMP process in parallel to the registration review process so as not to impact the approval times and accepting other international recognised GMP approvals such as PIC/S to save time and cost both for the agency and the companies and ultimately the patients.

As a result, considering these recommendations facilitated the mapping of an improved model with individual milestones, defined timelines and key enablers clearly described within the review process (Figure 7.4). The new model enables an effective parallel review namely for the GMP, pricing and quality control analysis as well as for the scientific assessment by committees. Moreover, it illustrates the key enablers and quality elements required to ensure that the review process is conducted in a timely, transparent, consistent manner leading to approvals of medicines based on their quality, safety and efficacy merit.

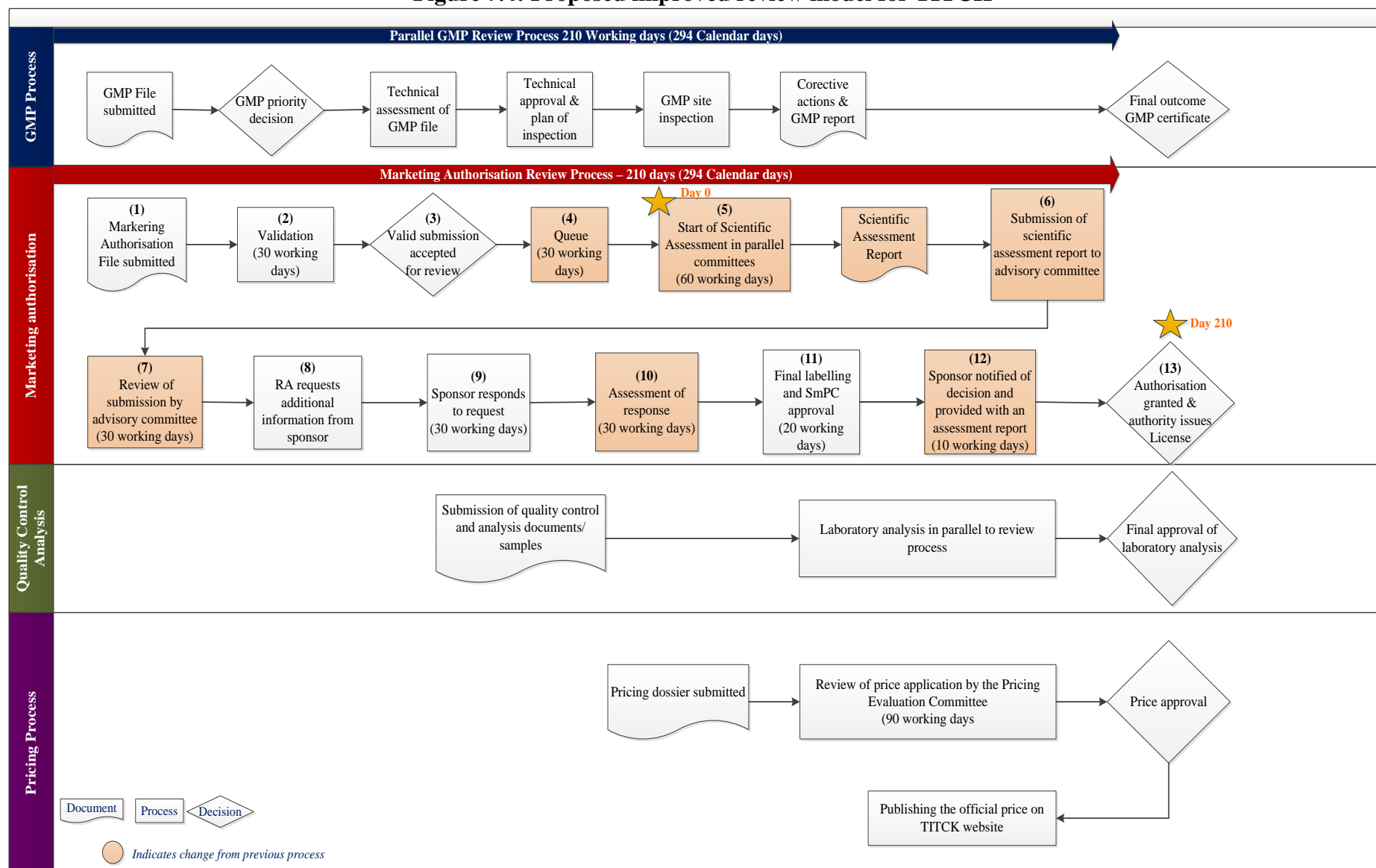
### **Key Steps for the Proposed Review Model**

The key steps for the TITCK improved review model are each given a number and described in details in this section. However, some of them may not include a change and the key milestones that are changed have been highlighted in the following process flow (Figure 7.4).

#### **GMP Process**

The current GMP steps as demonstrated in this study require a pre-requisite approval, which can then enable a marketing authorisation application for a NAS. Therefore the proposed model includes firstly conducting the TITCK GMP in parallel to the review process which can start by submitting a GMP application at the same time as the new drug application. Secondly, the milestones for this process, though remaining the same, will have an overall target approval time of two hundred and ten working days so as to ensure that it is completed prior to the license issuance. Thirdly, with this model, it should be possible to accept other PIC/S countries GMP certificates in view of the fact that Turkey is currently in the process of becoming a member of PIC/S.

**Figure 7.4: Proposed improved review model for TITCK**



## **Marketing Authorisation Process**

### **Step 1 - Marketing authorisation application submitted**

This step in the current process requires the submission of an e-CTD application of the NAS uploaded electronically via the agency's website. This step remains unchanged in the new model.

### **Step 2: Receipt and validation**

This step involves the validation of the application in terms of the content of the file including the format and compliance to the required sections of the CTD dossier. The date of application is formally recorded and TITCK has to complete the validation review within thirty working days and in the case of an incomplete application, the applicant is requested, via an electronic mail, to complete the missing data within another thirty days. If the application is evaluated in a second validation review and missing documents are not submitted, the application will be rejected. This step has not changed.

### **Step 3: Valid application accepted for review – Day 0**

Following the thirty days validation review, if the application is complete, the file is accepted officially and the date of acceptance is recorded formally and notified to the applicant via an e-mail, marking the start of the two hundred and ten (working days) registration review process. This is a proposed change to the review model.

### **Step 4: Queue time (Thirty working days / forty-two calendar days)**

On acceptance of the file following the validation step, the application is held in a queue. The queue time should be thirty working days (six weeks). However, prioritised products are taken out of the queuing system and the time for fast track applications should be approximately two – four weeks.

This step is proposed for the project management of the file and applications should be allocated to internal project managers to be prepared and presented to the scientific committees for further review. Thus, the committees are notified about the application receipt in order for them to plan their acceptance for review within the target of thirty days. At this step the applicant must pay the assessment fees required for the scientific review process to commence. This is a proposed change to the current review model.

**TITCK project managers:** The new model proposes the appointment of project managers, who are internal to whom files can be allocated following the validation step depending on the type of applications and their area of expertise. They would be responsible for managing the application and following it internally within the agency during the review by the different committees as well as being the contact point for applicants in case of questions or further clarifications. Moreover, internal project managers would also be responsible to consolidate the different assessment reports from the scientific committees to be presented to the scientific advisory committee for peer review and assessment for final approval. The advantage of having a project manager is that it provides applicants with a single point contact that is beneficial for communication and avoids the previous concerns of bias, which could occur if the contact was the reviewer. It has been shown in previous situations that this improves the efficiency, transparency and communication of the process.

**Step 5: Start of scientific assessment by committees in parallel (Sixty working days / eighty-four calendar days)**

The scientific assessment of the application is conducted in parallel by five scientific committees with a target time for the conclusion of their assessment in sixty working days. This includes the parallel assessment of clinical, safety, efficacy and technical sections by the current committees along with the external reviewers. These committees are the Clinical Evaluation Committee, the Technological evaluation committee, the Bioavailability and Bioequivalence Committee, the Pharmacological Evaluation Committee and the Risk Management and Pharmacovigilance Committee.

Each committee will have to provide its scientific assessment report including the proposed questions to the project manager within the target time. These should have been reviewed based on a structured decision-making process taking into account the ten quality decision-making practices and incorporating a framework for benefit risk assessment.

The new model continues to employ the current committees in the TITCK. However, the roles and responsibilities of the committees, in particular for the previous clinical commission, will change as well as defining a target approval time for this step. Therefore, this is a new proposed process to be incorporated into the new review model, as it would save time, be a more efficient process and ensure that the committees are working within a consistent decision-making process in their areas of expertise.



### **Step 6: Submission of scientific assessment report**

The project manager should consolidate the assessment reports from the five committees as well as review the questions to avoid any repetitions to be presented to the scientific advisory committee assessment as a peer review. This is another new step proposed for the review model.

### **Step 7: Review of submission by advisory committee (Thirty working days / forty-two calendar days)**

The advisory committee would review the consolidated report prepared by the project manager and assess whether the suggested questions are valid and are not already answered in the submission. The advisory committee may also suggest additional questions. In this way, the advisory committee would provide a peer review of the overall submission, which is in line with the recommendation made by the TITCK focus group and reflects the current review model in EU where the CHMP peer reviews the reports from the rapporteur and co-rapporteur regulatory authorities to ensure consistency and validity of the decision.

### **Step 8: Additional information requests from the applicant**

In case there is any additional information required by the advisory committee from the applicant, questions should be batched and sent to the applicant online by the project manager. This is a new approach for the TITCK to consider when communicating questions to the applicants during the review.

### **Step 9: Applicants response to additional request (Thirty working days / forty-two calendar days)**

Once the additional requests and questions are sent to the applicant, a thirty working-day period would start in order for the company to respond. Nevertheless, if required, applicants could request an extension to respond while the review clock would stop. Thus batching the questions and establishing deadlines would enable companies to anticipate the type of questions they might receive in order to be prepared to meet the target times and consequently plan the required resources. In addition, this would ultimately encourage applicants to ensure that their local regulatory representatives are well trained with the appropriate level of expertise required to coordinate the responses. Applicants may also be given the opportunity to present to the project manager and committee if further clarification is required. This is a

new approach to handle the questions and additional requests from the TITCK by the applicants, which is in line with other established authorities such as the EMA.

**Step 10: Assessment of response (Thirty working days / forty-two calendar days)**

Once the response is received from the applicant, the project manager would coordinate and consolidate the reports, which are to be submitted to the advisory committee for their final peer review.

**Step 11: Final labelling and SmPC approval (Twenty working days / twenty-eight calendar days)**

As soon as the advisory committee provides its positive opinion on the application in view of all the additional information submitted by the applicant, the final review of the proposed labelling and SmPC would commence. This would be based on the recommendations of the pharmacological committee and thus the final review will be made by the administrative and licensing department to approve the final SmPC and patient leaflet based on the provision of the commercial samples. This step would be completed in twenty working days after which the applicant would be notified. This step is currently in place; however, with the new model it would have a structured approach with a target approval time.

**Step 12: Sponsor notified of decision and provided with an assessment report (Ten working days / fourteen calendar days)**

Once all the review steps as well as the GMP and the quality analysis are completed in parallel, the overall assessment by the agency should be made available to the applicant where the rationale for the decision and a summary basis of approval are provided with a notification that the authorisation license would be issued in ten working days. At this stage, the applicant must pay the required fees. This is a new step proposed to be included in the review model as it would enhance the transparency of the decision-making.

**Step 13: Authorisation granted and authority issues License**

The final registration approval and authorisation license is provided to the applicant and the approved SmPC will be published on the TITCK website.

**Pricing Process:**

The new model suggests the separation of pricing from the scientific review process and this should be under the jurisdiction of a different department within the TITCK and independent of the registration review process. Thus, it should commence at the same time as the scientific review to ensure that only accepted applications are assessed in terms of pricing. The current reference pricing system can continue based on the five reference countries but the calculation should be based on the relevant exchange rate. However, as the existing pricing process allows, the Pricing Evaluation Committee (FDK) can still review price negotiations based on the pharmacoeconomic evaluation. Therefore, the process remains unchanged, although the sequence has been modified.

**Quality Control and Laboratory Analysis process**

The quality control and laboratory analysis of the new medicine can start at any time in relation to the marketing authorisation review process. Thus in practice this step is initiated as soon as the scientific review of the application commences and can be conducted in parallel to the registration review process. Therefore, this remains unchanged in the new model, however, it is also suggested that only the first commercial batch is subject to laboratory analysis.

In conclusion, the new proposed model has a number of advantages in terms of providing an optimum use of the TITCK capacity and resources as well as enhancing the approval timelines. It suggests setting target approval times for each milestone, which could facilitate appropriate planning of the applications to be allocated to each committee and enhance the predictability of the process. Furthermore, the TITCK could benefit from the use of project managers who are scientifically qualified agency staff and who could both coordinate the assessment of applications and participate in review committees to provide the administrative support required for each scientific committee. This could create an effective tracking and monitoring system of applications and provide overall governance on the review process enabling the TITCK to meet its targets and achieve timely approvals.

## SUMMARY

- This study focused on assessing the TITCK regulatory review process, evaluating its main dynamics and characteristics as well as the quality measures and systems implemented by the agency to ensure the timely approval for safe, effective and high quality medicines.
- A comparative analysis of the outcomes from the four studies identified the common key issues that need to be addressed when developing and improving the review model, which is a prelude to making appropriate recommendations.
- The comparative analyses were presented in three parts namely, the organisational structure of the TITCK and the regulatory environment, the Turkish regulatory review process and the regulatory review times as well as patients' access to new medicines.
- A final step in the critical assessment of the outcomes was achieved during a two-day workshop with a focus group study with TITCK experts who reviewed the challenges and opportunities to improve the review system in order become an international centre of regulatory excellence.
- A number of recommendations for a new improved system for the TITCK were identified namely enhancing the organisational capacity, alignment of the requirements with international standards and streamlining the review process and timelines.
- It is recommended that the TITCK implement a structured approach for GReP and the Benefit-Risk Assessment of medicines to enhance consistency, predictability and transparency of the decision-making process.
- The TITCK should work towards streamlining the regulatory review process by implementing a systematic approach to measure its regulatory review performance based on its capacity the number of applications received, reviewed and approved.

## **CHAPTER 8**

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### **GENERAL DISCUSSION**

## INTRODUCTION

The TITCK is a young and dynamic agency with a focus on implementing learning with an improving culture at all levels in order to keep pace with the rapid development of medicines. Thus, a reforming period has been initiated within the TITCK since 2015 mainly in the review and approval system for medicines and medical devices. Accordingly, eight main areas have been identified as success factors for an efficient regulatory environment. Each of these should be compatible with the other and the TITCK has taken appropriate action to ensure certain concrete improvements within each area, which includes:

- 1. Streamlining the GMP process:** The GMP accreditation processes and inspections should be conducted in optimum conditions. The TITCK focused on this area and the quality has improved significantly over the last five-year period. The number of GMP inspectors and assessors increased from ten to forty. There was an important focus on enhancing the competency level of inspectors as well as training the TITCK GMP experts through different means such as participating in the EMA related meetings, conferences and the organisation of in-house high level GMP training. Moreover, the TITCK submitted a full membership application to PIC/S in May 2013 and was recently inspected to become a full member, which is expected to be finalised shortly.
- 2. Laboratory analysis and quality:** A significant effort was particularly made to improve the physical infrastructure and quality of the laboratories used for the analysis of medicines, which included the renovation of the laboratories used as well as investing in new modern technological equipment and tools to enhance the reliability of the laboratory tests and analysis.
- 3. Risk Management within pharmacovigilance:** The TITCK introduced a number of measures to ensure the safety of medicines by implementing risk management plans. Thus, the TITCK has significantly improved the preparation and control of Risk Management Plans related to new medicines.
- 4. Clinical Research:** Several action plans and new regulations were put in place to improve the regulatory environment for the conduct of clinical trials and the scientific evaluation of medicines in Turkey.
- 5. Commissions and expert committees:** The number of committees as well as committee members has increased over the past few years in response to the increasing number of applications for review. The TITCK also increased their working time and enhanced the collaboration between their staff and external assessors. They

increased the number of qualified TITCK staff with Ph.D. degrees and facilitated their active participation within committees. In this way, they ensured an optimum working environment for all scientific committees while providing them with the technical support they would need.

- 6. Administrative reviews:** The reviews were pursued under two departments previously however, the bureaucratic barriers between these departments were decreased to streamline and improve the review processes.
- 7. Information Technology (IT) systems:** The IT infrastructure of the TITCK has improved dramatically over the past few years. Currently e-submissions and e-review systems are well established and functioning and there are still more initiatives and plans to implement and expand the use of electronic systems.
- 8. Communication with the Industry/ applicants:** The TITCK is striving to ensure that all the requirements are clear for the applicants so that sponsors can make complete and precise submissions, which can progress on time. For this purpose, the TITCK is continuously organising workshops and meetings with the pharmaceutical industry to discuss processes and areas of concern. As a result, such dialogue can also be considered as a training opportunity for the industry.

With these in mind, the limitations of the current registration review system of new medicines in Turkey are generally related to delayed approval timelines as it was identified that the time required for a new medicine to reach Turkish patients is longer in comparison with other developed and comparable countries. This is mainly due to the misalignment of local requirements with global standards, TITCK capacity and structural issues, ineffectiveness monitoring, the disconnection of key review milestones, lack of overall governance of the review process, inconsistent concerns about the decision-making process as well as internal and external communication challenges.

Thus, the main objective of addressing these limitations was to identify the opportunities for the development of a new improved review model, which could enhance the current approval process and accelerate the patients' access to medicines. For this purpose, this research study evaluated the Turkish regulatory review process and its impact on patients' access to medicines. Thus, four studies were conducted to evaluate the key issues from the viewpoint of the TITCK, other comparable regulatory agencies, pharmaceutical companies and patients. Accordingly, data collected from each study were analysed and reviewed individually in order

to determine the different areas of concerns and perceptions about the Turkish review process and access to new medicines.

The study commenced with a thorough examination of the TITCK review system as well as the agency's dynamics and key milestones influencing the approval process and timelines in chapter three. The focus of the second study in chapter four was to evaluate the Turkish review process in comparison with other mid-sized regulatory agencies with the aim to gain more insight into the key characteristics of the Turkish review system. This included the identification of the similarities and differences of the regulatory review process and the quality elements employed by each authority to optimise the decision-making process and outcomes. Being a critical stakeholder in the pharmaceutical regulatory environment, the pharmaceutical companies' experiences concerning the Turkish review process was also examined in chapter five. Similar previous studies were conducted to evaluate the regulatory review systems in several emerging countries such as Iran (Mostafavi, 2011), the Gulf region (The Gulf Cooperation Council (GCC)) (Al-Essa, 2011), Saudi Arabia (Hashan, et al., 2016) and Jordan (Al Haqaish, et al., 2016). Each study included different methods of data collection and analysis from different sources of regulatory agencies where the regulatory performance of these agencies was evaluated in terms of review/approval times and quality measures employed in decision-making.

Moreover, comparative studies with similar data obtained from pharmaceutical companies and/or other regulatory agencies were incorporated to evaluate the regulatory environment from different perspectives and identify the key areas to be addressed. For example, the Saudi Arabia and Jordan studies included similar comparative evaluations with other mid-sized regulatory agencies in Australia, Canada and Singapore with the result of developing similar proposals to help the agency improve its review process to become an internationally recognised reference agency. For example, to optimise agency resources, it was recommended that the agencies implement a risk-stratification approach utilising a verification review for new medicines that have been approved by two or more reference agencies and conducting an abridged review for products that have been assessed by only one reference agency (Al Haqaish, et al., 2016).

