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STORYBOARDING AS BEST PRACTICE FOR MARKETING APPLICATIONS

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Storyboarding; Development; Application; Dossier preparation; Project team; Key messages; eCTD; Authoring; Review.

ABSTRACT

This article describes the concept of storyboarding and best practices for preparing and running a 'key messages' meeting (known as a storyboarding meeting) to support an authoring and review team for a marketing authorisation application (MAA), new drug application (NDA), or biologics license application (BLA). These practices are based on the authors' conduct of storyboarding meetings for six projects of varying sizes and scope, including large and small molecules across different therapeutic areas, completed during, or subsequent to, Phase III clinical trials. Storyboarding can prevent stressful and inefficient rework during dossier preparation while facilitating the timeliness and quality of the final application.

THE PURPOSE OF STORYBOARDING

It is unusual for those involved early in product discovery and development to follow a compound/product all the way through to regulatory approval and, ultimately, marketing. It is also common for the competitive landscape and medical practice to evolve during the development programme. A regulatory dossier is stronger if it tells a coherent story regarding product development, including the challenges, setbacks and successes, informed by an institutional knowledge of project history. For products out-licensed during development, developed in an academic environment, or where some or all portions of R&D activity or operations are outsourced, a storyboarding process can be beneficial for aligning key messages between documents and among stakeholders, and thus managing expectations regarding timelines. Potential objectives for a storyboarding meeting might include:

- To share information and thus provide development continuity both within and across disciplines
- To align team members around a common goal and establish a network and mentoring framework where all contributions are valued and respected
- To develop key messages that should be consistently addressed across all disciplines – this often includes identification of new data presentations or analyses that will be germane to positioning the product scientifically or commercially
- To share outputs of gap analyses and discuss or confirm plans for remediation in context with upcoming regulatory submission strategies and timelines.

A successful storyboarding meeting prevents time-consuming and stressful rework during the subsequent authoring and review process. Discussing the content of key figures and analyses in a proactive, prospective manner instead of recognising their absence at a late stage enhances the quality of the final application. Early engagement of internal stakeholders who will review final drafts or approve draft labelling or commercial messages is especially useful for preventing late stage changes.

OPTIMAL TIMINGS FOR STORYBOARDING MEETINGS

A "taking stock" review of a target product profile is typically part of the R&D governance process at several traditional milestones during development, for example, at proof of concept, end of Phase II, or on receipt of topline Phase III results. Regulatory affairs representatives typically support project teams by facilitating a detailed review of the data in context with the desired labelling at these milestones. However, there are other thresholds when teams may benefit from this exercise, for example, as a consequence of mergers and acquisitions, or when an asset transitions to a new team or geographic region, to prevent loss of institutional memory between organisations. Teams may also benefit from storyboarding meetings during project handover meetings when contract research organisations reduce or expand their involvement in a programme.

A storyboarding meeting is especially useful in the 6–10 months prior to completion of a global or regional marketing application. At this point, the design and direction of Phase III is largely set, the stability studies with the to-be-marketed product presentation have been initiated or are planned, and the core nonclinical package is largely complete, if not fully reported. At this point, there are many draft documents to be prepared, often with numerous contributing authors and reviewers, of varying experience levels, and many different ways of summarising and editing the most important data.

One commonly neglected interface is the translation of meaningful clinical endpoint results into statistically robust graphics that will ultimately be included in advertising materials or presentations to regulatory agencies, such as an FDA Advisory Committee. Considering graphic elements early in the process and facilitating a transparent and open dialogue between commercial and statistical subject matter experts aids nimbleness later. Therefore, a storyboarding meeting is

recommended before the statistical analysis plan for the pivotal Phase III study is finalised, and certainly, before the analysis plan for integration of clinical safety data is completed.

MEETING CONDUCT AND ATTENDEES

To 'start with the end in mind,' the team may need a little push from the meeting chair and internal regulatory staff, and busy professionals sometimes need convincing that a full day of storyboarding is a beneficial use of time. Ideally, the storyboarding meeting should be chaired by a person who has a broad understanding of drug or biologic development, has reviewed or authored the content of most MAA/NDA/BLA modules for several other products (especially clinical summaries), and is familiar with the typical content of prescribing information (EU summary of product characteristics [SmPC] and/or US package insert [PI]). To prepare, they should have taken a fairly deep dive into all the documents pertinent to gap analyses, as well as a swim through the publicly available information about competitors and precedent products. A global regulatory lead, experienced project leader, or regulatory subject matter expert is usually well suited to the task. Meeting organisers should be sensitive to institutional norms and ready to facilitate discussion of difficult or contentious topics with diplomacy, promote collaboration, and drive for solution-oriented outputs. Preparation of the minutes and capturing actions in real time by project managers and project leaders is recommended and serves as a development opportunity for regulatory staff seeking to take on the lead role for future projects. Attendees should include:

- All members of the project team
- Authors of the active ingredient and finished product chemistry, manufacturing, and controls sections
- Nonclinical subject matter experts and summary writers
- Clinical summary writers and medical writers involved with outstanding clinical study reports
- Statisticians responsible for designing analysis plans for pivotal data and integrated analyses
- Marketing staff involved in the global commercial plan
- Regulatory operations staff assigned to publishing the submission
- Regulatory leads for key regions.

Depending on the organisation's size and culture, senior stakeholders responsible for approving the core prescribing information and key summaries should either attend the whole meeting or at the very least the closing summary debrief sessions.

MEETING PREPARATION

There is an emotional intelligence dimension to storyboarding and time spent preparing and engaging a team through storyboarding will pay dividends later. During the meeting, watch for interdisciplinary moments of realisation when the consequences of results in one technical area spark input from another area. These moments are easy to miss when teams are geographically dispersed without long-standing professional relationships or when teams have been working remotely for long periods.

During preparation of the NDA/BLA/MAA, the pain points are often at the interfaces between disciplines. It is most effective to develop an agenda that is focused on key sections of the prescribing information. This helps to maintain focus on cross-functional topics and major gaps in the data package and not on individual team members or departments. The chair should encourage engagement of all participants throughout the meeting and, to be most effective, team members should be briefed about their respective roles ahead of time.

The agenda should be structured like a diamond, with ice-breaking topics first, a data-rich centre, and a short lunch break to prompt reflection and allow for side-bar conversations to crystallise potential solutions. The meeting should conclude with action-oriented summary segments, and a top-level review of the submission timeline, so that the whole team leaves with a sense of purpose and alignment.

Every project has unique challenges. If a gap analysis has already been conducted on the project, the meeting agenda should include a risk assessment and discussion about how to address these gaps. As an example, a 'prompt list' of source documents to consult during preparation for a storyboarding meeting, and how the content might evolve into potential agenda topics, is provided in **Table 1**. The overall aim is for attendees to leave the meeting with a plan of action that includes how information will flow across and between Module 2 summaries or related reports (see **Figure 1**). .

Although each technical discipline should prepare for the meeting by assuring that all completed, ongoing, and planned studies are identified, the agenda should not be structured around the overall table of contents or submission plan. This can lead to distractions about where to place each report. Such decisions will be needed but will be largely driven by regulatory affairs staff fully familiar with eCTD and may have already been established by prior US IND submissions.[1] These decisions should take place at a separate submission team meeting. A better approach, if team members have never seen a completed submission, is to include a short demonstration presentation of the eCTD backbone for another marketed product as an optional pre-meeting or training session.