Furthermore, the findings of these studies demonstrated that although most of the regulatory authorities in the emerging markets recognise the importance of transparency and open



communication, yet they publish very limited information, which is mainly related to the approval dates of the marketing authorisation of new medicines. Therefore, these studies recommended the implementation of standard approaches for decision-making and publishing summary basis of approvals to enhance transparency as one of the key quality elements of GReP (Walker, et al., 2006). In addition, harmonising regulatory requirements with international practices and the standardisation of the review process by adopting assessment template and SOPs were also proposed in these studies in order to minimise variations in the review procedures and approval times (Al-Essa, et al., 2012).

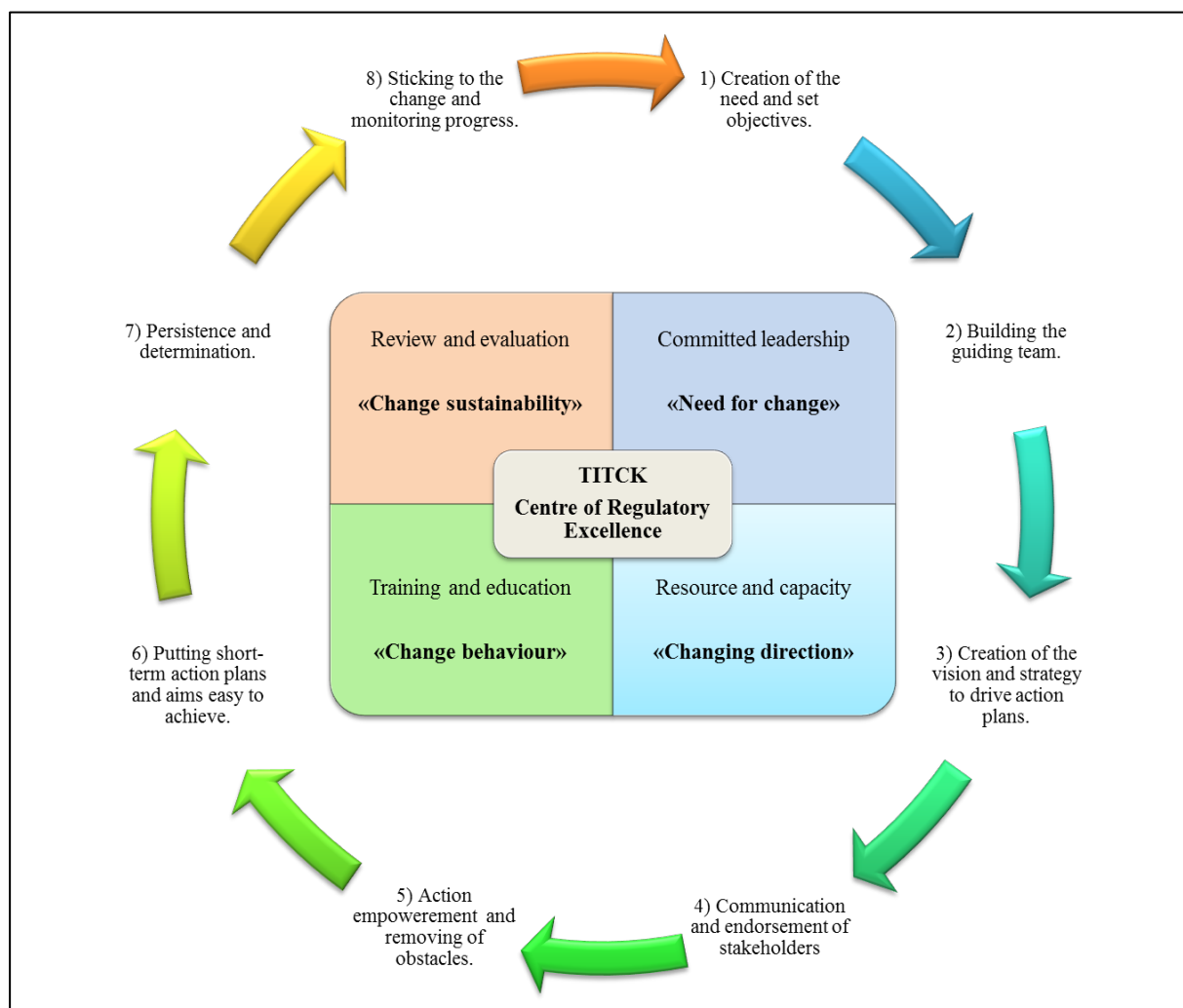
Interestingly, the findings and proposals of this research study were generally in line with those of previous studies and mainly related to enhancing transparency, predictability and timeliness. Nevertheless, there were special aspects and outcomes for this research project, which included a unique study that evaluated patients' approach and knowledge of the regulatory environment in Turkey and the impact of the Turkish review process on their access to medicines. This study identified that Turkish patients have a reasonable understanding and interest in the pharmaceutical regulatory environment where they were able to recognise the positive developments made by the authorities to improve their access to new medicines as well as the key challenges for faster approvals. Moreover, in terms of requirements, the major concern within the Turkish review process and timely market access was identified to be related to the local GMP process and pricing. The quality elements of review practices including transparency and communication policies as well as the TITCK capacity and organisation were among the key areas of concern compared with other regulatory agencies.

The analysis of the outcomes from all the studies in this research project in conjunction with review of previous studies, facilitated the development of a proposed improved review model for the TITCK. The main outcomes of the four studies were then discussed with senior management and experts of the TITCK in a focus group and round table discussions to affirm the identified key issues. This assisted in the establishment of a set of recommendations, which were considered in the development of a new proposed improved review model for the TITCK.

Additionally, the outcomes of this research project underlined the fundamental areas of concern and the gaps that needed to be addressed in order to improve the regulatory review

system at the TITCK. Thus, the TITCK should follow a strategic plan to enable the implementation of the key recommendations from this study and ultimately the proposed improved model. This would require a structured change management approach and a good planning step to implement successful organisational and procedural changes. For John Kotter, change has different aspects both on processes and people and therefore it is essential to manage it in a systematic method for which he proposed an eight-step model (Kotter, 2012). The implementation of the new TITCK improved model can be achieved using Kotter's change management approach as it can be applied in healthcare organisations as well (Campbell, 2008) (Figure 8.1).

**Figure 8.1: Change management steps for the TITCK to implement the improved review model**



*Based on John Kotter's Model, Leading Change, 1995*

The process should be first initiated by developing the need for the change and ensuring that all relevant stakeholders are acknowledging it as evidence-based. Accordingly, clear, relevant

and achievable objectives can be set. In this study, the need to improve the TITCK review process was recognised by the president and senior management of the TITCK during their focus group workshop. The second step of the change management process would include the creation of a clear vision for the future TITCK as an agency. Hence, the president of the agency indicated that the ultimate vision is for the TITCK to become a centre for regulatory excellence in the region. Furthermore, a key principle of change management relates to people's response and approach to change. Therefore, it is important to establish robust strategic action plans that are clearly communicated to all stakeholders to enable them to endorse, implement and monitor the success of progress. Thus, the TITCK should develop concrete and measurable action plans and map the key deliverables for the improvement of each milestone in the review process. This step would require a structured design and planning of individual steps and new procedures to be endorsed as well as the review of available resources, capacity, technological infrastructure and additional costs or risks to implement the new processes. These include the introduction of a peer review among existing committees, the use of project managers and adopting structured approaches for decision-making including the benefit-risk assessment of medicines.

It is important to identify and involve the relevant departments and staff who could be impacted as well as to communicate all changes to key stakeholders in a timely manner. For example, pharmaceutical companies should support or take part in the implementation of certain changes such as to follow the strict requirement of responding to questions raised during review within a limited period. The introduction of new processes and practices in the review system may also require the need to empower and encourage the agency staff to adapt to the change in the behaviour and approach in the new system. For this, breaking the objectives down into short-term deliverables could enhance the engagement of the TITCK staff and minimise the resistance to adopt new standard approaches. Therefore, for each change or new step, it is crucial to ensure that the appropriate education and training, both from local and international sources, are delivered in a timely manner. Finally, the TITCK should maintain an ongoing monitoring process of the new model and encourage the reporting of progress by highlighting the achieved and future milestones as well as identifying the value of the successful implementation of the new model. This could be identified through an improved review process quality, enhanced transparency and predictability. Thus, the new model would bring a number of advantages mainly by enhancing the approval timelines and increasing the efficiency of the TITCK in terms of resources and capacity. Additionally, it

would enable the TITCK to enjoy a standardised, consistent and efficient review system while still employing its current resources, staff and committees. Thus, by adopting an effective monitoring system and a standard structured approach for the decision-making process while setting target times for each milestone, it would be possible for the TITCK to handle the increasing number of new medicine applications and grant timely approvals as well as enhance its communication policies and transparency. Furthermore, the new model would enable a systematic monitoring of the TITCK performance and accordingly could facilitate its comparison with other developed and established regulatory agencies.

This would be immediately reflected in the pharmaceutical regulatory environment where pharmaceutical companies would be willing to invest in bringing innovative medicines to the Turkish market, which would ultimately be reflected, in an improved patients' access to medicines.

## **LIMITATIONS OF THE STUDY**

**Limitations of the TITCK study:** The approval timelines for the TITCK, which are based on mean rather than the median approval as well as data related to 2016, were not provided by the agency and the TITCK questionnaire did not include any questions to specifically evaluate the pricing requirements and process within the agency. Moreover, the opportunity to discuss the improved model with the TITCK did not occur due to the time limitations; nevertheless, this will be addressed in the near future to ensure that the TITCK reflections and endorsement of the model are obtained in order to facilitate its implementation.

**Limitations of the pharmaceutical industry study:** There were a number of limitations to this study and these are as follows:

- A response rate of 51% was achieved. Nevertheless, as indicated by the Research-Based Pharmaceutical Companies Association (AIFD) general secretary, this was the highest response rate achieved to date for similar questionnaire studies conducted by the Association on other topics. Thus, the data collected from the participating companies represented the top ten pharmaceutical companies in terms of market share and 41% of the total new active substances approved by the TITCK for the years from 2012 to 2015. Furthermore, only one out of the three identified local companies participated in this study.

- The question and answer phase during NAS review process was not appropriately covered in the questionnaire study so it was not possible to calculate the company time in terms of how long does an application or a response reside within a company. Therefore, further studies should be conducted to specifically focus on this issue to evaluate company time spent in answering questions and the reasons behind any response delays to TITCK. Accordingly, it would be possible to determine the appropriate changes, which will ultimately improve patients' access to medicines.
- The questionnaire was mainly focusing on the registration review process and therefore the pricing issues and requirements were not addressed since it is a separate process and is generally managed by different departments in companies.

**Limitations of the patient study:** This did not include a focus group discussion following the study due to logistic difficulties of bringing the patients together as well as confidentiality concerns. This could have been achieved by asking the participants in the questionnaire whether they would have been interested in a follow up discussion to this study as this was carried out in the pharmaceutical industry and the TITCK studies. Due to some aspects of confidentiality and the timing of the TITCK and the industry studies, it has not been possible to publish the outcomes in peer-reviewed journals. However, this is planned for the future. Whereas data from the patient study were presented at the DIA meeting in June 2016 as the data were available in a timely manner (Appendix V).

## **FUTURE RESEARCH**

The main themes addressed in each of the studies included in this research project are likely to remain key issues for the near future. Therefore, if the improved model or some of the recommendations were implemented by the TITCK, it would be of value to assess the agency's efficiency and effectiveness in two years' time and evaluate the impact of the new model on the approval timelines and ultimately on patients' access to medicines. Therefore, it is crucial for the TITCK to ensure the availability of the detailed regulatory metrics including approval times calculated with respect to mean and median values to facilitate comparison with other regulatory agencies and to measure the regulatory performance of the TITCK.

However, should there be no change in the regulatory review of the TITCK; it would still be beneficial to continue monitoring the approval trends by collecting, analysing and reviewing

approval times for new medicines in coming years as well as mapping the milestones within the review process in Turkey. This would provide an updated source of information on any new approval timeline trends, or possible changes and improvements in the review system over time and consequently on patients' access to medicines.

In addition, it is suggested to conduct a follow up meeting of the focus group with the TITCK to discuss and evaluate the applicability of a benefit-risk assessment framework. This could be possible by conducting a retrospective pilot study, which would familiarise the TITCK with the UMBRA framework and the related documentation system with a view, if thought appropriate, to conducting a prospective study.

Future studies should focus on the evaluation of alternative regulatory review models and pathways for the TITCK. It would be of value to examine the possibility of the TITCK adopting a risk stratification approach by putting some reliance on selected reference agencies that could maximise the use of their resources and expedite their approvals. Furthermore, it would be of benefit to examine the decision-making process among the different scientific committees (Priority Evaluation Committee, Clinical Evaluation Commission, Technological Evaluation Committee, Bioavailability and Bioequivalence Committee, Pharmacological Evaluation Committee, Risk Management and Pharmacovigilance Committee). Thus by providing them with the same QoDoS (Quality of Decision-making operating Scheme) tool and subsequently analysing the assessment outcome, data from each committee in terms of the ten quality decision-making practices could be determined (Bujar, et al., 2017). This would enable a comparison between the committees in order to make a recommendation as to what could be improved in the decision-making and assessment model of these committees so that they are consistent and aligned.

Finally, this research project presented for the first time, a comprehensive understanding of the regulatory review process for new medicines in Turkey, which also included a unique patient study. The initial aims and objectives of this research have been achieved and the findings have demonstrated the need to improve the registration review system for new medicines in Turkey by streamlining the TITCK review process and therefore enhancing patients' access to medicines. This research project identified the different views of stakeholders with regards to the Turkish review process including requirements, structure, procedures, quality measures and timelines that highlighted the degree of standardisation that

could be achieved. Therefore, it is hoped that the TITCK might recognise the value of the key recommendations to their review system, which aim to continually improve the efficiency of their processes. Therefore, the outcome of this research would enable the standardisation of the TITCK requirements and the enhancement of their regulatory performance, review procedures and decision-making, thus leading to a stronger regulatory authority and its transformation to become a reference agency and a centre for regulatory excellence in the region.

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# **Appendix I**

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## **QUESTIONNAIRE (1)**

### **Regulatory Review Process in Turkey**

**Review of key milestones, target times and  
quality of decision-making in the  
assessment and registration process**



## **Regulatory Review Process in Turkey**

**Review of key milestones, target times and  
quality of decision-making in the  
assessment and registration process**

**QUESTIONNAIRE**

**July 2016**

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<p style="text-align: center;"><b>The Centre for Innovation in Regulatory Science (CIRS)</b></p>
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### **Confidentiality**

CIRS recognises that much of these data may be highly sensitive. CIRS has more than 20 years of experience in handling similar data provided by agencies regarding individual products in regulatory review. **All information collected from individual agencies will be kept strictly confidential. No data that will identify an individual agency will be reported or made available to any third party.** External reports or presentations of the data will include only blinded results and any appropriate analytical interpretations.

**REGULATORY REVIEW PROCESS IN TURKEY**  
**Review of key milestones, target times and quality of decision-making in the**  
**assessment and registration process**

---

## **BACKGROUND**

This questionnaire is designed as part of a PhD project to evaluate the Turkish Regulatory environment and its impact on patients' access to innovative medicines. The aim of the questionnaire is to map the regulatory review process of new active substances within the Turkish Medicines and Medical Device Agency (TITCK) in terms of structure, relations. This questionnaire is designed in association with the Centre of Innovation for Regulatory Sciences (CIRS) and it aims to;

- Capture the actual registration requirements, review dynamics and practices followed by TITCK.
- Identify the review process in terms of type, timelines and availability of assessment framework and procedures.
- Identify the interrelations within the agency units and other external reviewers and regulatory commissions.
- Understand the decision making process and transparency of the assessment outcomes and review conclusions.

This questionnaire represents the third Phase of the CIRS Emerging Markets Programme which is studying the regulation of new medicines in the Emerging Markets **Argentina, Brazil, China, Egypt, India, Indonesia, Malaysia, Mexico, Saudi Arabia, South Africa, South Korea and Taiwan** and looking at the regulatory aspirations, barriers, problems and priorities, related to the review of new medicines that can have an impact on their availability to patients. The first phase was initiated in January 2004 to assess the current regulatory environment in some 30 countries, using comparative data, at the country and regional level, in order to identify the key issues for improving review practices and making new medicines available in an efficient and timely manner.

## **OBJECTIVES**

The objectives are to:

- To identify the key milestones and target times for TITCK and the main activities between milestones (for clinical trials applications and registrations).
- To identify the model(s) of the review which is being undertaken by TITCK.
- To assess how TITCK is building quality into the assessment and registration processes.

## **OUTPUT**

By the end of this questionnaire, TITCK will receive a report from which they can compare their regulatory procedures with those of peer agencies across the regions. This will include an analysis of where time is spent in the review process with the opportunity to identify where time is lost. The outcome will allow an analysis of the quality measures that are, or are not, in place for a certain type of

review and provide a baseline for subsequent comparative studies across agencies to establish best practices.

## ABOUT THE QUESTIONNAIRE

The attached questionnaire is divided into three sections:

**Part I: Key milestones in the registration of medicines**, which explores the review and approval process for new active substances (NAS) and major line extensions.

**Part II: Building quality into the assessment and registration process** which looks at the activities that contribute to the quality of the decision-making process and measures adopted to improve consistency, transparency, timeliness and competency in the review processes. The **Introduction** to the questionnaire asks the Authority to provide current information on its structure, organisation and resources. It also explores **review model(s)** for the scientific assessment in terms of the extent to which data is assessed in detail by the agency rather than relying on the results of assessments and reviews carried out elsewhere. The questionnaire is intended to be used as the basis for a face-to-face interview between Agency staff and CIRS.

## Focus of the Study

The study is intended, primarily, to document procedures and practices that relate to medicines that are the subject of **major** applications, i.e., new active substances and major line extensions.

### ***New Active Substance***

A new chemical, biological or pharmaceutical active substance including:

- a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product;
- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance not previously authorised as a medicinal product but differing in properties with regard to safety and efficacy from that chemical substance previously authorised;
- a biological substance previously authorised as a medicinal product, but differing in molecular structure, nature of the source material or manufacturing process;
- a radiopharmaceutical substance which is radionucleotide, or a ligand not previously authorised as a medicinal product, or the coupling mechanism to link the molecule and the radionucleotide has not been previously authorised

### ***Major line extension***

A major line extension is a change to an authorised Medicinal Product that is sufficiently great that it cannot be considered to be a simple variation to the original product, but requires a new product authorisation. Such changes include major new therapeutic indications or new disease states, extension to new patient populations (e.g., paediatrics), a new route of administration or a novel drug delivery system.



## PART I: ORGANISATIONA STRUCTURE & TYPE OF REVIEW

### 1. Information on the Regulatory Authority

As background to the discussions about your agency, its practices and procedures it would be helpful to have the following basic information on its structure and the way it is established:

**Title of the Agency/Division** responsible for the regulation of medicinal products for human use

.....

If this is part of a parent agency with a wider remit (e.g., Food and Drugs) please give the title:

.....