AFTER THE MEETING

The discussion should be summarised in comprehensive meeting minutes so that new team members have a detailed, robust reference. The team should determine in advance how agreed actions will be tracked and closed out. Next steps should include development of a detailed submission plan and timeline including dependencies, and preparation of an author's guide addressing project-specific terminology and any other writing style-related considerations. Assure stakeholder buy-in to the agreed approaches and revisit the key messages at a future date, optimally with Phase III results in hand. Debrief the team to confirm any key learnings from the storyboarding meeting or suggestions for process improvement.

Every significant application and development project is different; it is difficult to quantitate the benefits of storyboarding. Potential measures include the number of rework and review cycles for key documents; adherence to timelines during submission preparation, and cycle time for regulatory review. Qualitative measures might include consideration of the learnings from post-submission debrief meetings with the team and other stakeholders about what went well and what should be improved for the next submission.

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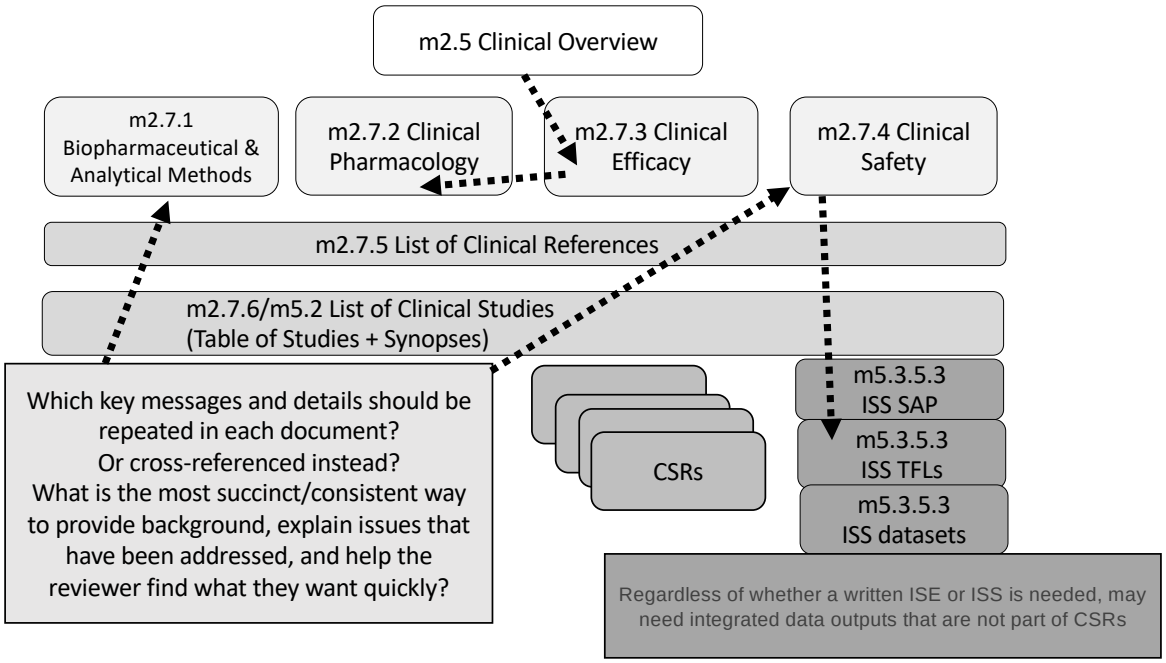
FIGURE 1 USE THE OUTPUT FROM STORYBOARDING TO PLAN THE FLOW OF INFORMATION/DETAIL ACROSS AND BETWEEN CLINICAL SUMMARIES – WRITE, REUSE OR CROSS-REFERENCE



Key: ISS = integrated summary of safety; ISE = integrated summary of efficacy; CSR = clinical study report.

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TABLE 1

PROMPT LIST TO HELP REGULATORY STAFF PREPARE FOR STORYBOARDING

	Source of information for review	Rationale for review and potential 'finds'	Potential storyboarding agenda topic
1.	Indication statement in target product profile	Review using regulatory guidance for labelling in each region. Prompt a team and stakeholder discussion about limitations of the data, plans for subsequent submissions to expand the indication or address special patient groups, potential subgroup analyses of clinical data to mitigate gaps.	Indication statement – prescribing information
2.	'How Supplied' section of prescribing information	Ensuring the whole team knows how the development pharmaceutics, stability and quality by design data line up with the to-be-marketed formulation, packaging and pack sizes for each region, through discussing the intended content of the 'How Supplied' section of the prescribing information, can be an important segment of the meeting. The interfaces between Module 3 CMC content and authoring of the Module 2.7.1 can be accelerated if information is shared early. Rework can be prevented if the commercial group members are clear about what they want the marketing and distribution plan to be.	To-be-marketed product vs development/clinical product
3.	ICH M3(R2) and the last version of Module 2.6 summaries/ investigator's brochure[2,3]	Does the completed nonclinical package fit the clinical regimen?	Nonclinical gap analysis or outstanding/planned nonclinical studies
4.	Route of metabolism in animals and humans	Ensure the nonclinical DMPK and clinical pharmacology team are aligned with respect to the best way to depict the route of metabolism in animals and humans and whether the supporting data package is complete compared with recently updated standards.[4] Decide how much detail to include in the 'Drug Interactions' section of the prescribing information.[5] Proactively plan to prevent rework and repetition of content by the authors of Module 2.6.4 and Module 2.7.2.[3]	Route of metabolism and potential for drug-drug interactions
5.	Investigational plan in DSUR or in FDA/EMA briefing documents	Prepare a rationale and schematic of the overall clinical data package that will provide a snapshot of the clinical programme and ensure understanding of the status and role of each study relative to the upcoming submission. Offer a draft for discussion at storyboarding, refine, include in Module 2.5 and then cite/cross reference many times. A summary graphic helps to position each completed study relative to the intended indication and its role in the integrated analysis of safety and/or efficacy. Writers will need to align and discuss the package and results relative to regulatory guidances within Module 2.7.[6] It can be helpful to review the studies in context with the FDA substantial effectiveness guideline, and guidance relating to integrated summaries, to determine how best to articulate a compelling case for how results may be appropriately extrapolated across studies to provide independent substantiation of safety and efficacy and to define plans for supporting integrated data analysis and presentation.[7,8]	Overview of clinical programme. Plans for ISE and ISS TFLs or SAP for Phase III.
6.	Prior correspondence with FDA/EMA	How has each question and answer cycle been resolved? Where will the reviewers find these data and be assured they were heard? How much detail should be included in reviewer guides/regional pre-submission meeting documents vs Module 2 summaries? Use this agenda item to get the sponsor/client talking about what they know about the product and to find out which team members present at the storyboarding meeting were also present at prior regulatory meetings and what they remember.	Agreements with regulatory agencies
7.	Information about the competitive landscape, EPARs or SBAs, FDA Advisory Committee meeting transcripts or summaries	Valuable sources of information about agency expectations and informative data presentations for inclusion in Module 2 summaries or analysis plans.	Plans for ISE and ISS TFLs or SAP for Phase III. Plans for FDA advisory committee or pre-submission meetings
8.	US and EU prescribing information	Consider other products in the same disease area, potential competitors, and products for administration to similar patient populations or by comparable routes/finished product presentations. Anticipate appropriate testing to address risk management/patient readability/ avoidance of medication errors as well as potential gaps in the data package.	Review of key sections of draft prescribing information and timeline for next draft