#### Scope and remit

1.1 Please indicate the scope of responsibility of the Agency:

Medicinal products for human use	<input type="checkbox"/>	YES	<input type="checkbox"/>	NO
Medicinal products for veterinary use	<input type="checkbox"/>	YES	<input type="checkbox"/>	NO
Medical devices and <i>in vitro</i> diagnostics	<input type="checkbox"/>	YES	<input type="checkbox"/>	NO

1.2 Indicate the main activities that are covered by the agency

<input type="checkbox"/> Marketing authorisations/Product licences	<input type="checkbox"/> Clinical trial authorisations
<input type="checkbox"/> Post-marketing surveillance	<input type="checkbox"/> Regulation of advertising
<input type="checkbox"/> Laboratory analysis of samples	<input type="checkbox"/> Price regulation
<input type="checkbox"/> Other	

#### Type of agency

1.3 Indicate which of the following best describes this agency

☐ Autonomous agency, independent from the Health Ministry administration

☐ Operates within the administrative structure of the Health Ministry

Date of establishment of the current agency

#### Size of agency

Please note that the following questions refer to the regulation of **medicinal products for human use**.

1.4 Please provide information on staff numbers

Total staff in the agency

Number of reviewers for applications for marketing authorisations/  
product licences

1.5 Please indicate the professional background and numbers of the **technical** agency staff assigned to the review and assessment of medicinal products

	Employed as assessors	Number
Physicians	<input type="checkbox"/> YES <input type="checkbox"/> NO	
Pharmacists	<input type="checkbox"/> YES <input type="checkbox"/> NO	
Other scientists	<input type="checkbox"/> YES <input type="checkbox"/> NO	
Project managers	<input type="checkbox"/> YES <input type="checkbox"/> NO	
Statisticians	<input type="checkbox"/> YES <input type="checkbox"/> NO	

### Fee structure

1.6 Are fees charged to sponsors for the review and assessment of applications for medicinal products for human use? ☐ YES ☐ NO

If **YES**, please provide the following information:

Marketing Authorisation Application fee for	Local currency	US\$
<input type="checkbox"/> New Active substance		
<input type="checkbox"/> Established ingredient - proprietary product		
<input type="checkbox"/> Generic product		
<input type="checkbox"/> Variations		
<input type="checkbox"/> Major line extension		
<input type="checkbox"/> Other (Please specify)		

Does the agency charge a fee for Scientific Advice

☐ YES ☐ NO : If Yes please provide

### Budget

Please indicate whether the following data ☐ are in the **public domain** or ☐ should be treated as **confidential**

1.7 Please provide the following information on the agency budget for the regulation of medicinal products for human use

	Local currency	US\$
<input type="checkbox"/> Total annual budget		
Year for which data are given		

If the budget is sub-divided according to different activities, please specify

**% of total budget**

☐ Clinical trial authorisations

☐ Marketing authorisations

☐ Pharmacovigilance

☐ Other post-marketing controls

☐ Other activities (specify)

### Sources of funding

1.8 Please provide the following information in relation to the way the agency is funded

Funded entirely by the government

☐ YES ☐ NO

Self funded entirely from fees

☐ YES ☐ NO

Partially funded from different sources (please give proportions of total budget)

\_\_\_\_% Government \_\_\_\_% Fees  
\_\_\_\_% Other (specify)

To assist CIRS to better understand your organisation please provide copies of any **organisation charts** that show the structure of the agency and its relationship to other regulatory bodies, e.g., medical device agency. It would also be very useful to have copies of any background papers that describe the **functions**, **remit** and **mission** of the agency.

## 2. Type of data assessment

Three basic types of scientific review have been identified as a result of discussions with regulatory agencies and presentations at the CMR International Institute Workshop on *The Emerging Markets: Regulatory issues and the impact on patients' access to medicines*, Geneva, Switzerland, March 2006. Many agencies apply a different level of data assessment to different applications, according to the type of product and/or its regulatory status with other agencies. The data assessment models for scientific review are described in section 2.1 below and further questions are set out in 2.2 to analyse the types of scientific review in more detail.

**2.1 Please indicate by checking the boxes below, which descriptions fit the model(s) used by your agency in the assessment of major applications i.e., new active substances (NASs) and major line extensions as described on page 2.**

### Data Assessment Type 1

This model is used to reduce duplication of effort by agreeing that the importing country will allow certain products to be marketed locally once they have been authorised by one or more recognised reference agencies, elsewhere. The main responsibility of the agency in the importing country is to 'verify' that the product intended for local sale has been duly registered as declared in the application and that the product characteristics (formulation, composition) and the prescribing information (use, dosage, precautions) for local marketing conforms to that agreed in the reference authorisation(s)

<b>TYPE 1</b>	<input type="checkbox"/> Not used	<input type="checkbox"/> Used for all major applications
	<input type="checkbox"/> Used for selected applications (please specify)	

### Data Assessment Type 2

This model also conserves resources by not re-assessing scientific supporting data that has been reviewed and accepted elsewhere but includes an 'abridged' independent review of the product in terms of its use under local conditions. This might include a review of the pharmaceutical (CMC) data in relation to climatic conditions and distribution infrastructure and a benefit-risk assessment in relation to use in the local ethnic population, medical practice/culture and patterns of disease and nutrition. Approval by a recognised agency elsewhere is a pre-requisite before the local authorisation can be granted but the initial application need not necessarily be delayed until formal documentation such as a Certificate of a Pharmaceutical Product (CPP) is available.

**TYPE 2** ☐ Not used ☐ Used for all major applications

<input type="checkbox"/> Used for selected applications (please specify)
--

### Data Assessment Type 3

In this model the agency has suitable resources, including access to appropriate internal and external experts, to carry out a 'full' review and evaluation of the supporting scientific data (quality, pre-clinical, clinical) for a major application. A Type 3 assessment could be carried out on a new application that has not been approved elsewhere but, in practice, legal requirements may dictate that the product must be authorised by a reference agency before the local authorisation can be finalised.

<b>TYPE 3</b>	<input type="checkbox"/> Not used	<input type="checkbox"/> Used for all major applications
	<input type="checkbox"/> Used under the following conditions (please specify)	

If your agency has recognised 'reference agencies' (as in Types 1 and 2) please provide the list:

## 2.2 Data requirements and assessment

Regulatory Status:	Type I	Type II	Type III	Priority/fast track products
<b>Evidence of authorisation by other authorities</b>				
Requirements for a CPP as part of the review	<input type="checkbox"/> with application <input type="checkbox"/> before authorisation <input type="checkbox"/> not essential	<input type="checkbox"/> with application <input type="checkbox"/> before authorisation <input type="checkbox"/> not essential	<input type="checkbox"/> before local authorisation <input type="checkbox"/> not essential	<input type="checkbox"/> with application <input type="checkbox"/> before authorisation <input type="checkbox"/> not essential
Other documentation from the authorising agencies accepted as evidence of registration	<input type="checkbox"/> letter of authorisation <input type="checkbox"/> copy of full authorisation <input type="checkbox"/> Internet evidence	<input type="checkbox"/> letter of authorisation <input type="checkbox"/> copy of full authorisation <input type="checkbox"/> Internet evidence	<input type="checkbox"/> letter of authorisation <input type="checkbox"/> copy of full authorisation <input type="checkbox"/> Internet evidence	<input type="checkbox"/> letter of authorisation <input type="checkbox"/> copy of full authorisation <input type="checkbox"/> Internet evidence
Other evidence accepted				
<b>Verification of identity between the authorised product and the local application</b>				
<i>The following are checked:</i>	Information must be: <i>Identical Closely similar</i>	Information must be: <i>Identical Closely similar</i>	<b>Not applicable</b>	Information must be: <i>Identical Closely similar</i>
Dosage form	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>		<input type="checkbox"/> <input type="checkbox"/>
Strength	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>		<input type="checkbox"/> <input type="checkbox"/>
Ingredients	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>		<input type="checkbox"/> <input type="checkbox"/>
Indications and dose	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>		<input type="checkbox"/> <input type="checkbox"/>
Warnings and precaution	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>		<input type="checkbox"/> <input type="checkbox"/>
Product label	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>		<input type="checkbox"/> <input type="checkbox"/>

## INTRODUCTION

Regulatory Status:	Type I	Type II	Type III	Priority/fast track products
Other (specify)				
<b>Scientific data required to support the application</b> (Reference is made below to sections of the ICH Common Technical Document (CTD) as an example of the level of detail but does not imply that the CTD is necessarily accepted)				
Pharmaceutical quality/CMC	<input type="checkbox"/> Summary data (Mod 2.3) <input type="checkbox"/> Summary + full stability <input type="checkbox"/> Full data (Mod 3)	<input type="checkbox"/> Summary data (Mod 2.3) <input type="checkbox"/> Summary + full stability <input type="checkbox"/> Full data (Mod 3)	<input type="checkbox"/> Summary data (Mod 2.3) <input type="checkbox"/> Summary + full stability <input type="checkbox"/> Full data (Mod 3)	<input type="checkbox"/> Summary data (Mod 2.3) <input type="checkbox"/> Summary + full stability <input type="checkbox"/> Full data (Mod 3)
<b>Scientific data required to support the application</b> (continued)				
Nonclinical data	<input type="checkbox"/> Written summary (2.4) <input type="checkbox"/> Tabulated data (2.5) <input type="checkbox"/> Full data (Module 4)	<input type="checkbox"/> Written summary (2.4) <input type="checkbox"/> Tabulated data (2.5) <input type="checkbox"/> Full data (Module 4)	<input type="checkbox"/> Written summary (2.4) <input type="checkbox"/> Tabulated data (2.5) <input type="checkbox"/> Full data (Module 4)	<input type="checkbox"/> Written summary (2.4) <input type="checkbox"/> Tabulated data (2.5) <input type="checkbox"/> Full data (Module 4)
Clinical data	<input type="checkbox"/> Written summary (2.5) <input type="checkbox"/> Tabulated data (2.6) <input type="checkbox"/> Full data (Module 5)	<input type="checkbox"/> Written summary (2.5) <input type="checkbox"/> Tabulated data (2.6) <input type="checkbox"/> Full data (Module 5)	<input type="checkbox"/> Written summary (2.5) <input type="checkbox"/> Tabulated data (2.6) <input type="checkbox"/> Full data (Module 5)	<input type="checkbox"/> Written summary (2.5) <input type="checkbox"/> Tabulated data (2.6) <input type="checkbox"/> Full data (Module 5)
<b>Extent of Scientific Review</b>				
Quality/CMC data	<input type="checkbox"/> Only examined if there is a query <input type="checkbox"/> 'Check list' review for completeness of data	<input type="checkbox"/> Only examined if there is a query <input type="checkbox"/> 'Check list' review for completeness of data	<input type="checkbox"/> 'Check list' review for completeness of data <input type="checkbox"/> Selective review in detail (e.g. stability, specification)	<input type="checkbox"/> Only examined if there is a query <input type="checkbox"/> 'Check list' review for completeness of data

## INTRODUCTION

Regulatory Status:	Type I	Type II	Type III	Priority/fast track products
	<input type="checkbox"/> Selective review in detail (e.g. stability, specification) <input type="checkbox"/> Detailed assessment and evaluation report	<input type="checkbox"/> Selective review in detail (e.g. stability, specification) <input type="checkbox"/> Detailed assessment and evaluation report	<input type="checkbox"/> Detailed assessment and evaluation report	<input type="checkbox"/> Selective review in detail (e.g. stability, specification) <input type="checkbox"/> Detailed assessment and evaluation report
Comment				
Non-clinical data	<input type="checkbox"/> Only examined if there is a query <input type="checkbox"/> 'Check list' review for completeness of data <input type="checkbox"/> Detailed assessment and evaluation report	<input type="checkbox"/> Only examined if there is a query <input type="checkbox"/> 'Check list' review for completeness of data <input type="checkbox"/> Detailed assessment and evaluation report	<input type="checkbox"/> 'Check list' review for completeness of data <input type="checkbox"/> Detailed assessment and evaluation report	<input type="checkbox"/> Only examined if there is a query <input type="checkbox"/> 'Check list' review for completeness of data <input type="checkbox"/> Detailed assessment and evaluation report
Comment				
Clinical data	<input type="checkbox"/> Only examined if there is a query <input type="checkbox"/> 'Check list' review for completeness of data <input type="checkbox"/> Selective review in detail (e.g. bridging studies) <input type="checkbox"/> Detailed assessment and	<input type="checkbox"/> Only examined if there is a query <input type="checkbox"/> 'Check list' review for completeness of data <input type="checkbox"/> Selective review in detail (e.g. bridging studies) <input type="checkbox"/> Detailed assessment and	<input type="checkbox"/> 'Check list' review for completeness of data <input type="checkbox"/> Selective review in detail (e.g. bridging studies) <input type="checkbox"/> Detailed assessment and evaluation report	<input type="checkbox"/> Only examined if there is a query <input type="checkbox"/> 'Check list' review for completeness of data <input type="checkbox"/> Selective review in detail (e.g. bridging studies) <input type="checkbox"/> Detailed assessment and

## INTRODUCTION

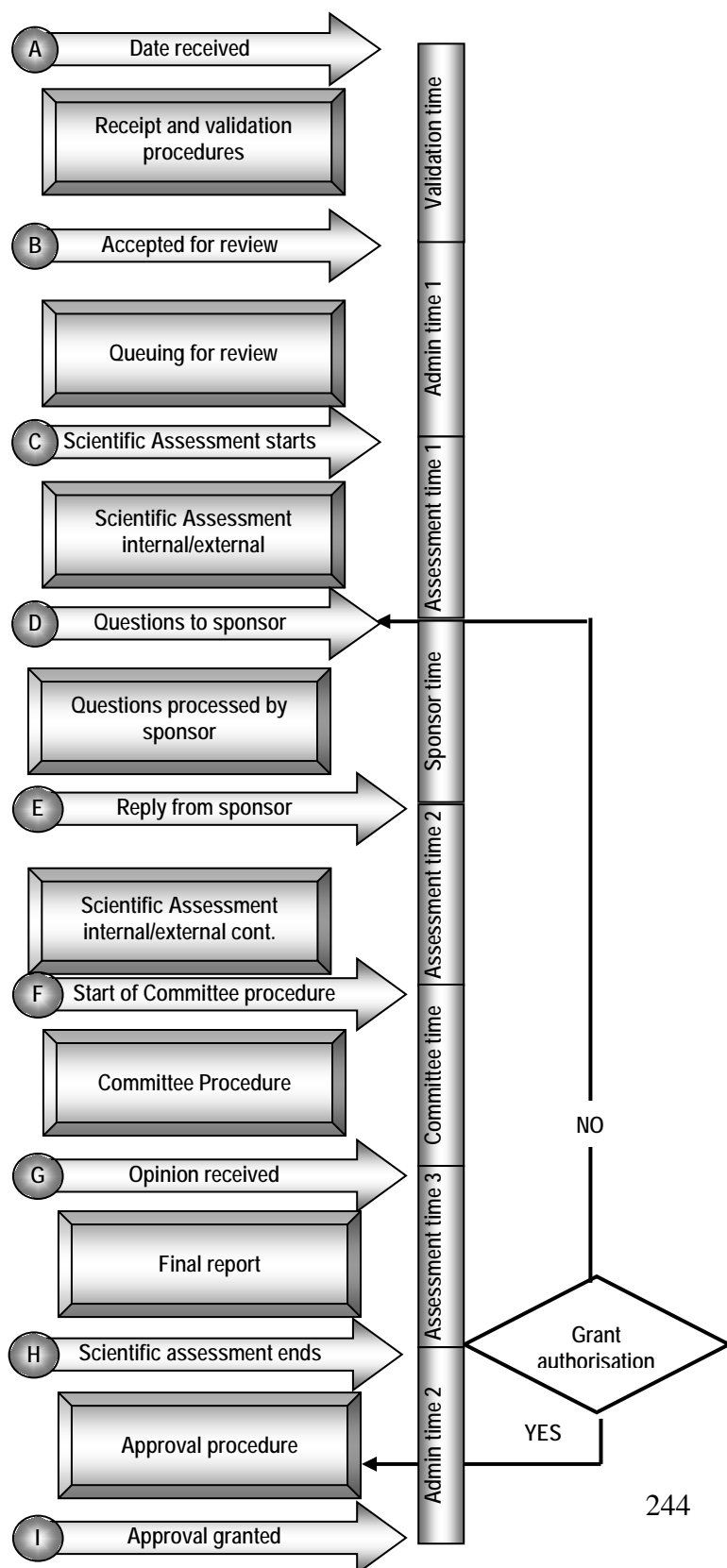
Regulatory Status:	Type I	Type II	Type III	Priority/fast track products
	evaluation report	evaluation report		evaluation report
Comment				
<b><i>Clinical evaluation: factors included in the risk-benefit assessment</i></b>				
<i>The clinical opinion takes account of:</i>	<i>Never sometimes always</i>	<i>Never sometimes always</i>	<i>Never sometimes always</i>	<i>Never sometimes always</i>
Differences in medical culture/practice	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Ethnic factors	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
National disease patterns	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Unmet medical need	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
<b><i>Additional information, not in the application</i></b>				
<i>The agency tries to obtain</i>	Information is sought: <i>Never sometimes always</i>	Information is sought: <i>Never sometimes always</i>	Information is sought: <i>Never sometimes always</i>	Information is sought: <i>Never sometimes always</i>
Other agencies' internal assessment reports	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Reports available on the Internet (e.g., EPARS)	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
General Internet search	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>
Other data (specify	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>



## PART II - KEY MILESTONES IN THE REGISTRATION OF MEDICINES

### Review Process Map and Milestones

This part of the questionnaire is based on the General Model below giving a process map and milestones that has been developed from studying procedures followed in 'established' and 'emerging' regulatory agencies. It captures the main steps in the review and approval process and identifies key 'milestone' dates in the process for monitoring and analysing timelines.



#### Notes

**Receipt and validation** may include administrative registration (reference number) and checks on legal requirements, status of company, local agent, manufacturer etc. as well as a 'checklist' validation of the application content (e.g., technical sections, CPP status).

**Queuing for review:** *Administrative time 1* is a measure of the 'backlog' time (if any) while valid applications wait for action to begin.

**Scientific Assessment** extends from milestone C to milestone H and is a measure of 'review time'. In some systems the 'clock' stops when questions are asked and **Sponsor time** (milestone D to milestone E) can be measured and deducted from the agency review time.

**Questions to sponsor** may be batched and sent at one time or asked throughout the review process, in which case the *Sponsor time* is not easily measured.

In some systems, questions may only be sent to the sponsor after the end of the 'first cycle' scientific assessment (at milestone H).

**Committee Procedure:** Most review procedures for major applications include a step where the opinion of an expert advisory committee is sought. In this scheme, the Committee procedure is 'nested' within the Scientific Assessment but it may take place after the Agency's scientific assessment is complete.

**Second cycle:** If the application cannot be granted immediately, on technical grounds, it enters a second review cycle (new data point D: questions to sponsor) and a further scientific assessment is made of the additional data. The Committee Procedure may or may not need to be included in the second and subsequent review cycles.

**Approval procedure:** The time interval after scientific review (*Admin time 2*) while the formal authorisation is issued may be extended by pricing negotiations and finalisation of analytical and GMP checks.

**Approval time** is measured from milestone A to milestone I.

## Review stages and milestones

This section of the questionnaire is based on the **General Model** shown on page 6.

We recognise that not all systems conform to the general model and it would be very helpful if you could provide an outline of the model used by your authority. If this differs according to the **Type of data assessment** (see page 5) please provide information on the different models

When information is given on target or actual times please indicate here whether these are counted in:

☐ **Calendar days**

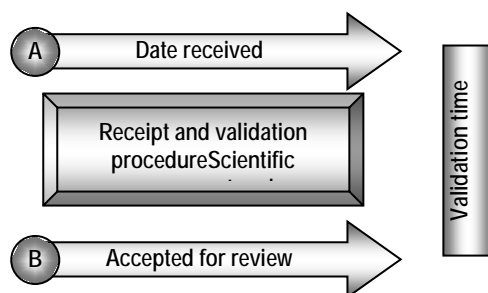
☐ **Working days**

When 'milestone' dates are recorded during the review process is the information entered into an electronic tracking/recording system?

☐ **YES**, System in current use      ☐ **NO**, System in development (Target date: \_\_\_\_\_)

☐ **NO**, A manual system will be used for the foreseeable future

### 3. Receipt and Validation



#### Pre-submission requirements

3.1. Are there any formal requirements before an application is submitted, for example, notification of intent to submit, assignment of registration code etc.

☐ **NO**, milestone A is the formal start of the application procedure

☐ **YES** (please specify)

#### Validation

3.2 Is the date of receipt (milestone A) formally recorded?	<input type="checkbox"/> <b>YES</b>	<input type="checkbox"/> <b>NO</b>
3.3 Are the following administrative items checked in the pre-review validation process?		
Legal status of applicant/local agent	<input type="checkbox"/> <b>YES</b>	<input type="checkbox"/> <b>NO</b>
GMP status of manufacturer	<input type="checkbox"/> <b>YES</b>	<input type="checkbox"/> <b>NO</b>
Patent/IP status of active ingredient	<input type="checkbox"/> <b>YES</b>	<input type="checkbox"/> <b>NO</b>
Whether company has paid the correct fee	<input type="checkbox"/> <b>YES</b>	<input type="checkbox"/> <b>NO</b>
Other:		
3.4 For those applications <b>where prior authorisation elsewhere is essential</b> (see Section 2) please answer the following questions about the <b>Certificate of a Pharmaceutical Product</b> (CPP)		
Is the inclusion of a CPP an absolute requirement before accepting the application as valid?		
<input type="checkbox"/> <b>YES</b> <input type="checkbox"/> <b>NO</b> <input type="checkbox"/> For some applications (please specify)		
If <b>YES</b> must the CPP be legalised by an Embassy or Consulate?	<input type="checkbox"/> <b>YES</b>	<input type="checkbox"/> <b>NO</b>
If <b>NO</b> , please indicate which of the following apply		
A CPP must be provided before the authorisation is issued	<input type="checkbox"/> <b>YES</b>	<input type="checkbox"/> <b>NO</b>
Other evidence of authorisation by other countries is accepted place of the CPP (e.g., copy of authorisation, Internet reference)	<input type="checkbox"/> <b>YES</b>	<input type="checkbox"/> <b>NO</b>
Comment		

### Validation (cont.)

3.5 Is the application also checked for the following items?

Acceptable format (e.g. ICH CTD or local requirements)

☐ YES ☐ NO

Correct sections of scientific data (quality, safety, efficacy)

☐ YES ☐ NO

Other technical items:

### Acceptance for review/refusal to file

3.6 Is the date of acceptance (milestone B) formally recorded?

☐ YES ☐ NO

3.7 What happens if the application is incomplete?

☐ **Refusal to file:** New application must be made

☐ **File pending:** A request for the missing data is sent to the applicant

What is the time limit for the applicant to reply?

Notes:

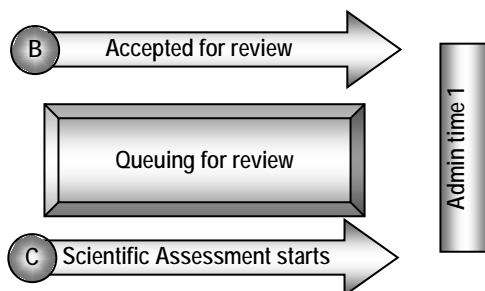
### Target time for validation

3.8 Is there a target validation time?

☐ YES (specify)

☐ NO

## 4. Queuing/backlog



4.1 Which of the following applies to the queuing system for new applications?

- ☐ Held in queue after validation (as in the General Model)
- ☐ Held in queue before validation starts (milestone A)

4.2 What is the current queue time (approximately)?

- ☐ Less than 2 weeks ☐ 2-8 weeks
- ☐ 2-6 months ☐ 6 months-1 year
- ☐ More than 1 year

4.3 Are priority products taken out of turn in the queuing system

- ☐ YES, always
- ☐ YES, sometimes
- ☐ NO, all applications await their turn

Comment:

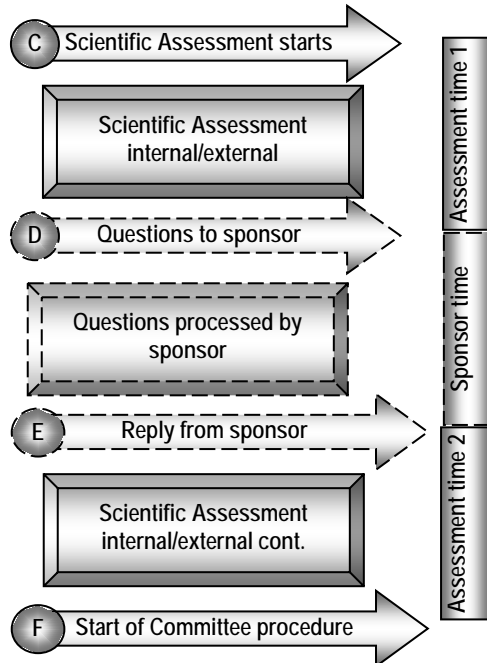
4.4 Does the Agency regard the backlog of applications as a problem

☐ YES ☐ NO

If YES, how is this being addressed?

## Scientific Assessment

### 5.1 Initiation of scientific review



5.1.1 Is the start of the Scientific Assessment formally recorded (milestone C)? ☐ YES ☐ NO

5.1.2 Is the scientific data separated into three sections (quality, safety, and efficacy) for review? ☐ YES ☐ NO

5.1.3 In what order are the different sections assessed:

☐ In parallel ☐ In sequence

If in sequence, please give order

5.1.4 Who carries out the **primary** scientific assessment?

☐ Agency technical staff ☐ Sent to outside experts

☐ Different procedure for different sections

Please describe the process

### 5.2 Use of outside experts

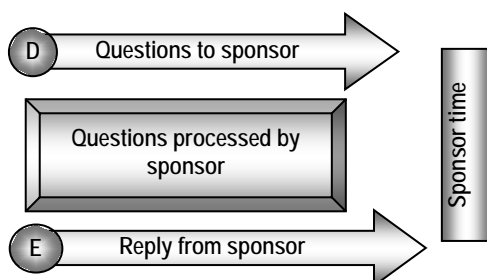
If outside experts are used for the assessment of scientific data (5.1.4 above) please complete the following:

5.2.1 Number of experts on the agency's list or panel:

5.2.2 Main responsibility: ☐ To provide a detailed assessment report and recommendation  
☐ To provide a clinical opinion on the product  
☐ To provide advice to the agency staff on specific technical issues  
☐ Other (specify

5.2.3 Is there a contractual agreement on working within deadlines set by the agency? ☐ YES ☐ NO

### 5.3 Interaction with the Sponsor



5.3.1 How are questions sent to the Sponsor

☐ as they arise during the assessment ☐ Collected into a single batch

5.3.2 When are batched questions sent to the Sponsor

☐ After the initial assessment but before reporting to the Scientific Committee (as in the General model)  
☐ Not until the Scientific Committee has given its advice  
☐ Before and after reference to the Scientific Committee

5.3.3 Does the scientific review cease while questions are being processed by the Sponsor ('clock stop')	<input type="checkbox"/> YES	<input type="checkbox"/> NO
5.3.4 Can the sponsor time be calculated, i.e., are milestones D and E recorded?	<input type="checkbox"/> YES	<input type="checkbox"/> NO
5.3.5 Is the sponsor given a time limit to reply	<input type="checkbox"/> YES	<input type="checkbox"/> NO
If <b>Yes</b> , what time is allowed?		

### Meetings

5.3.6 Can the Sponsor hold meetings with the agency staff to discuss questions and queries that arise during the assessment	<input type="checkbox"/> YES	<input type="checkbox"/> NO
If <b>Yes</b> , what conditions and restrictions (if any) are applied?		

## 5.4 Review by Scientific Committee

	<p>5.4.1 Is a Committee of Experts (internal and/or external) used in the review process</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
	<p>5.4.2 If <b>Yes</b>, at which stage in the review?</p> <p><input type="checkbox"/> Responsible for the whole assessment of the dossier from the start of the review</p> <p><input type="checkbox"/> Integrated into the agency's own internal/external scientific review procedure</p> <p><input type="checkbox"/> Consulted after the agency has reviewed and reported on the scientific data</p> <p><input type="checkbox"/> Other (specify)</p>
<p>5.4.3 Are the dates at the start and end of the Committee Review recorded (milestones F and G)?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>	
<p>5.4.4 Is the agency mandated to follow the Committee recommendation?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>	
<p>5.4.5 Is there a time limit for the Committee Procedure?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>If <b>Yes</b>, please give the target</p> <p>If <b>No</b>, what is the time range (e.g., 1-3 months)</p>	
<p>5.4.6 Is there an additional step in the scientific review process, after the Committee has given its opinion?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>If <b>Yes</b>, please describe briefly the work carried out at this stage (e.g., final report and agency opinion)</p> <p>If <b>No</b>, the milestone G will mark the end of the scientific review for the purpose of calculating the review time</p>	

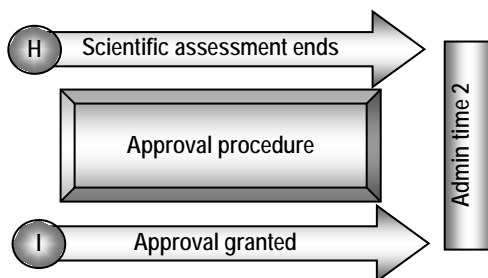
### Target for scientific review

5.4.7 Is a target time set for the scientific review (milestones C to H)

☐ YES ☐ NO

If YES please give target

## 6. Decision on the Application



At the end of the Scientific Review (see General Model, page 6) there is normally recommendation that either:

The product meets the scientific criteria for authorisation (proceed to approval procedure) or

Further data is required before the scientific criteria are met (application enters a **second cycle** at milestone D (questions to Sponsor) or

The application should be refused (not shown in the General Model)

### 6.1 Responsibility for the authorisation decision

6.1.1 Who makes the decision that a marketing authorisation can be granted?

☐ The Scientific Committee

☐ The Head of the Agency

☐ The Minister of Health

☐ Other (please specify)

### 6.2 Other Criteria to be met

6.2.1 Is the issue of the authorisation dependent on a **pricing agreement**

☐ YES ☐ NO

If YES, when are the pricing negotiations started?

☐ At the start of the scientific review

☐ After the end of the scientific review

☐ After the start but before the end of the scientific review

6.2.2 Is the issue of the authorisation dependent on **sample analysis**

☐ YES ☐ NO

If YES, when is the analytical work started?

☐ In parallel with the scientific review

☐ At the end of the scientific review

☐ After the start but before the end of the scientific review

6.2.3 Is there a separate negotiation of the **product labelling/ product information** after the scientific opinion is given but before the approval is issued?

☐ YES ☐ NO

Comments:

6.2.4 Please specify any other legal/administrative matters that must be finalised before the approval can be issued

### 6.3 Approval procedure

6.3.1 Is the Sponsor informed of a positive scientific opinion at milestone G, i.e., before the authorisation is issued? ☐ YES ☐ NO

6.3.2 Approximately how long does it take from receiving a positive scientific opinion (at milestone H) to issuing an approval (milestone I)

☐ Less than a month ☐ 1-3 months ☐ 3-6 months ☐ Over 6 months

Comment:

### 7. Metrics on the Approval Process for NAS

It would be very helpful to have the following information on processing times for marketing authorisations that have been received and/or determined in the three years 2004, 2005, 2006.

#### 7.1 Applications received

Type	Number of applications received in each year			Current backlog
	2011	2012	2013	
New Active Substance				
Major line extension				

#### 7.2 Applications determined

Type	Number of applications determined in each year		
	2011	2012	2013
New Active Substances approved			
New Active Substances refused			
Major line extensions approved			
Major line extension refused			

#### 7.3 Average approval times

Type	Time from receipt of application to issue of approval		
	2010	2011	2013
New Active Substances			
Major line extensions			

#### 7.4 Target for approval times

Is a target time set for the overall approval process (milestones A to I) ☐ YES ☐ NO

If YES please give target

Please comment on the actual review times in relation to the authority's target time

## PART III: GOOD REVIEW PRACTICE (GREVP)

### BUILDING QUALITY INTO THE ASSESSMENT

#### AND REGISTRATION PROCESS

Quality in the assessment and registration process is important to regulatory authorities as it ensures consistency, transparency, timeliness and competency in the review processes. Regulatory authorities are continuously developing and implementing a variety of measures to improve and achieve higher quality standards and to meet the expectations of industry and the general public.

The purpose of this section of the questionnaire is to obtain an insight into the strategies, measures and resources that agencies have in place to develop and maintain quality in their review processes.

#### 8. General Measures used to achieve quality

Please indicate the quality measures currently in place and, where none, plans to introduce such measures in the foreseeable future.

**Good Review Practice (GRevP):** A code about the process and the documentation of review procedures that aims to standardise and improve the overall documentation and ensure timeliness, predictability, consistency and high quality of reviews and review reports

8.1 *How does your agency define GRevP?:*

Is it different from the Glossary? ☐ YES ☐ NO

If different, please define in here:

Please Outline the key elements that make up GRevP in your agency:

*Has the Agency formally or informally implemented GRevP?*

☐ YES(Formally)

☐ YES(Informally) ☐ NO

If YES please give the title and date of **formal** implementation:

How has this been implemented: (Please tick the appropriate Box(s))

☐ Guidelines ☐ Standard Operating Procedures ☐ GRevP Training Program

☐ Other: Please specify:



Are these documents open and available to the Public? <input type="checkbox"/> YES <input type="checkbox"/> NO If Yes please describe:
Was the establishment of your GRevP based on other agencies or International standards? <input type="checkbox"/> YES <input type="checkbox"/> NO
If Yes: please state the name of the agency(ies)/ or International standards on which your GRevP has been based:
Are you satisfied with your existing GRevP framework? <input type="checkbox"/> Satisfied <input type="checkbox"/> Could be improved <input type="checkbox"/> Unsatisfied  If <b>could be improved</b> or <b>Unsatisfied</b> , please select reason(s) that best describes your situation. <input type="checkbox"/> System still evolving <input type="checkbox"/> Requires additional training to understand and learn about Good Review Practice <input type="checkbox"/> Poor acceptance/utilisation by staff <input type="checkbox"/> Benefits of implementing GRevP are not apparent so far <input type="checkbox"/> Other (please provide details)
If you <b>do not have</b> a formal GRevP system in place are there plans to establish this within the next two years? <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Quality Policy:</b> Overall intentions and direction of an organisation related to quality as formally expressed by top management.  8.2 Does the Agency have an internal Quality Policy? <input type="checkbox"/> YES <input type="checkbox"/> NO If <b>NO</b> are there plans to establish this within the next two years? <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>SOPs</b> (Standard Operating Procedures) are written documents that describe in detail the routine procedures to be followed for a specific operation.  8.3 Are there SOPs for the guidance of scientific assessors <input type="checkbox"/> YES <input type="checkbox"/> NO If <b>NO</b> are there plans to establish SOPs within the next two years? <input type="checkbox"/> YES <input type="checkbox"/> NO
8.4 Are there SOPs for the advisory committee consulted during the review process <input type="checkbox"/> YES <input type="checkbox"/> NO <div style="text-align: right;"><input type="checkbox"/> No committee</div> If <b>NO</b> are there plans to establish SOPs within the next two years? <input type="checkbox"/> YES <input type="checkbox"/> NO

8.5 Are SOPs used for any other procedures in the regulatory review process (e.g., validation)?	<input type="checkbox"/> YES	<input type="checkbox"/> NO
Please specify:		
<b>Assessment Templates</b> set out the content and format of written reports on scientific reviews.		
8.6 Are there Assessment Templates for reports on the scientific review of a NAS?	<input type="checkbox"/> YES	<input type="checkbox"/> NO
If <b>NO</b> are there plans to establish this within the next two years?	<input type="checkbox"/> YES	<input type="checkbox"/> NO
If <b>Yes</b> are these based on another agencies assessment template	<input type="checkbox"/> YES	<input type="checkbox"/> NO
If Yes, which agency was the assessment template based? Please specify:		
Is there an SOP for completing an assessment template		
	<input type="checkbox"/> YES	<input type="checkbox"/> NO
Can you tick what elements from the list below are included in your agency assessment template?		
<div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> <input type="checkbox"/> Drug substance         </div> <div style="width: 50%;"> <input type="checkbox"/> GCP aspects         </div> <div style="width: 50%;"> <input type="checkbox"/> Drug product         </div> <div style="width: 50%;"> <input type="checkbox"/> Clinical Pharmacology (PK and PD)         </div> <div style="width: 50%;"> <input type="checkbox"/> Comments on label         </div> <div style="width: 50%;"> <input type="checkbox"/> Clinical Efficacy         </div> <div style="width: 50%;"> <input type="checkbox"/> Non clinical GLP Aspects         </div> <div style="width: 50%;"> <input type="checkbox"/> Clinical Safety         </div> <div style="width: 50%;"> <input type="checkbox"/> Non clinical Pharmacokinetics         </div> <div style="width: 50%;"> <input type="checkbox"/> List of questions for sponsors         </div> <div style="width: 50%;"> <input type="checkbox"/> Toxicology         </div> <div style="width: 50%;"> <input type="checkbox"/> Benefit risk discussion         </div> <div style="width: 50%;"> <input type="checkbox"/> Regulatory background (worldwide status on regulatory agencies)         </div> <div style="width: 50%;"> <input type="checkbox"/> Ethnic factors (eg consideration of bridging studies)         </div> <div style="width: 50%;"> <input type="checkbox"/> Other (please specify):         </div> </div>		
Would the agency be open to sharing their assessment template or points to consider with CIRS?		<input type="checkbox"/> YES <input type="checkbox"/> NO
Do you produce an assessment report (AR) following the review?		<input type="checkbox"/> YES <input type="checkbox"/> NO
If Yes :		
Is there an SOP for completing the AR:	<input type="checkbox"/> YES <input type="checkbox"/> NO	
What language is the AR prepared in:	<input type="checkbox"/> Local language <input type="checkbox"/> English	
Do you share your AR with other regulatory authorities	<input type="checkbox"/> YES <input type="checkbox"/> NO	
Do you put your full AR on the website	<input type="checkbox"/> Sometimes	
Do you put your abridged AR on the website	<input type="checkbox"/> YES <input type="checkbox"/> NO	
	<input type="checkbox"/> Sometimes	

Do sponsors get a copy of the <b>full</b> assessment report?				<input type="checkbox"/> YES	<input type="checkbox"/> NO
Do Sponsors have any involvement in the following in relation to AR:					
Preparation of assessment reports				<input type="checkbox"/> YES	<input type="checkbox"/> NO
Comments on the assessment reports				<input type="checkbox"/> YES	<input type="checkbox"/> NO
Translation of assessment reports				<input type="checkbox"/> YES	<input type="checkbox"/> NO
Distribution of Assessment reports					
<p><b>Peer Review</b> is an additional evaluation of an original assessment that is carried out by an independent person or committee. Peer review can occur either during assessment of a dossier or at the time of sign-off.</p> <p>8.7 Are <b>external</b> peer reviews carried out when a NAS is assessed?</p> <p>If <b>NO</b> are there plans to introduce these within the next two years?</p>					
				<input type="checkbox"/> YES	<input type="checkbox"/> NO
				<input type="checkbox"/> YES	<input type="checkbox"/> NO
<p>8.8 Are <b>internal</b> peer reviews carried out when a NAS is assessed?</p> <p>If <b>NO</b> are there plans to introduce these within the next two years?</p>					
				<input type="checkbox"/> YES	<input type="checkbox"/> NO
				<input type="checkbox"/> YES	<input type="checkbox"/> NO
Do you have <b>target times</b> for following activities and if so can you provide your target times?				<b>Yes</b>	<b>No</b>
Overall approval times				<input type="checkbox"/>	<input type="checkbox"/>
Validation of dossier				<input type="checkbox"/>	<input type="checkbox"/>
Scientific assessment				<input type="checkbox"/>	<input type="checkbox"/>
Company (clock stop), time				<input type="checkbox"/>	<input type="checkbox"/>
Other: Please specify: _____					
If Target times given are they in working days?					
<p>8.9 Are there other general procedures in place to monitor the quality of the review process?</p> <p>What other tools does your agency use to build quality into the assessment process?</p> <p>(eg Internal procedure could include; Quality assurance and quality control meeting; Stakeholder meeting; Channel for grievance; Survey of performance from sponsors) Please specify:</p>					

## 9 Quality Management

### *Reasons for introducing quality measures in the authority*

9.1 Please select, from the following list, the **three** most important reasons for the introduction of quality measures

- |  |   |
|--|---|
| <input type="checkbox"/> To be more efficient                | <input type="checkbox"/> To minimise errors                         |
| <input type="checkbox"/> To ensure consistency               | <input type="checkbox"/> To reduce costs                            |
| <input type="checkbox"/> To achieve stakeholder satisfaction | <input type="checkbox"/> To increase transparency                   |
| <input type="checkbox"/> To improve process predictability   | <input type="checkbox"/> To improve communications in the authority |
| <input type="checkbox"/> Other (please specify)              | <input type="checkbox"/> To allocate the regulatory resources       |

### *Monitoring to improve quality*

9.2 Which of the following activities are undertaken by the authority to bring about continuous improvement in the assessment and registration process?