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	Source of information for review	Rationale for review and potential 'finds'	Potential storyboarding agenda topic
9.	Regulatory guidance and treatment guidelines for the disease or therapeutic area of interest and searches of Clinicaltrials.gov – for the disease and for compounds in the same class	Likely agency expectations and examples of informative data presentations for inclusion in Module 2 summaries or analysis plans. Check reports whose value to the submission may be impacted by recently updated guidelines. Also allows early discussion about the degree of regional tailoring needed for summaries. Helps kickstart the Risk:Benefit section of Module 2.5 by examining the potential contribution of the new product to the existing treatment armamentarium.	Plans for ISE and ISS or SAP for Phase III. Plans for FDA advisory committee or pre-submission meetings
10.	Dose rationale	Decide how much emphasis to place on nonclinical efficacy and safety data in the clinical rationale included in Module 2.7.2 and Module 2.7.3, how much detail from the Phase III protocol dose rationale or EoP2 meeting briefing documents can be repurposed, and whether the intended pack size/strength supports minimisation of medication errors.	Dose regimen
11.	CMC	Does the intended pack size and presentation in each region match the stability data package? Are there appropriate plans for development of immediate and secondary labelling in place? Are DMFs involved and have the rights of access been addressed? How close to completion are the Module 3 documents? Ensuring the CMC/nonclinical/clinical strategy are aligned is always helpful and highly recommended when a drug is eligible for expedited programmes for serious conditions.	
12.	Safety margin	There should be a clear description of the safety margin between the NOAEL in animal studies and the intended human dose in the Module 2.6.6 or Module 2.4 prepared at the FTIH stage of development. How does that need to be refined now that the intended dose regimen is clearer? How does it apply to special patient groups now that the metabolic route is better understood? How do you want to express this margin in the 'Pregnancy' and 'Nonclinical' sections of the prescribing information?	Safety margin and extent of exposure
13.	Extent of exposure	Although the targets described in ICH E1[9] still stand, many programmes stumble through multiple edits of the simple statements of how many patients were treated/exposed to the intended product and for how long. Be sure that all sources of clinical exposure can be added up, traced back to source, and reviewed in context of the intended clinical regimen.	Safety margin and extent of exposure
14.	Prevalence and incidence of disease in special patient subgroups compared with clinical experience accrued to date, including pregnancies, subjects with renal or hepatic impairment, and paediatrics	Take time to evaluate the incidence and prevalence – and relevance – of each special patient group and consider how to position the available data or lack of data in upcoming briefing documents and draft labelling.[5] Confirm intentions with respect to subgroup analysis of safety in the ISS SAP, or planned PopPK analysis, or post-submission studies regarding intrinsic factors subgroups. There may be extensive concomitant medication data in the Phase III dataset that partially address gaps in the Phase I drug-drug interaction study package. Understand the prevalence and incidence of the disease in the paediatric patient population and associated considerations with respect to formulation, nonclinical coverage, and timing of pediatric indications. A complete or advanced draft EU PIP and a US iPSP should be in place.[10,11]	Special patient subgroups sections of prescribing information
15.	SAP for Phase III protocol(s)	Understand the planned analysis for presentation of primary efficacy. Confirm the extent of regulatory agency buy-in to the suitability of the primary endpoint and relative contribution of secondary endpoints or biomarkers. Check the degree of replication of efficacy endpoints and safety measurements across clinical studies ready to anticipate an approach to data integration for ISS and ISE TFLs. Consider which figures or tables are likely to be desirable for inclusion in the prescribing information or advertising materials.	Clinical studies section of prescribing information
16.	Adverse reactions (approach to presentation, study selection, approach to PV)	Regardless of whether a separate written report of clinical safety will be needed in the US in addition to a Module 2.7.4,[12] some part of the clinical safety package will need integration to assure accurate representation of overall exposure. Early discussion of the desired approach to summarising the adverse event profile across studies/indications in both EU and US prescribing information, and which potential AESI may need in-depth review, is important. Development of the pharmacovigilance plan and risk management plans in major regions may introduce new departments to the team and to the overall discussion.	Adverse events/reactions, ISS, risk management plan
17.	Microbiology	For anti-infective products, additional reporting, integration or data presentations may be necessary to address nonclinical and clinical aspects of the microbiological mechanism of action, sensitivity, genotype and potential for resistance.[13,14] Specialist writers may be needed to support preparation of these reports and analyses.	Microbiology
18.	Literature search output in DSURs	Anticipate literature searches that may be needed to support the marketing application and avoid duplication of effort in gathering the most relevant literature.	Clinical references in Module 5.4 Nonclinical references in Module 4.3 CMC references in Module 3.3
19.	Intellectual property	Consider the best regulatory route for application and any associated implications for dossier content/positioning. IP lawyers may or may not be in-house, or part of regular project teams, or well versed in aspects of preparation of a regulatory submission, or aware of the submission timeline.	Intellectual property