- |  |                              |                             |
|--|------------------------------|-----------------------------|
| Reviewing assessors' feedback and taking necessary action  | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Reviewing stakeholders' feedback (e.g. through complaints, meetings or workshops) and taking necessary action                            | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Using an internal tracking system to monitor (e.g. consistency, timeliness, efficiency and accuracy)                                     | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Carrying out internal quality audits (e.g. self-assessments) and using findings to improve the system                                    | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Having external quality audits by an accredited certification body to improve the system   | <input type="checkbox"/> YES | <input type="checkbox"/> NO |
| Having a 'post approval' discussion with the sponsor to provide feedback on the quality of the dossier and obtain the company's comments | <input type="checkbox"/> YES | <input type="checkbox"/> NO |

### *Management responsibility*

9.3 Does the authority have a dedicated department for assessing and/or ensuring quality in the assessment and registration process? ☐ YES ☐ NO

If **YES**, how many staff are involved?

**How often do you assess and/or ensure quality in assessment and registration process?**

☐ Annually ☐ Semi-Annually ☐ Adhoc ☐ Other (please specify) \_\_\_\_\_

To whom does this section report (e.g. the Chief Executive Officer of the authority)?

If **NO**, is the Authority thinking of setting up such a department? ☐ YES ☐ NO

## 10. Quality in the Review and Assessment Process

### *Improving the quality of applications*

10.1 Does the authority have official guidelines to assist industry in the registration of medicinal products? ☐ YES ☐ NO

If **YES**, how are these guidelines made available? (Please indicate all that apply)

- ☐ Through the authority's website ☐ Through official publications  
☐ On request ☐ Through Industry Associations  
☐ Other, please specify:

What language are the guidelines available in:

- ☐ Local language only ☐ English ☐ Other, please specify:

### *Improving quality through interaction with applicants*

10.2 Does the authority provide pre-submission scientific advice to applicants? ☐ YES ☐ NO

If **YES** how is the quality of that advice monitored?

10.3 Is the applicant given details of technical staff that can be contacted to discuss an application during review? ☐ YES ☐ NO

10.4 Please indicate which of the following best describes the level of contact that companies have with agency staff or outside experts during development and during the agency's assessment.

	Development	Assessment
<b>Extensive formal</b> contact (including scheduled meetings)	<input type="checkbox"/>	<input type="checkbox"/>
<b>Extensive informal</b> contact (frequent telephone or email contact)	<input type="checkbox"/>	<input type="checkbox"/>
<b>Some formal</b> contact (possibility of meetings)	<input type="checkbox"/>	<input type="checkbox"/>
<b>Some informal</b> contact (possibility of telephone or email contact)	<input type="checkbox"/>	<input type="checkbox"/>
<b>None, or minimal formal</b> contact (rare occurrences of contact, via letter or fax)	<input type="checkbox"/>	<input type="checkbox"/>
<b>None, or minimal informal</b> contact (rare telephone or email contact)	<input type="checkbox"/>	<input type="checkbox"/>

Please comment on general policy for contact with applicants:

### *Committee Procedure*

10.5 If your review procedure includes obtaining the advice of a scientific committee of internal and/or external experts (as in Section 5.4) please complete the following:

Name of the Committee \_\_\_\_\_

Number of Committee Members \_\_\_\_\_

How frequently does the Committee meet?

- ☐ Once a week ☐ Once a month ☐ Other, please specify:

For NAS applications and major line extensions does the Committee review?

- ☐ All applications ☐ Selected dossiers (specify) \_\_\_\_\_

Does the Committee review?

- ☐ The complete dossier ☐ Assessment reports from the reviewers

### ***Shared and Joint reviews with other Regulatory Agencies outside of your country***

A ***shared review*** is one where each participating authority takes responsibility for reviewing a separate part of the dossier. A ***joint review*** is one where the whole dossier is reviewed by each authority and the outcome is discussed before a decision is taken.

Are bilateral-multilateral information sharing agreements in place with other jurisdictions?

☐ **YES**      ☐ **NO**

If Yes, What is the general nature of those agreements?

*10.6 Does your authority conduct shared or joint reviews with other regulatory authorities?*

☐ **YES regularly. Please state which authorities**

☐ **YES occasionally. Please state which authorities**

☐ **NO this has never been undertaken**

If **YES** do you have formal measures in place to ensure consistent quality during the review?

☐ **YES**      ☐ **NO**

If **Yes**, please specify

If **NO**, do you anticipate undertaking such reviews within the next two years?

☐ **YES**      ☐ **NO**

*10.7 Have these joint reviews influenced the way in which your authority conducts reviews in general? If so, please comment*

☐ **YES**      ☐ **NO**

## **11. Training and continuing education as an element of quality**

The following questions relate to training and continuing education of assessors working within the authority, including those employed on a full-time basis and those contracted for specific assessments were necessary.

*11.1 Do you have a formal training programme for assessors?*

☐ **YES**      ☐ **NO**

*11.2 Which of the following methods are used for training assessors?*

☐ Induction training

☐ External courses

☐ On-the-job training

☐ Sponsoring of Post-graduate degrees

☐ Placements and secondments in other regulatory authorities

☐ Participation in international workshops/conferences

☐ External speakers invited to the authority

☐ In-house courses

☐ Training in advanced DRA

☐ Other, please specify:

Does your authority seek <b>direct</b> assistance of more experienced agencies for development of SOPs and Guidelines?	<input type="checkbox"/> YES	<input type="checkbox"/> NO
If Yes please give details:		
Does your authority mainly develop SOP, Guidelines etc based on information published by more experienced agencies:	<input type="checkbox"/> YES	<input type="checkbox"/> NO
11.3 Does your authority collaborate with other agencies in the training of assessors?	<input type="checkbox"/> YES	<input type="checkbox"/> NO
If <b>Yes</b> , please give details:		
11.4 Is training tested in examination situations once completed?	<input type="checkbox"/> YES <input type="checkbox"/> Partly	<input type="checkbox"/> NO
11.5 Is completion of training courses required for professional advancement?	<input type="checkbox"/> YES <input type="checkbox"/> Partly	<input type="checkbox"/> NO

### **Transparency to companies on application progress**

12.5 Are companies able to follow the progress of their own applications?	<input type="checkbox"/> YES <input type="checkbox"/> NO
If <b>YES</b> please indicate the mechanisms available to industry	
<input type="checkbox"/> Electronic access to the status of applications	<input type="checkbox"/> E-mail contact
<input type="checkbox"/> E-mail contact	<input type="checkbox"/> Other, please specify:
12.6 Are companies given detailed reasons for rejecting an application for registration?	<input type="checkbox"/> YES <input type="checkbox"/> NO

### **Facilities for providing information**

12.7 Is there an electronic system for registering and tracking applications	<input type="checkbox"/> YES <input type="checkbox"/> NO
If <b>YES</b> please indicate whether it has the following capabilities	
Tracing applications that are under review and identifying the stage in the process	<input type="checkbox"/> YES <input type="checkbox"/> NO
Signalling that target review dates have been exceeded	<input type="checkbox"/> YES <input type="checkbox"/> NO
Recording the terms of the authorisation once granted	<input type="checkbox"/> YES <input type="checkbox"/> NO
Archiving information on applications in a way that can be searched	<input type="checkbox"/> YES <input type="checkbox"/> NO
If <b>NO</b> are there plans to introduce such a system?	<input type="checkbox"/> YES <input type="checkbox"/> NO
If so, please give target date for implementation:	<input type="text"/>

## **13. Concluding Observations**

The purpose of the following two questions is to try to identify the Agency's own perception of its unique positive qualities and the major impediments it faces in carrying out the review of new medicines and making them available to meet patients' needs.

13.1 List three factors that make a major contribution to the effectiveness and efficiency of your agency's review procedures and decision-making processes for NAS applications
1.
2.
3.
13.2 List three factors that act as barriers to making new medicines available in a timely manner through the regulatory process



1.
2.
3.

13.3 Any important documents related to GRevP that you would like to share with CIRS?

☐ YES ☐ NO

If yes please list and provide directly to CIRS

#### 14. Sharing Assessment reports: Agency perceptions

It has been suggested thorough various platforms that in the future the sharing of assessment reports for pharmaceutical assessment between member Economies would be of value. Please read the following statements and mark one of the given options: **Strongly agree / Agree / Indifferent / Disagree / Strongly disagree.**

	Strongly Agree	Agree	Indifferent	Disagree	Strongly disagree
Sharing of assessment reports for pharmaceuticals between economies would be of value to streamlining the review process by my agency	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
In order for Agencies to share assessment reports, assessment templates should contain the same key elements	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sharing of assessment reports will enable agencies to utilise their resources more effectively and efficiently	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sharing assessment reports will reduce the review time for a dossier by my agency	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Strongly Agree	Agree	Indifferent	Disagree	Strongly disagree

Sharing activities of assessing a new drug with other agencies for simultaneously submitted products will reduce the review time for the dossier	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ARs should be region-specific rather than global in their content if they are to be of value in meeting the agencies' needs?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
A single aligned standard operating procedure can be developed to guide agencies to the use of an assessment template and provide consistency in the completion process.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sharing AR will improve the quality of review by providing my agency insight and understanding of differences and regulatory controversies encountered by other agencies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sharing AR will ensure that the industry submit similar dossiers across DRAs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sharing AR will facilitate regulatory interactions among reviewers of DRAs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**14.1: Please List three benefits you envision to sharing assessment reports**

- 1)
- 2)
- 3)

**14.2: Please list three hurdles you envision to sharing assessment reports**

- 1)
- 2)
- 3)

**Thank you for completing this questionnaire**

*Please sign and date:*

Signature	Position
Name	
Date	Email address

## GLOSSARY AND ABBREVIATIONS

<b>Additional information</b>	Additional data or additional analyses of existing data requested from the sponsor by the regulatory authority during the review process.
<b>Advisory Committee</b>	An expert committee that advises the regulatory authority of the safety, quality and efficacy of new medicines for human use.
<b>Approval</b>	The approval of a drug product by a regulatory authority, signified by the granting of a marketing authorisation, or the issue of a technical approval letter. However the product may still not be marketable until negotiations for pricing and reimbursement are concluded.
<b>Clinical summary</b>	Summary of clinical study data that typically includes biopharmaceutic studies and associated analytical methods, clinical pharmacology studies, clinical efficacy, clinical safety, literature references, and synopses of individual studies. Refers to Module 2.7 in CTD format.
<b>Common technical document (CTD) format</b>	Common technical document (CTD) as outlined in the ICH guideline M4 (Organisation of the common technical document for the registration of pharmaceuticals for human use; M4).
<b>CMC</b>	Chemistry, manufacturing and controls. All activities conducted to optimize, scale-up and validate the processes and technologies for transfer to manufacture and all QA, QC and CMC support activities (e.g. CMC project management including CMC contribution to project teams). This includes all drug substance R&D i.e. process research and process development, all drug product R&D i.e. formulation development and process development, all analytical work for drug substance R&D and drug product R&D, clinical supplies and CMC's involvement in the compilation of regulatory documentation.
<b>GCP</b>	Good Clinical Practice.
<b>Good Review Practice (GRevP)</b>	A code about the process and the documentation of review procedures that aims to standardise and improve the overall documentation and ensure timeliness, predictability, consistency and high quality of reviews and review reports.
<b>ICH</b>	International Conference on Harmonisation.
<b>Internal reviewers</b>	Internal reviewers are employees of the Authority.
<b>Joint review</b>	The whole dossier is reviewed by each authority and the outcome is discussed before a decision is taken.

<b>Marketing Authorisation</b>	Authorisation issued by a regulatory to launch a drug product on the market.
<b>Marketing Authorisation Application (MAA)</b>	Authorisation application submitted to a regulatory authority to launch a drug product on the market to which the application has been submitted.
<b>Milestone</b>	A milestone must involve some form of dated written document to which the regulatory authority can refer. In addition, a milestone must be considered by the regulatory authority to be the point at which one event stops and the next one begins so that the times for events are interdependent.
<b>Major Line Extension</b>	A major line extension is a modification to an authorised Medicinal Product that is sufficiently great that it cannot be considered to be a simple variation to the original product, but requires a new product authorisation. Such modifications include major new therapeutic indications or new disease states, extension to new patient populations (e.g., paediatrics), a new route of administration or a novel drug deliver system.
<b>NAS (New Active Substance)</b>	<p>A new chemical, biological or pharmaceutical active substance includes:</p> <ul style="list-style-type: none"> <li>a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product;</li> <li>an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance not previously authorised as a medicinal product but differing in properties with regard to safety and efficacy from that chemical substance previously authorised;</li> <li>a biological substance previously authorised as a medicinal product, but differing in molecular structure, nature of the source material or manufacturing process;</li> <li>a radiopharmaceutical substance which is radionucleotide, or a ligand not previously authorised as a medicinal product, or the coupling mechanism to link the molecule and the radionucleotide has not been previously authorised.</li> </ul>
<b>Non-clinical summary</b>	Summary of non-clinical data including: pharmacology, pharmacokinetics and toxicology. Refers to Module 2.6 in CTD format.

<b>Peer review</b>	Peer review means an additional evaluation of an original assessment carried out by an independent person or committee. Peer review can occur either during assessment of a dossier, or at sign-off.
<b>Quality control</b>	Quality control is operational techniques and activities that are used to fulfil requirements for quality. It involves techniques that monitor a process and eliminate causes of unsatisfactory performance at all stages of the quality cycle.
<b>Quality policy</b>	Overall intentions and direction of an organisation related to quality as formally expressed by top management.
<b>Questions to sponsor</b>	The process of asking the sponsor for additional data or additional analyses of existing data. The requests are made by the regulatory authority during the review process.
<b>Scientific assessment</b>	Review of the dossier in terms of safety, quality and efficacy of data submitted.
<b>Shared review</b>	Each authority takes responsibility for assessing a separate part of a dossier.
<b>Sponsor</b>	A company, person, organisation or institution that takes responsibility for initiating, managing or financing a clinical study.
<b>Standard Operating Procedures (SOPs)</b>	Detailed, written instructions to achieve uniformity of the performance of a specific function.
<b>Validation of a dossier</b>	The process whereby the authority verifies that all parts of the submitted dossier are present and complete and suitable to be assessed as part of the assessment and registration process.

## **Appendix II**

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# **CONFIDENTIALITY AGREEMENT**

**MUTUAL CONFIDENTIAL  
DISCLOSURE AGREEMENT**

**Confidentiality Agreement**

This Agreement, dated as of \_\_\_\_\_, is between *the Centre for Innovation in Regulatory Science Ltd, (hereafter, "CIRS") The Johnson Building, 77 Hatton Garden, London, EC1N 8JS, UK* and \_\_\_\_\_, doing business at \_\_\_\_\_.

Each party intends to disclose certain confidential information to the other party so that the parties may develop proposals for possible services by CIRS or for CIRS to conduct any actual work using any such Confidential Information. In consideration of each party making such confidential information available to the other party, the parties hereby agree as follows:

1. As used in this Agreement, the term "Confidential Information" means any technical or business information provided by one party (the "Disclosing Party") to the other party (the "Receiving Party") pursuant to this Agreement. Such Confidential Information include, without limitation, trade secrets, know-how, inventions, technical data, business or financial information, research and development activities, product and marketing plans, and customer and supplier information.
2. The Receiving Party agrees that it shall:
  - a. maintain all Confidential Information in strict confidence, except that the Receiving Party may disclose or permit the disclosure of any Confidential Information to its employees and advisors who are obligated to maintain the confidentiality of such Confidential Information
  - b. use all Confidential Information solely for the purposes of this Agreement; and
  - c. allow its employees and advisors to use or reproduce the Confidential Information only to the extent and purposes of this Agreement. With all reproductions being considered Confidential.
3. The obligations of the Receiving Party under Section 2 above shall not apply to the extent that the Receiving Party can demonstrate that certain Confidential Information:
  - a. was in the public domain prior to the time of its disclosure under this Agreement;
  - b. entered the public domain after the time of its disclosure under this Agreement through means other than the Receiving Party;
  - c. was independently developed or discovered by the Receiving Party without use of the Confidential Information
  - d. is or was disclosed to the Receiving Party at any time, whether prior to or after the time of its disclosure under this Agreement, by a third party having no fiduciary relationship with the Disclosing Party and having no obligation of confidentiality with respect to such Confidential Information; or
  - e. is required to be disclosed to comply with applicable laws or regulations, or with a court or administrative order, provided that the Disclosing Party receives prior notice of such disclosure and that the Receiving Party takes all reasonable and lawful actions to obtain confidential treatment for such disclosure.

Acknowledged and agreed:

**CIRS**  
**SIGNATURE:** \_\_\_\_\_  
**NAME:** \_\_\_\_\_  
**TITLE:** \_\_\_\_\_  
**DATE:** \_\_\_\_\_

**Company:** \_\_\_\_\_  
**SIGNATURE:** \_\_\_\_\_  
**NAME:** \_\_\_\_\_  
**TITLE:** \_\_\_\_\_  
**DATE:** \_\_\_\_\_

## **Appendix III**

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# **INDUSTRY QUESTIONNAIRE STUDY QUESTION AND ANSWER DOCUMENT**



**“EVALUATION OF THE ATTITUDES AND EXPERIENCES OF  
PHARMACEUTICAL COMPANIES TOWARDS THE REGULATORY AND  
REIMBURSEMENT PROCEDURES FOR INNOVATIVE MEDICINES IN TURKEY”**

**PHARMACEUTICAL INDUSTRY PERSPECTIVE QUESTIONNAIRE  
TURKEY**

**QUESTION & ANSWER**

25 Feb. 2016

1

**1. What is the aim of this questionnaire?**

This survey is designed in association with the Centre for Innovation in Regulatory Science (CIRS) as part of a PhD project at Cardiff University to evaluate the Turkish Regulatory environment and its impact on patients' access to innovative medicines. The questionnaire is designed to be complementary to another two questionnaires sent out to patients and to the Turkish medicine & medical device agency (TITCK). The aim of the questionnaire is to assess the experience and attitude of the pharmaceutical companies in Turkey towards the regulatory review and reimbursement review processes in terms of:

- Review process: requirements of the Turkish authorities and timelines.
- Level of interaction with the Turkish Medicines Agency
- Process review in terms of predictability, transparency and consistency.

**2. What are the objectives expected to be achieved through this study?**

In this survey the aim is to identify:

1. The key issues companies are facing in the Turkish regulatory environment.
2. Changes in regulatory approval timelines and processes since 2011.
3. Improvements that the pharmaceutical industry would like to see in the registration process.

**3. Who will participate to this questionnaire in Turkey?**

The survey will target 38 innovative pharmaceutical companies officially registered as full members of the Research Based Pharmaceutical Companies' Association (AIFD) operating in Turkey. The survey will also be completed by member companies of the pharmaceutical manufacturers association of Turkey (IEIS) who are also involved in the registration of new active substances (NAS's).

**4. How will the data from this questionnaire be collected?**

The collected data from the participating companies will be anonymised to ensure confidentiality and avoid any potential conflict of interests. The data from companies will be collected by CIRS and only blinded data will be analysed.

**5. How long would it take to complete this questionnaire?**

It is estimated that it would take 30 minutes for each individual company to complete the questionnaire

**6. How would the confidentiality of data be secured?**

CIRS recognises that much of these data may be highly sensitive. CIRS has more than 30 years of experience in handling similar data provided by agencies and companies regarding individual products in regulatory review. Therefore:

- All information collected from individual companies will be kept strictly confidential.
- No data that will identify an individual company will be reported, or made available to a third party.
- External reports or presentations of the data will include only anonymised figures.

Companies that may wish to have a confidentiality agreement with CIRS prior the completion of this questionnaire, should complete the confidentiality agreement attached and send to the scientific director of CIRS Dr. Neil McAuslane. [nmcauslane@cirsci.org](mailto:nmcauslane@cirsci.org).

**7. What is the expected outcome of this study questionnaire?**

The study has been designed to be complementary to two other projects that are targeting the public perception as well as the key issues facing the Turkish Pharmaceuticals and Medical Device Agency (TITCK). It is expected that the outcome of this study will also enable improvements in the regulatory and access process to be identified that the pharmaceutical industry would like to see implemented so that the drug approval process is efficient and effective and access to innovative medicines is enhanced.

**8. What will be the study deliverables?**

The blinded data will be analysed to generate a study report. The study report will be prepared as a word document as well as a power point presentation to enable the results to be assessed in comparison with the overall objectives of the study. The outcome report and data will be first shared and discussed with AIFD and participating companies. The report will then be used to generate comprehensive comparison reports with other studies in other countries and in respect to TITCK questionnaire outcome report as well. Important aspects of the study will be submitted within the PhD thesis to Cardiff University.

**9. Will individual companies receive the final report?**

All participating companies will receive a confidential report of the results of this survey based on the anonymised data.

**10. Will the report be shared with public or with the health authorities?**

CIRS is committed to all terms of confidentiality and confirms that no outcome reports or data will go into the public domain or shared with the authorities before discussion and agreement of the results with AIFD and participating member companies.

**11. Where should I return the completed questionnaire?**

This Questionnaire is being communicated by AIFD to all member companies by the 1<sup>st</sup> of March 2016. Please return this questionnaire to CIRS scientific director Dr. Neil McAuslane; [nmcauslane@cirsci.org](mailto:nmcauslane@cirsci.org) latest by 21<sup>st</sup> of March 2016.

*For further information about the project and the potential impact of the study, please contact*

<p>Emel Mashaki University of Cardiff Department of Pharmaceutical Sciences Phone Number: +90 532 296 88 85 e-mail: <a href="mailto:Mashakie@cf.ac.UK">Mashakie@cf.ac.UK</a> <a href="mailto:emel_meshaki@hotmail.com">emel_meshaki@hotmail.com</a></p>	<p>Professor Stuart Walker CIRS &amp; the University of Cardiff Address: London – UK Phone Number: +44 20 8395 54 74 e-mail: <a href="mailto:swalker@cirsci.org">swalker@cirsci.org</a></p>	<p>Dr.Neil McAuslane, CIRS, Scientific Director Address: London – UK Phone Number: +44 207 433 41 45 e-mail: <a href="mailto:nmcauslane@cirsci.org">nmcauslane@cirsci.org</a></p>
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**Thank you very much for your time.**

25 Feb. 2016

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## **Appendix IV**

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### **TITCK WORKSHOP REPORT**



# **Challenges & Opportunities for The TITCK To Become An International Centre Of Regulatory Excellence**

**Turkish Medicines and Medical  
Devices Agency  
23 & 24 February 2017  
Ankara, Turkey**

## **WORKSHOP REPORT**

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### **Organised by:**

Professor Stuart Walker PhD. MFPM. FRSC. FIBiol. FRCPATH.  
Founder of the Centre for Innovation in Regulatory Science  
Professor at the School of Pharmacy & Pharmaceutical Sciences  
University of Cardiff, Wales, UK  
&  
Ms Emel Mashaki, Pharm. Msc. MBA  
PhD Student with the  
School of Pharmacy & Pharmaceutical Sciences  
University of Cardiff, Wales, UK

CIRS - The Centre for Innovation in Regulatory Science - is a neutral, independent UK-based subsidiary company, forming part of the Intellectual Property and Science business of Thomson Reuters. The mission of CIRS is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and HTA policies and processes. CIRS provides an international forum for industry, regulators, HTA and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards and its funding is derived from membership dues, related activities and grants.

Centre for Innovation in Regulatory Science (CIRS)  
The Johnson Building, 77 Hatton Garden, London, EC1N8JS, UK  
Email: [cirs@cirsci.org](mailto:cirs@cirsci.org)  
Website: [www.cirsci.org](http://www.cirsci.org)

Report date: March 2017

## Section 1: Executive Summary

### Background to the Workshop

Determining the benefit-risk balance of a medicine is one of the most important steps in its development, review and post-approval reassessment. There is a general agreement amongst agencies and companies that there is a need for both to be utilizing a structured, standardized, systematic approach for the benefit-risk assessment of medicines using a framework that should ideally be feasible and practical within the regulatory review process.

The advantage of a systematic standardised approach for the benefit-risk assessment of medicines is that the review would be more transparent, predictable and consistent. This would be in line with the WHO Good Review Practices for regulatory authorities released in 2015. In addition, the systematic standardisation of the benefit-risk assessment of medicines could be of considerable value to agencies as a cornerstone with respect to building quality into their decision making process as well as in communicating their views and decisions. Such a system would be of further value to agencies conducting both abridged and verification reviews where there is reliance to some degree on the assessment by reference or comparable agencies.

CIRS has been involved in this area for over a decade, including the development of the Universal Methodology for Benefit-Risk Assessment (UMBRA) framework and its documentation system, both within drug development and during the regulatory review. Furthermore, CIRS has undertaken a collaborative initiative with agencies in Australia, Canada, Switzerland & Singapore & more recently agencies in Southeast Asia have been assessing the UMBRA framework and the associate summary documentation together with the user manual. In addition, CIRS have also engaged with the US FDA & the European Medicine Agency to discuss this and other issues relating to the Review of Medicines.

### Workshop objectives

**The objectives of this workshop for the TITCK were to:**

- Provide an independent assessment of the TITCK in comparison with other medium sized international Regulatory agencies.
- Understand the key issues of concern from the pharmaceutical industry and patients regarding the pharmaceutical regulatory environment and possible solutions.
- Explain the importance of quality decision-making and a systematic structured approach for the benefit risk assessment of medicines.
- Determine the challenges and opportunities for TITCK to become a International Centre of Regulatory Excellence.

## Agenda of the Meeting

Day 1: 23<sup>rd</sup> February 2017

SESSION ONE	
10:30	<b>Welcome and Introduction - Overview of the TITCK organisation and its approach to clinical assessment of new medicines</b> Dr. Hakkı Gürsöz, TITCK
11:15	<b>Introduction and overview of the Centre for Innovation for Regulatory Science (CIRS)</b> Prof Stuart Walker, CIRS
11:45	<b>Evaluation of the regulatory review process and timelines of the TITCK</b> Emel Mashaki
12:30	Discussion
SESSION TWO	
14:00	<b>An evaluation of the TITCK review process in comparison with the regulatory agencies in Australia, Canada, Saudi Arabia and Singapore</b> Prof Stuart Walker, CIRS
14:45	Discussion
15:00	<b>An Evaluation of the attitude and experiences of pharmaceutical companies towards the Regulatory review process</b> Emel Mashaki
SESSION THREE	
16:15	<b>A structured approach to the benefit risk assessment of medicines: the key to improving decision-making in drug development and to the Regulatory review</b> Prof Stuart Walker, CIRS
17:00	Discussion

Day 2: 24<sup>th</sup> February 2017

SESSION FOUR	
08:30	<b>Introduction and summary of day one</b> Prof Stuart Walker, CIRS
08:40	<b>Public awareness of the Regulatory environment in Turkey and its impact on patients' Access to medicines</b> Emel Mashaki
09:20	Discussion
09:30	<b>Quality decision-making in medicines development and the Regulatory review: the key to patients' Access to medicines</b> Prof Stuart Walker, CIRS
SESSION FIVE	
10:30	<b>Key issues to be addressed by an agency to become a Centre of Regulatory Excellence</b> Emel Mashaki and Prof Stuart Walker
11:15	<b>Round table discussion</b> Participants will be in groups to review the key issues and provide feedback to the plenary
11:45	<b>Summary and way forward for the TITCK</b>



## Key points from presentations

### SESSION 1, PRESENTATION 1: INTRODUCTION & OVERVIEW OF THE TITCK ORGANISATION AND ITS APPROACH TO CLINICAL ASSESSMENT OF NEW MEDICINES, *PRESIDENT HAKKI GURSOZ (HEAD OF TITCK)*

**Dr. Hakkı Gürsöz**, (*head of the Turkish Medicines and Medical Devices Agency (TITCK)*), opened the meeting by giving a brief historical background to the idea behind having the meeting with the CIRS as well as the aims he was hoping to achieve from such meetings. He spoke of the major developments achieved recently in Turkey through the Healthcare Transformation Program (HTP) in which he was personally involved and which was initiated first by the preparation of a comprehensive report examining the Turkish healthcare system from different perspectives and an international point of view would help significantly in improving the regulatory system. The TITCK is a young and dynamic agency with a focus on implementing learning with an improvement of culture at all levels in order to keep pace with the rapid development of medicines. Thus a reforming period has been initiated within the TITCK since 2015 mainly in the review and approval system for medicines and medical devices. Accordingly eight main areas have been identified as success factors for an efficient regulatory environment. Each of these should be compatible with the other and the TITCK has taken appropriate action to ensure certain concrete improvements within each area including:

- 1. Streamlining the GMP process:** GMP accreditation processes and inspections should be conducted in optimum conditions. The TITCK focused on this area and the quality has improved significantly over the last five-year period. The number of GMP inspectors and assessors increased from ten to forty. There was an important focus on enhancing the competency level of inspectors as well as training the TITCK GMP experts through different means such as participating in the EMA related meetings, conferences and the organisation of in house high level GMP training. Moreover, the TITCK was recently inspected to become a full member of the PIC/S and this is expected to be finalised shortly.
- 2. Laboratory analysis and quality:** A significant effort was particularly made to improve the physical infrastructure and quality of the laboratories used for the analysis of medicines which included the renovation of the labs used and investing in new modern technological equipment and tools to enhance the reliability of the laboratory tests and analysis.
- 3. Risk Management within pharmacovigilance:** The TITCK introduced a number of measures to ensure the safety of medicines by implementing risk management plans. Thus the TITCK has significantly improved the preparation and control of Risk Management Plans related to new medicines.
- 4. Clinical Research:** Several action plans and new regulations were put in place to improve the regulatory environment for the conduct of clinical trials and the scientific evaluation of medicines in Turkey.
- 5. Commissions and expert committees:** The number of committees as well as committee members has increased over the past few years in response to the increasing number of applications for review. The TITCK also increased their working time and enhanced their

collaboration between the TITCK staff and external assessors. They increased the number of TITCK staff with PhDs and facilitated their active participation within committees. In this way they ensured an optimum working environment for all scientific committees while providing them with the technical support they would need.

6. **Administrative reviews:** The reviews were pursued under two departments previously however, the bureaucratic barriers between these departments were decreased to streamline and improve the review processes.
7. **IT systems:** The IT infrastructure of the TITCK was improved dramatically over the past few years. Currently e-submissions and e-review systems are well established and functioning and there are still more initiatives and plans to implement and expand the use of electronic systems.
8. **Communication with the Industry/ applicants:** The TITCK is striving to ensure that all the requirements are clear for the applicants so that sponsors can make complete and precise submissions which can progress on time. For this purpose, the TITCK is constantly organising workshops and meetings with the pharmaceutical industry to discuss areas of concerns and processes; thus such dialogue can also be considered as a training opportunity for the industry.


Finally, **Dr. Gürsöz**, highlighted that five years ago the TITCK had established its vision to become a leading and reference regulatory agency worldwide. Thus to become an international centre of regulatory excellence is a journey which requires commitment and high quality work and partnership with all national and international stakeholders. **Dr. Gürsöz** believed that this workshop would be the first step for a long-term partnership with CIRS in this journey to excellence.


## SESSION 1, PRESENTATION 2: INTRODUCTION & OVERVIEW OF CIRS, PROF. STUART WALKER (CIRS)

**Professor Walker**, (*Founder of the Centre for Innovation in Regulatory Science (CIRS)*), gave workshop participants an overview about of the CIRS organisation in terms of structure and membership including the scientific advisory council, partner agencies and member companies. He also summarised the current initiatives of CIRS in the four major focus areas; Global Drug Development, Regulatory Review Workshops, Health Technology Assessment and Frameworks for Benefit Risk Assessment & Decision-Making.

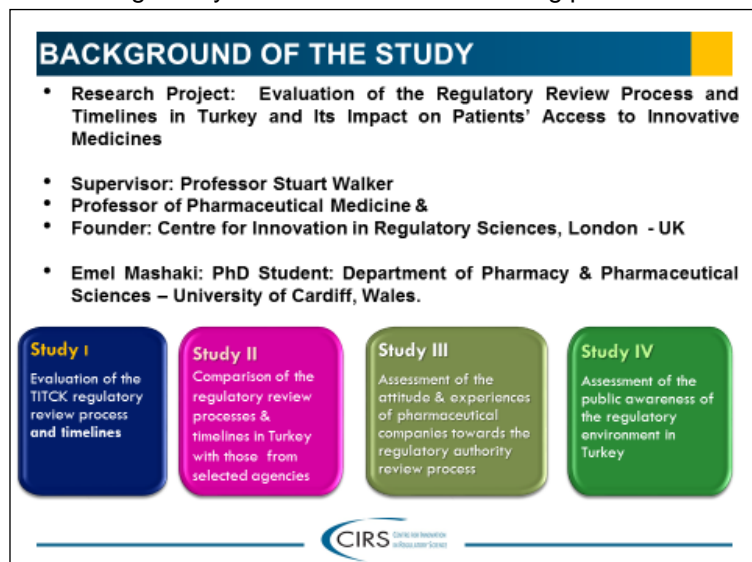
**SUMMARY: Achievements of CIRS**

1. Encouraged the sharing and exchange of information on **Good Review Practices and best practices** in the Regulatory Review of Medicines.
2. Established a system of **benchmarking regulatory authorities & HTA agencies** in order to evaluate where they have best practices or where improvements might be considered.
3. Developed an agreed common **Eight-step Framework** and a documentation system for the **Benefit-Risk Assessment of Medicines** currently being evaluated by agencies in more than twelve countries.
4. Organised workshops for Regulatory Authorities on **Risk Stratification of Medicines** in line with the WHO programme of reliance in order to maximise resources in Regulatory Agencies
5. Assessed the role of **Good Decision Making (GDM) practices** in the Pharma Industry, Regulatory Authorities & Health Technology Assessment agencies, identified the ten GDM Practices & developed a tool for evaluating GDM in individuals & organisations.





He also informed the participants that the CIRS benchmarked regulatory agencies using agency-supplied data since 1995 which was used to identify where time is spent in the review process, increase internal transparency, and establish programmes of internal benchmarking and to monitor the effects of change initiatives. Examples of the different CIRS services, workshops and meetings in the areas of regulatory review and decision-making processes were shared with the audience.



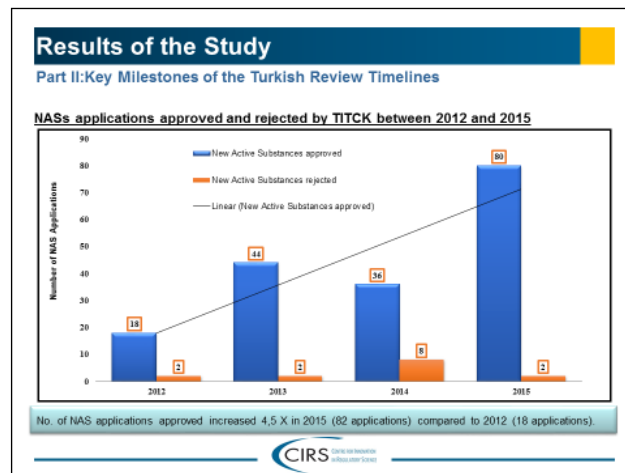
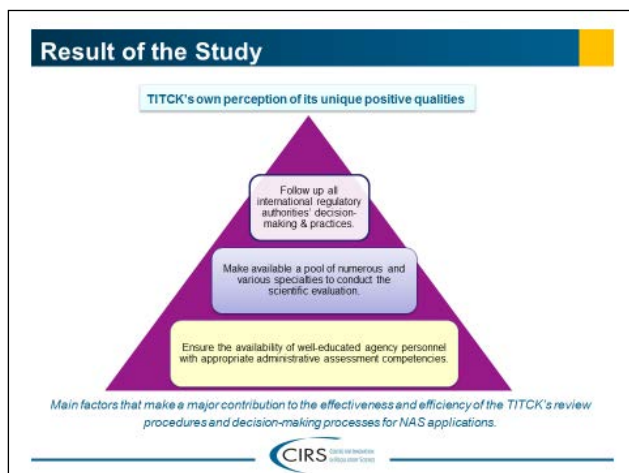
Finally, **Professor Walker**, set the scene for the meeting and reviewed the agenda and clarified the academic background of the study within the workshop with the TITCK.