	Source of information for review	Rationale for review and potential 'finds'	Potential storyboarding agenda topic
20.	Lists of completed/ reported/ ongoing studies	Perhaps a collection of final completed reports with all appendices and electronic datasets is readily available by looking at the eCTD backbone for the US IND but it is often the case that some of those appendices are not quite marketing application ready, and early identification of those gaps, as well as the requirements for BIMO submissions, is worthwhile.[1,15] A detailed submission plan will be needed to publish the marketing application. Typical pain points include bioanalytical reports and validation of PK assays used early in clinical and nonclinical development, SDTM clinical datasets, TEAE datasets originally coded in an earlier version of MedDRA and thus not yet ready for pooling and integration with later clinical studies, SEND datasets for nonclinical reports, and financial disclosure documentation for inclusion in Module 1 of the US NDA.[16–19]	Action plan/timeline for completion of rate limiting reports/appendices
21.	Transfer of obligations lists	Use the transfer of obligations lists and contracts to figure out who should be supplying any outstanding appendices. This is particularly the case when outsourcing has involved a number of CROs or if the development programme has spanned several years.	Timeline for completing reports

DMPK = drug metabolism and pharmacokinetics; DSUR = development safety update report; FDA = Food and Drug Administration; EMA = European Medicines Agency; ISE = integrated summary of efficacy; ISS = integrated summary of safety; TFL = tables, figures and listings; SAP = statistical analysis plan; EPAR= European public assessment report; SBA = US FDA's summary basis of approval; EoP2 = end of phase 2; CMC = chemistry, manufacturing and controls; DMF = drug master file; NOAEL = no observed adverse effect limit; FTIH = first time in human; ICH = international conference on harmonisation; PopPK = population pharmacokinetics; PIP = paediatric investigational plan; iPSP = initial pediatric study plans; AESI = adverse events of special interest; IP = intellectual property; eCTD = electronic common technical document; IND = investigational new drug application; SDTM = Study data tabulation model: TEAE = treatment emergent adverse event; SEND = implementation of the SDTM standard for nonclinical studies; CRO = contract research organisation.

CONCLUSION

Early recognition and resolution of data gaps can prevent last-minute time pressures and rework, as well as inadvertent errors borne of haste. This also assures that key labelling statements are supported by the most meaningful data outputs and with internal stakeholder engagement.

Ensuring that the whole team participates in an exercise to "start with the end in mind" can accelerate cohesiveness of the completed application and serve to educate the team about the general content in areas outside their immediate areas of responsibility. The internal dialogue to develop key messages that should be conveyed throughout the application serves as a training opportunity and ensures transparency of the overall product strategy. Reducing the number and complexity of review cycles by establishing key messages that are consistent across CTD summaries can maximise opportunities for intelligent cross-referencing and secondary hyperlinking within the published submission and keep documents succinct. This support for the 'read thread' (Figure 1) reduces late-stage setbacks during the publishing stage and will help to establish a credible position with regulatory reviewers as they follow the data through the completed submission.

The submission team-building and emotional intelligence elements of storyboarding should not be overlooked: use the meeting to accelerate the 'Form, Storm, Norm, and Perform' stages of team development. A team that recognises their interdependencies will pull together to resolve review comments and challenges, benefiting the submission, their employer, and ultimately, the patient.

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