### SESSION 1, PRESENTATION 3: EVALUATION OF THE REGULATORY PROCESS AND TIMELINES OF THE TITCK, *Ms. EMEL MASHAKI*

**Emel Mashaki**, (*PhD Student at Cardiff University*), reported on the main outcomes of the study conducted with the TITCK which aimed to evaluate the TITCK review process, timelines and implementation of Good Review Practices for the period from 2012 to 2015.

The findings identified that the TITCK performs a full review (Type 3A) as its assessment model for all new active substance (NAS) applications. Therefore, a new marketing authorisation application for an NAS can be submitted in Turkey prior to any approval in the world. However, evidence for approval in the country of origin, European Union (EU) or United States (US) must be submitted prior to the final approval by the TITCK. Marketing authorisation applications must be submitted to TITCK in compliance with the common technical document (CTD) with quality, safety and efficacy modules covering both the active drug substance and the finished product and it is therefore fully aligned with the ICH content requirements and international standards. However, local GMP accreditation of all manufacturing sites of the product is a pre-requisite to the marketing authorisation application. The results indicated that there is an official procedure for priority/fast track products to accelerate the marketing authorisation process for critical applications for certain products such as orphan drugs and life-saving medicines and products meeting medical needs which are given priority in the queuing line and assessment process. The study identified that the TITCK has a number of quality measures and policies in place to ensure consistency and standard performance including SOPs, review templates and an electronic submission tracking system. However, Good Review Practice (GRoP) guidelines have still to be fully developed and implemented.

In addition, the results identified that the TITCK review performance was improving over the past few years. There was an indication that, while the number of approved applications by TITCK was increasing, there was a decreasing trend in the approval timelines which is a positive development even though the target timeline of two hundred and ten working days is still to be achieved.



Finally, **Ms. Mashaki** indicated that the study provided for the first time a comprehensive overview of the TITCK registration review with all the milestones based on accurate data directly obtained from the TITCK since it was established as an agency and took over the responsibility for pharmaceutical regulations from the Ministry of Health in 2011. Thus, this facilitates the in depth analysis and understanding of the Turkish review system's strengths and areas for improvement. Therefore this enabled the establishment of the required action plans by all stakeholders be it the agency or the industry in order to enhance the ultimate target of enhancing patients' access to medicines.

#### DISCUSSION:

There was a question as to whether detailed information about the assessors and assessment process should be shared with the industry about the processes, and an example was requested from other agencies. **Professor Walker**, emphasized the importance of effective open communication between the industry and the authority on the quality of the review process and shared the example of some agencies where the key milestones of the assessment process are well informed to the industry including key contacts for each application within the regulatory agency which could facilitate the dialogue during the review process.

Furthermore, **Ms. Eda Cindoğlu**: (*TITCK International Relations Department Head*), commented that placements and secondments of the TITCK staff in other agencies do not effectively occur within the TITCK and thus perhaps the TITCK could consider implementing these as one of the training tools to enhance the quality and competencies of the agency staff.

**Dr. Ali Alkan**, (*TITCK Vice President*), commented on the different aspects of the presentation mentioning both the current challenges of meeting target approval timelines as well as a number of

actions implemented by the TITCK to ensure the timely access of patients to new medicines such as parallel submissions and review of GMP and marketing authorisations of orphan drugs, the early access of medicines via the named patient supply, the pricing system which is based on the lowest reference price which makes Turkey one of the countries with lowest medicines' price and finally the introduction of compulsory licencing application which would enable the availability of all medicines needed regardless of the price and patent.

He also highlighted that the TITCK is already working on streamlining the regulatory review process and timelines by implementing a systematic approach to measure the regulatory review performance of the TITCK based on the number of applications received, reviewed and approved versus the capacity of the TITCK. By providing several examples on the number of applications under review and number of approvals granted versus approval timelines, he emphasized that the TITCK is taking serious actions to systematically calculate the time both spent within the agency and from submission to approval for each application following the pre-assessment evaluation of 30 days. Thus the TITCK aims to measure individual performance within their systems by implementing key indicators for each milestone and evaluate the target approval timeline of 210 working days excluding the pre-assessment review. He added that the agency will be able to implement this system by the beginning of 2018 as soon as they can deal with all pending applications towards the end of this year (by November 2017). Accordingly, TITCK will be announcing to the industry the new process and the expected capacity of the TITCK to receive and review new drug applications (expected to be 60 to 70 regulatory applications/ month).

**Dr. Alkan**, also mentioned that as a second action to manage applications and review backlog, the TITCK will start to impose "application suspension fee" (20.000TL/year) for all companies who continue to hold their medicine applications as suspended and that will be only for a maximum period of 2 years. This way, they may allow companies either to withdraw their applications or de-register products which they no longer market or ensure the transfer of the suspended applications and licenses to other local companies to manufacture or register. Finally, he indicated that they are currently looking at improving the pricing process and are therefore considering separating the pricing approval from final approval of the marketing authorisation so as not to impact the total approval timeline as generally companies obtain the price approval for their applications before regulatory approval. The conclusion was that the TITCK is recognising the challenges they face regarding meeting target approval timelines and therefore they are implementing a number of improvements within the process including a systematic approach to monitor the individual timelines. **Professor Walker**, commented that Turkey is similar to other countries in terms of the challenges of the number of approved products, however, this study focused on New Active Substances (NASs) only. In addition, he recommended that the TITCK track their approval timelines calculated from the date of submission to the date of approval including documenting the median and mean so as to enable scientific comparisons with industry data and approval timelines from other authorities.

## SESSION 2, PRESENTATION 1: AN EVALUATION OF THE TITCK REVIEW PROCESS IN COMPARISON WITH THE REGULATORY AGENCIES IN AUSTRALIA, CANADA, SAUDI ARABIA AND SINGAPORE, *PROF. STUART WALKER (CIRS)*

**Professor Walker**, compared the TITCK's review process with other mid-sized regulatory agencies like Australia, Canada, Saudi Arabia and Singapore which enables the development of several proposals to assist the agency in its efforts to become an internationally recognised reference agency. He also shared brief overviews and comparisons of the different quality elements these agencies implement within their overall quality management system. He shared the outcomes of the comparative study which identified that the TITCK review model and the marketing authorisation requirements are in general similar to other regulatory agencies'.

Summary of Key Features of Key features for TITCK in comparison with Australia, Canada, Saudi Arabia and Singapore					
Quality in the Review Process	TITCK	Saudi Arabia	Australia	Canada	Singapore
11. <b>Consistency:</b> A priority reason for implementing quality measures is to improve the overall consistency of the regulatory process	✓	✓	✓	✓	✓
12. <b>SOPs:</b> Standard operating procedures have been implemented as part of the quality measures adopted by the authority	✓	✓	✓	✓	✓
13. <b>Assessment templates:</b> are used to standardise the content and format of written reports	✓	✓	✓	✓	✓
14. <b>Quality Management:</b> The authority has measures in place to bring about continuous improvement through monitoring and feedback	✓	✓	✓	✓	✓
15. <b>Transparency:</b> The authority assigns a high priority to being open and transparent in its relationships with the public, professions and industry	✓	✓	✓	✓	✓
16. <b>Monitoring application progress:</b> An electronic tracking system is in place	X	✓	✓	✓	✓



Summary of Key Features of Key features for TITCK in comparison with Australia, Canada, Saudi Arabia and Singapore					
Marketing Authorisations	TITCK	Saudi Arabia	Australia	Canada	Singapore
6. <b>Company response time:</b> Recording procedures allow the company response time to be measured and differentiated in the overall processing time	X	✓	✓	✓	✓
7. <b>Priority Reviews:</b> The authority recognises medical urgency as a criteria for accelerating the review and approval process for qualifying products	✓	✓	X	✓	✓
8. <b>Parallel processing:</b> The different sections of technical data (Quality, Safety, Efficacy) are reviewed in parallel rather than sequentially	✓	✓	✓	✓	✓
9. <b>Price negotiation:</b> Discussion of pricing is separate from the technical review and does not hold up the approval of products	✓	X	✓	✓	✓
10. <b>Sample analysis:</b> The focus is on checking quality in the market place and therefore requirements for analytical work do not hold up the marketing authorisation	✓	✓	✓	✓	✓



Furthermore, the study identified that Good Review Practices (GReP) are implemented informally to a certain extent within the TITCK. The comparative study also indicated that the TITCK is currently lacking some elements that could contribute to transparency and the communication of a regulatory agency. These would include publicly available summaries of the basis for approval, developing standards for scientific and advisory meetings for applicants prior to submission as well as developing relationships with other reference agencies to encourage training through secondments and job shadowing.

### DISCUSSION AND KEY RECOMMENDATIONS:

In response to participants' questions, **Professor Walker** provided some examples of improving transparency of decision-making among different regulatory authorities such as EMA who publish the summary basis of approvals (EPARs for stakeholders) and assessment reports to be shared with the applicants. Furthermore, the audience discussed whether Turkey as a country should be following and fully aligned with the decision-making process of other developed regulatory authorities such as FDA and EMA or not. **Professor İsmail Balık**, (*Academic Member and Head of the Clinical Evaluation Commission at the TITC*), shared previous experiences of the TITCK independent decisions regarding product safety assessment which were not aligned with other authorities, but proven afterwards to be

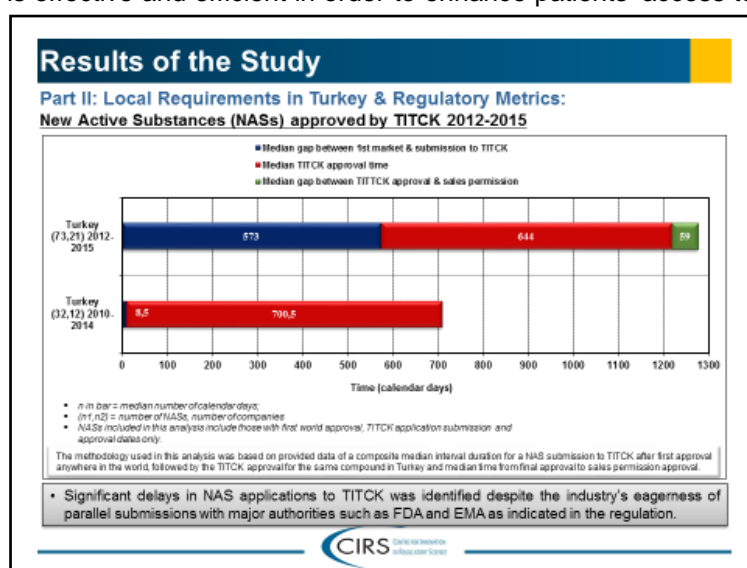


timely and correct. Similarly, he gave examples where the TITCK did follow the regulatory decision of major authorities which were constantly questioned during the post-approval phase.

Accordingly, the key recommendations that were made in this session were mainly in the following areas; alignment of regulatory review process and requirements while still maintaining the local decision-making and review models, implementation of a structured approach for Good Review Practices (GReP) and Benefit-Risk Assessment to become mandatory and carefully monitored as well as enhancing transparency of the decision-making process. Furthermore, it was suggested that the TITCK could conserve resources and reduce the time in the review process, by exploring the possibility of introducing shared or joint reviews with other similar regulatory authorities. It was recommended that the TITCK define target times for each review milestone in addition to the predefined overall authorisation procedure approval timing as well as improving internal tracking systems to monitor these milestones and thus enable this information to be available to all stakeholders as **Dr. Ali Alkan**, (TITCK VP), stated that such an electronic tracking system is planned to be in place by the end of 2017.

## SESSION 2, PRESENTATION 2: AN EVALUATION OF THE ATTITUDE AND EXPERIENCES OF PHARMACEUTICAL COMPANIES TOWARDS THE REGULATORY REVIEW PROCESS, **Ms. EMEL MASHAKI**

**Emel Mashaki**, presented the background, aims and methods of the study which focused on evaluating the attitudes and experiences of companies towards the regulatory review process in Turkey. It aimed to evaluate the changes in the regulatory approval timelines and processes between 2012 and 2015 and identified the key issues companies are facing in the Turkish regulatory environment with regards to the review process as well as possible solutions and improvements to ensure that the drug approval process is effective and efficient in order to enhance patients' access to innovative medicines. The results of the survey conducted among twenty-one pharmaceutical companies indicated that the majority of companies experience significant delays in obtaining marketing authorisation approval for their products and therefore access of patients to their products is prolonged compared with other developed countries. The median time of NASs from the first approval anywhere in the world to TITCK



approval time was identified to be 1217 calendar days which is approximately 41 months (3.4 years) despite the industry's eagerness of parallel submissions with major authorities such as FDA and EMA as indicated in the regulation.

This is mainly due to several factors such as long GMP processes; increased number of questions asked by the TITCK thought to be outside of global requirements, constant changes in the TITCK organisational structure and commission members, pricing procedure and long laboratory analysis steps. Furthermore, 62% of companies agreed that the maximum time for the TITCK to complete the review process for a NAS application should be 12 months which is approximately 257 working days compared with the 210 working days for target approval stated in the regulation. With regards to the TITCK transparency (in terms of ability to track applications), findings indicated that the majority of companies evaluated the TITCK to be generally transparent. Furthermore, most of the companies were supportive of the TITCK utilising a structured Benefit-Risk Framework for the decision making process.

#### **KEY RECOMMENDATIONS:**

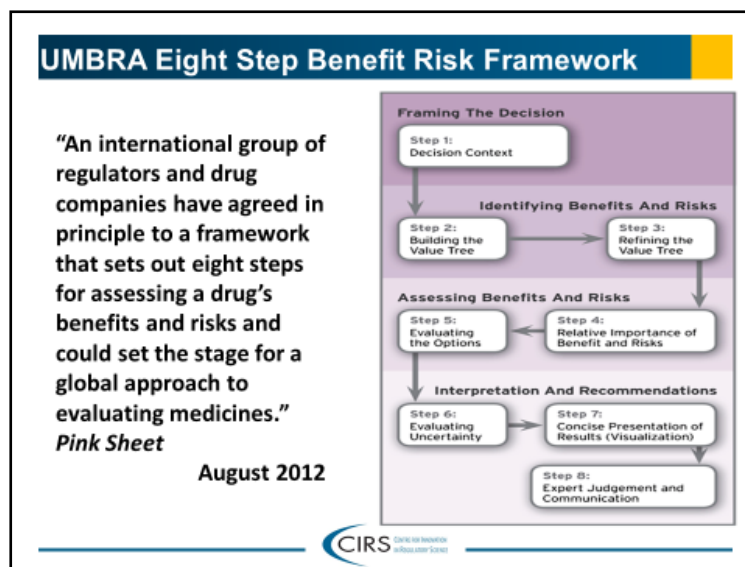
The key issues, which were identified by the industry regarding review process, as well as the industry's proposed possible were as follows:

- 1. GMP Process.** The key recommendations from the industry to improve this process includes:
  - Increase in the use of a risk-based inspection approach,
  - Transition from line based inspection into pharmaceutical form inspection,
  - Expansion of the content of the parallel GMP and NDA submission to category 2 (priority 2).
  - Recognition of internationally accredited GMP approvals following PIC/S membership.
- 2. Early Access to New Innovative medicines.** The industry suggested the following;
  - Adopt flexible regulatory pathways to ensure faster approvals for the different varieties of applications including biological products and orphan drugs.
  - Alignment of guideline and regulations with international standards.
  - Determine the prioritisation criteria based on scientific, clinical and unmet medical need basis.
- 3. Communication and Transparency.** The key recommendations of the industry were as follows:
  - Enhance the dialogue with the pharmaceutical industry at all levels.
  - Build a structured framework for the agency communication policy.



### SESSION 3: A STRUCTURED APPROACH FOR THE BENEFIT RISK ASSESSMENT OF MEDICINES: THE KEY TO IMPROVING DECISION-MAKING IN DRUG DEVELOPMENT AND FOR THE REGULATORY REVIEW, *PROFESSOR STUART WALKER (CIRS)*

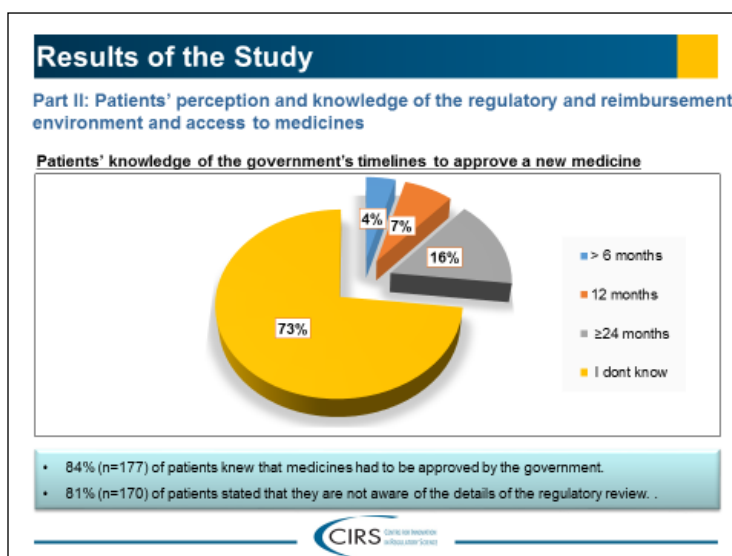
**Professor Walker** gave a comprehensive background to the structured approach of the Benefit Risk (B-R) assessment of medicines and mentioned why such a structured framework is crucial for benefit risk (Harm) assessment of new medicines as well as the added value it could provide to the regulatory agency decision-making process in terms of consistency, transparency and predictability. He also reviewed the current B-R Frameworks implemented by other regulatory agencies and shared examples of how these contributed to the improvement of the decision making process.



### SESSION 4, PRESENTATION 1: PUBLIC AWARENESS OF THE REGULATORY ENVIRONMENT IN TURKEY AND ITS IMPACT ON PATIENTS' ACCESS TO MEDICINES, *Ms. EMEL MASHAKI*

**Emel Mashaki** shared the objective, methodology and conclusions of the patient study which demonstrated the importance of patients' awareness, knowledge and their role with regard to the regulatory review and reimbursement procedures in Turkey.

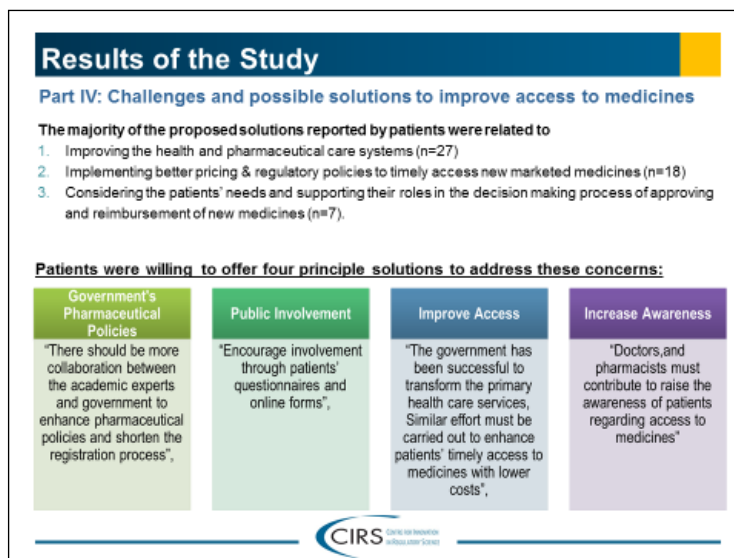
In summary, the three most important improvements that patients identified in obtaining their medicines were; access to medicines, improved health and pharmaceutical care as well as price. The major challenges patients perceive as facing the government to provide new medicines were; the cost of innovative medicines being too high as well as the lack of government resources and scientific expertise.



The patients provided four principle solutions to address the access issues which included;

- 1. Collaboration between academic experts and government to enhance pharmaceutical policies and shorten the registration process,
- 2. Encourage involvement through patients' questionnaires and online forms,
- 3. Government to enhance patients' timely access to medicines with lower costs,
- 4. Encourage healthcare professionals to raise the awareness of patients regarding access to medicines.

The role of patients in the decision-making process for the approval and reimbursement of new medicines should be encouraged. Patients suggested that to ensure that their needs are met in a timely way that patients' associations become more involved in decision-making by ensuring a fair representation in the process. The use of patient questionnaires online or via doctors & pharmacists together with the use of social media could raise the awareness of patients to regulatory changes and access procedures.



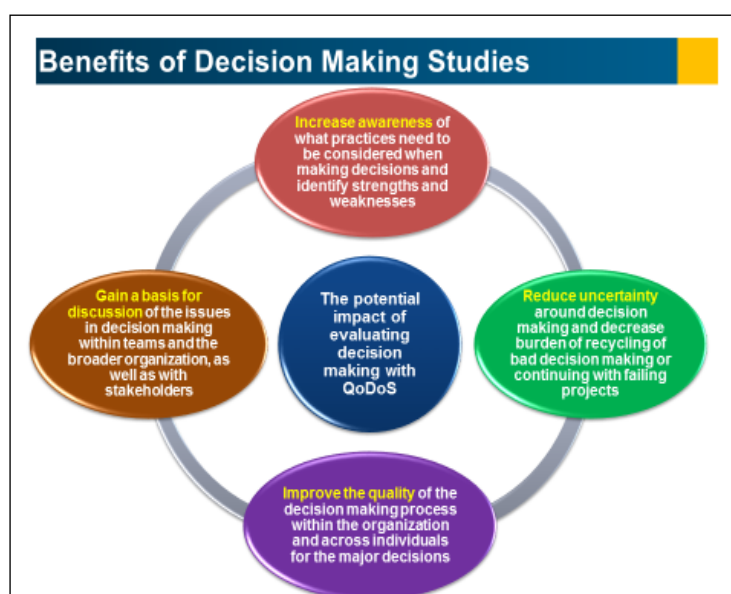
## DISCUSSION:

**Dr. Ali Alkan** raised the concern of the active role and willingness of the pharmaceutical companies to increase the awareness of the patients through establishing patient's organisation regarding possible treatments and access to medicines, which in general is supported due to commercial objectives. He highlighted the importance of supporting the establishment of patient's organisations on their own initiative to address the public unmet needs. **Professor Walker**, added that there are similar concerns in different countries such as the UK, however, he emphasized the importance of the public and patients associations' role in the decision-making process of medicines access particularly in the reimbursement process. Furthermore, **Emel Mashaki**, responded to the audience by stating that patients' involvement in the decision-making process may not necessarily shorten the approval timelines, but rather ensures a high quality decision that would have a better impact on patients' access to treatment. She also added that some regulatory agencies facilitate public awareness about new approvals by publishing summaries for the public such as the EPAR in the EU and organise the involvement of patients in reimbursement. It is believed that it is the responsibility of the HCPs and regulatory authorities to ensure a transparent communication and briefing to the public regarding medicines approvals and accessibility. Finally, **Dr. Ali Alkan**, concluded that in such studies the

opinion of the non-governmental organisations like TEB (Turkish Pharmacist Association) who take an active role in ensuring patients' access to medicines in Turkey, should be included in similar studies in the future since their opinion could be very important while the TITCK is aiming to become a centre of excellence.

#### SESSION 4, PRESENTATION 2: QUALITY DECISION-MAKING IN MEDICINES DEVELOPMENT AND THE REGULATORY REVIEW: THE KEY TO PATIENTS' ACCESS TO MEDICINES, PROFESSOR STUART WALKER

**Professor Walker** emphasized the importance of Quality Decision Making (QDM), the development of a Decision Making tool, the practicality and the practicality of applicability of QDM Practices in the Regulatory Environment. A summary of this work was presented in the (CIRS R&D Briefing no. 61).



#### SESSION 5, PRESENTATION 2: KEY ISSUES TO BE ADDRESSED BY AN AGENCY TO BECOME A CENTRE OF REGULATORY EXCELLENCE - ROUND TABLE DISCUSSION.

*PARTICIPANTS WERE GIVEN THE OPPORTUNITY TO REVIEW THE KEY ISSUES AND PROVIDE FEEDBACK TO THE PLENARY*

#### Recommendations from Roundtable Discussions

**Q1. Please list the three most important key issues that you believe, as an agency should be addressed?**

- ❖ **TITCK organisation and capacity:** The Agency should increase the number of qualified staff/personnel in the organization and ensure a stable structure as much as possible.
- ❖ **Training and staff competencies:** There should be a formal and a standard process for training within the agency to ensure a high calibre of reviewers as well as the consistency and

quality of assessment. Thus the following should be considered to further improve the TITCK training process:

- Establish a formal induction training programme for all new employees of the TITCK.
- Deliver focused training that is specific to the different scientific areas in order to increase the expertise of the staff and reviewers within their own areas of responsibility.
- Increase the partnership with the other regulatory agencies and encourage secondments and job shadowing as well as participation of TITCK staff in international training abroad.
- Ensure the transfer and sharing of best practices from those staff who participated in international training.
- Follow a structured approach for “on the job” and in-house training for staff and ensure they are also monitored and evaluated.
- Transparent policy for staff training (who should be trained within the TITCK).
- Establish a **Regulatory Science Academy** within the TITCK in collaboration with the universities and/or pharmaceutical industry where specific regulatory science and Good Regulatory Practice training can be delivered mainly to reviewers whether internal or external.

❖ **Transparency and communication with all stakeholders:**

- The TITCK should enhance the transparency and consistency of its decision-making process. Accordingly, the agency could consider publishing the summary basis of approvals for stakeholders and assessment for applicants to justify how and why the agency took certain decisions.
- TITCK should consider the implementation of a structured framework for pre-submission scientific advice/consultation meetings for the industry in order to minimize rejections, optimise the approval process and enhance communication with applicants before and during submission.
- Increase the number of scientific commissions to meet the increasing number of applications.
- Establish a formal process for tracking all the review process milestones and target timelines.
- Develop regulations and SOPs for standardisation/ alignment with international standards
- Increase the cross-functional coordination within the agency and streamline the review process.
- Implement a structured approach for the decision-making process and build quality systems to ensure consistency and business continuity.
- Assignment of specific staff or departments for external communication to improve the consultancy process with applicants.

- ❖ **Improve the IT Infrastructure of the agency.**
  - Full adaptation to electronic system (e-CTD).
- ❖ **Increase the focus on the TITCK quality management systems and ensure a standard policy for quality.**
  - Ensure the efficiency and appropriate training of internal reviewers within the TITCK by preparing the required standard operations procedures (SOPs) for the key tasks and define roles and responsibilities clearly.

**Q2. What is the area you would like the agency to address in order to improve and become an International Centre of Regulatory Excellence?**

The following were identified by all the participants to be areas to be focused on in the future;

- 1. Good Review Practices (GReP):** This area was identified by the majority of participants to be a priority on which the TITCK should focus if it wants to improve and become a recognised centre of excellence. They highlighted that the TITCK would need to review the best practices from other regulatory agencies.
- 2. Standard approach for Decision- Making process.**

**Q3. What would you like to change and improve in the regulatory review process of the TITCK?**

- Increase focus on specialization, experience and expertise during regulatory processes and acceleration of review timelines.
- Develop local regulations, SOPs and assessment templates.
- Improve the quality of the regulatory process.
- Establishing the TITCK Regulatory Science Academy which would be capable of delivering various regulatory affairs training modules and conduct research programmes in collaboration with the universities and industry to continuously improve the regulatory review process, the TITCK competencies and the overall regulatory environment in Turkey.

## APPENDIX: WORKSHOP ATTENDEES

Regulatory agencies		
Participant	Role/Position	Institute
Dr. Hakkı Gürsöz	TITCK President	TITCK
Dr. Ali Alkan	TITCK Vice President	TITCK
Prof. Dr. Akın Kaya	TITCK academic commission member	Ankara University
Dr. Bahar Kayserilioğlu	International Relations Department	TITCK
Dr. Banu Bayar	Economical Evaluation & Drug Supply Department Head	TITCK
Assoc. Prof. Dr. Berrin Erdağ	TITCK academic commission member	TÜBİTAK
Çisem Budak	Drug Regulatory Department	TITCK
Dr. Demet Aydınkaraahaloğlu	Pharmacovigilance Department Head	TITCK
Ecem Bulut	Licensed Medicines Department	TITCK
Eda Cindoğlu	International Relations Department Head	TITCK
Elif İnci Somuncuoğlu	Clinical Research Department – Unit supervisor	TITCK
Emel Aykaç	Pharmacovigilance Unit Head	TITCK
Prof. Dr. Filiz Öner	TITCK academic commission member	Hacettepe University
Gökçe Yıldırım	Drug Regulatory Department	TITCK
Handan Çelikel	Technological Evaluation Unit	TITCK
Hülya Karahasanoğlu	Clinical Review Department	TITCK
Prof. Dr. İsmail Balık	TITCK Head of Clinical Evaluation Commission.	Ankara University
Prof. Dr. İsmail Tuncer Değim	TITCK academic commission member	Gazi University
Manolya Kivılcım	Clinical Review Department	TITCK
Prof. Dr. Müzeyyen Demirel	TITCK academic commission member	Anadolu University
Nihan Burul Bozkurt	Clinical Research Department Head	TITCK
Nihal Saat Yerlikaya	Technological Evaluation Unit Head	TITCK
Oğuzhan Koyuncu	CTD Department	TITCK
Pelin Aksungur	International Relations Department	TITCK
Dr. Sabiha Alper Hayta	Managerial Regulatory Department	TITCK
Senem Sevtap Ölmez	International Relations Department	TITCK
Serkan Yener	Drug Regulatory Department	TITCK
Prof. Dr. Sevda Şenel	TITCK academic commission member	Hacettepe University
Süheyla Taş	Clinical Research Department	TITCK
Şule Gülşen	CTD Department	TITCK
Tuncay Paşaoğlu	Drug Regulatory Department	TITCK
Yasemin Akyürek	International Relations Department	TITCK
Dr. Yasemin Karabey	Drug Regulatory Department	TITCK
Yelda Çakıcı	Pharmacovigilance Risk Management Unit Head	TITCK
Züleyha Yavuz	Medicines and Pharmacy Department	TITCK
Centre for Innovation in Regulatory Science		
<b>Emel Mashaki Ceyhan</b>	PhD Student – Cardiff University – UK	
<b>Professor Stuart Walker</b>	Founder of the Centre for Innovation in Regulatory Science – UK	
<b>Şebnem Uslu Şenoldu</b>	External Consultant and rapporteur	

## PARTICIPANTS' EVALUATION OF THE MEETING

- **88%** of the participants rated the overall quality of the presentations as **“Excellent”** or **“Very Good”**.
- **76%** of the participants rated the workshop as **“Excellent”** or **“Very Good”**
- **94%** of the participants agreed that such studies described **should be encouraged** in Turkey.
- **52%** of the participants believed that the outcome of these studies can **contribute to the**

## COMMENTS FROM PARTICIPANTS

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*“The meeting was very useful, especially in that it provided us, as an agency, the opportunity to compare the TITCK with other regulatory agencies’ practices which will definitely help us improve our regulation process in terms of improving our review timelines as well as consistent decision making”.*

*“It gave us the guidance on how to implement Good Review Practices (GReP) and Quality Decision-Making which is crucial for an effective & efficient regulatory agency”.*

*“The studies provided us with a comprehensive perspective with regards to the regulatory review perception in Turkey, particularly the public awareness study which was innovative and a topic that we need to consider significantly in the future”.*

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## SUGGESTIONS FROM PARTICIPANTS

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*“It is crucial to identify the areas of concerns in such meetings, however, it is equally important to decide on concrete action plans as well and share a structured set of recommendations for the improvement of the TITCK in the future”*

*“In the future, it would be very useful to see concrete examples of regulatory review models and practices from other countries and discuss these in detail”.*

*“I suggest that we ensure that there will be a follow up process for the action plans from this CIRS workshop and evaluate the progress of the TITCK over time following such meetings.”*

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## **Appendix V**

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### **PATIENT STUDY DIA POSTER**

**(June 2016)**



# Public Awareness of The Regulatory Environment in Turkey and Its Impact on Patients' Access To Medicines



Emel Mashaki Ceyhan<sup>1</sup>, Evrim Yurtlu<sup>2</sup> & Stuart Walker<sup>1,3</sup>



<sup>1</sup>School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, UK; <sup>2</sup>Engineering Sciences, Istanbul University, Istanbul, Turkey; <sup>3</sup>Centre for Innovation in Regulatory Science (CIRS), London, UK

## Background

Patient access to medicines is a major concern both for regulatory authorities as well as for the pharmaceutical industry. Currently, it is estimated that two billion people still cannot access the medicines they need mainly due to the increasing cost of healthcare expenditure. The challenges in medicines' access are constantly being addressed by global health organizations, governments and other related stakeholders.

Access to healthcare in Turkey has undergone dramatic changes in the past decade as a positive outcome of the economic growth and the HealthCare Transformation Program which was initiated in 2002. The reforms resulted in major developments in the pharmaceutical regulatory environment which improved public access to healthcare services. However, a number of measures were taken by the government to control the increasing healthcare budget, mainly for pharmaceuticals.

Restricting expenditures may have a negative impact on patients' access to improved healthcare as well as medicines. Therefore, it is anticipated that there might be a different perception by patients towards the recent developments in the pharmaceutical environment as to whether they are in line with international standards.

## Objectives

The objectives of this study were to:

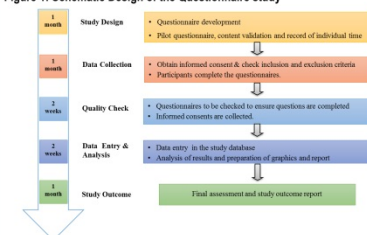
- Identify public awareness and knowledge of the regulatory environment in Turkey.
- Evaluate the impact of the regulatory and reimbursement processes on patients' access to innovative medicines.
- Assess the patients' perspective of their role in the decision-making process for approval and market access of medicines.
- Identify patients' views of the barriers to accessing medicines and the possible solutions.

## Methods

- A comprehensive paper-based questionnaire was designed, piloted and distributed through associations, pharmacies and clinics to 350 outpatients receiving chronic disease treatment mainly in cardiovascular, diabetes, CNS and hormonal disorder.
- The questionnaire was designed to include a total number of thirty questions mainly in relation to the patients' knowledge and understanding of the regulatory review and reimbursement processes, as well as their role in decision-making.
- Face to face semi-structured interviews were also carried out with twenty-two patients.
- The questionnaire was structured in three sections:
  - General demographic details; i.e. age, gender, education background,
  - Knowledge of the regulatory environment including the review and reimbursement processes in Turkey,
  - Key challenges and possible solutions regarding patients' access to medicines

The study was conducted over a three months period and the approximate time for patients to complete the questionnaire was estimated to be ten to fifteen minutes.

Figure 1: Schematic Design of the Questionnaire study



**Pilot Study:** The pilot study was conducted with thirteen patients and five doctors as semi structured interviews. This was designed with the aim of content validation to identify areas of improvements in the questionnaire in terms of wording, terminology, deletion and / or addition of questions. The questionnaire was presented to patients in Turkish.

### Pilot Study Questions

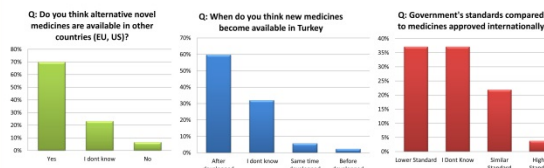
- In general how did you find the questionnaire?
- How do you evaluate the language of the questionnaire?
- Are there any questions you found difficult to answer, and if so, please state why you think they were difficult?
- Are there any repetitive questions in the questionnaire?
- Are there any questions you think are not relevant?
- Are there any other questions you would like to add?

## Results

### 1. Patients' awareness and knowledge of their medicines

Two hundred and ten patients (60%) completed the questionnaire (50% males). 84% of patients (n=176) knew that medicines had to be approved by the government. Yet, 81% of patients (n=170) were not aware of the regulatory review process.

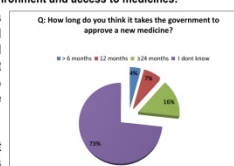
Furthermore, 37% described the Turkish approval process to be of a lower standard compared to US and EU. However, 70% of patients believed that there are novel alternative medicines for their disease available in other developed countries. Similarly, 60% of patients thought that new medicines only become available in Turkey after other developed countries.



### 2. Patients' perception and knowledge of the regulatory environment and access to medicines:

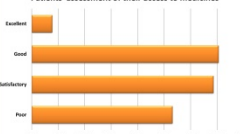
This study identified that the majority of patients demonstrated a good knowledge of the pharmaceutical regulatory environment and the registration review and reimbursement processes. 84% of patients knew that medicines had to be approved by the government with 73% unaware of and how long it takes the government to approve a new medicine.

However, patients knew more about the reimbursement system where 50% were satisfied and 34% described access to new medicines to be adequate.



### 3. Role of patients in the regulatory review and reimbursement processes

#### Patients' assessment of their access to medicines



Currently the role and responsibility of patients in the decision-making process of approving new medicines is becoming a high priority for all stakeholders. Patients stated that they do not have any role in the decision-making process for approving new medicines (71%) nor in the reimbursement process (72%). Therefore most of them indicated that in the future they need to be more involved in the reimbursement (60%) as well as in the approval process (58%).

### 4. Challenges and possible solutions to improve access to medicines

As a result of this study the following major challenges facing the government were identified by the patients.

Challenge	Percentage
• Cost of new medicines is high	23%
• Lack of government resources	19%
• Lack of scientific expertise at government	18%
• Have no information	17%
• Pharmaceutical companies pricing policies	14%
• The patients' needs not taken into account	10%

**Important barriers to access:** Only sixty patients out of two hundred and ten (29%) were able to list the most important barriers they face in obtaining the medicines they need. The top four barriers were;

- The high price of medicines,
- Patients' access to the treatments,
- A lack of an appropriate healthcare system infrastructure and
- The unavailability of new products

## CONCLUSION

This study has demonstrated the importance of patients' awareness, knowledge and role with regard to the regulatory review and reimbursement processes in Turkey. The three most important improvements to obtaining the medicines they need were; access to medicines, improved health and pharmaceutical care as well as price of medicines. Patients were willing to offer four principle solutions to address these concerns:

Government's Pharmaceutical Policies	Public Involvement	Improve Access	Increase Awareness
"There should be more collaboration between the academic experts and government to enhance pharmaceutical policies and shorten the registration process",	"Encourage involvement through patients' questionnaires and online forms",	"The government has been successful to transform the primary health care services. Similar effort must be carried out to enhance patients' timely access to medicines with lower costs",	"Doctors and pharmacists must contribute to raise the awareness of patients regarding access to medicines"

The role of patients in the decision-making process for the approval and reimbursement of new medicines should be encouraged. Patients suggested that to ensure that their needs are met in a timely manner that patients' advocacy associations become more involved in decision-making. It is concluded that online patient questionnaires or via doctors & pharmacists together with the use of social media could raise the awareness of patients to regulatory changes and access processes.

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