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White paper: Understanding, informing and defining the regulatory science of microneedle-based dosage forms that are applied to the skin☆

Maria Dul [a,1], Mohammed Alali [b], Mahmoud Ameri [c,v], Matthew Douglas Burke [d,w], Benjamin Paul Creelman [e], Lisa Dick [f], Ryan F. Donnelly [g], Michael N. Eakins [h], Collrane Frivold [e], Angus Harry Forster [i], Philippe-Alexandre Gilbert [j], Stefan Henke [k,x], Sebastien Henry [l], Desmond Hunt [m], Hayley Lewis [n], Jessica Joyce Mistilis [e], Jung-Hwan Park [o], Mark R. Prausnitz [p], David Kenneth Robinson [j], Carmen Amelia Rodriguez Hernandez [b], Juyeop Shin [q], Tycho Joseph Speaker [r], Caroline Strasinger [s], Kevin M.G. Taylor [t,y], Darin Zehrung [u,2], James C. Birchall [a,2], Courtney Jarrahian [e,*,2], Sion A. Coulman [a,*,2]

[a] Cardiff School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, UK
[b] World Health Organization, Geneva, Switzerland
[c] Americeutics Consulting, USA
[d] Stemline Therapeutics Inc, a Menarini Group Company, USA
[e] PATH, Seattle, USA
[f] Previously Kindeva Drug Delivery, USA
[g] School of Pharmacy, Queen's University Belfast, Belfast, UK
[h] Eakins & Associates, USA
[i] Vaxxas Pty Ltd, Australia
[j] Bill & Melinda Gates Foundation, Seattle, USA
[k] Bioaxxent – Drug Delivery, Germany
[l] Micron Biomedical, Inc., USA
[m] United States Pharmacopeia, USA
[n] Previously Zosano Pharma, USA
[o] Department of Bionano Technology, Gachon University, Seongnam, Republic of Korea
[p] School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, GA, USA
[q] Raphas Co. Ltd, Republic of Korea
[r] AbbVie Inc, USA
[s] Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA), USA
[t] University College London School of Pharmacy, UK
[u] Zehrung Global Health LLC, USA
[v] previously Zosano Pharma, USA
[w] previously Radius Health, Inc., USA
[x] previously LTS Lohmann Therapie-Systeme AG, Germany
[y] previously British Pharmacopoeia Commission, UK

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ABSTRACT

The COVID-19 pandemic has accelerated pre-clinical and clinical development of microneedle-based drug delivery technology. However the regulatory science of this emerging dosage form is immature and explicit regulatory guidance is limited. A group of international stakeholders has formed to identify and address key issues for the regulatory science of future products that combine a microneedle device and active pharmaceutical ingredient (in solid or semi-solid state) in a single entity that is designed for application to the skin. Guided by the

☆ All authors are/were members of the Microneedle Array Patch Regulatory Working Group (MAP-RWG). Further information about this group is available at www.microneedleregulatory.org.

* Corresponding authors.
E-mail address: coulmansa@cardiff.ac.uk (S.A. Coulman).

[1] First author.
[2] Co-last authors.

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Critical quality attributes
Test methods

principles of Quality by Design (QbD) and informed by consultation with wider stakeholders, this 'White Paper' describes fundamental elements of the work in an effort to harmonise understanding, stimulate discussion and guide innovation. The paper discusses classification of the dosage form (combination/medicinal product), the regulatory nomenclature that is likely to be adopted and the technical vocabulary that best describes its form and function. More than twenty potential critical quality attributes (CQAs) are identified for the dosage form, and a prioritisation exercise identifies those CQAs that are most pertinent to the dosage form and that will likely require bespoke test methods (delivered dose, puncture performance) or major adaptions to established compendial test methods (dissolution). Hopefully the work will provide a platform for the development of dosage form specific guidance (from regulatory authorities and/or international pharmacopoeias), that expedites clinical translation of safe and effective microneedle-based products.

1. Introduction

Conception [1] and manufacture [2] of microneedle structures that can facilitate delivery of active pharmaceutical ingredients (APIs) into the body has stimulated development of numerous potential microneedle-based products, and the emergence of a potentially new dosage form [3]. A range of therapeutic uses, related to both drug delivery and diagnostic applications, have been proposed for microneedle technology, but the recent COVID-19 pandemic has augmented and accelerated interest in the technology as a platform for vaccination [4]. The principal motivators for development of microneedle-based delivery systems relate to the clinical (patient and practitioner) advantages afforded by their minimally invasive nature and the logistic advantages of producing an integrated, and potentially thermostable, dosage form that may not need to be administered by a trained individual and does not produce sharps waste. This may be particularly advantageous in low- and middle-income countries (LMICs) [5]. Most proposed microneedle-based products are applied to the skin [6], although the eye [7], oral mucosa [8] and gastrointestinal tract [9] are other notable anatomical application sites.

Potential microneedle-based products are transitioning from pre-clinical development to Investigational New Drug (IND)-enabling studies, and numerous proposed products have now been clinically evaluated [10], including two major Phase 3 trials [11,12]. These two trials alone describe tens of thousands of microneedle applications to hundreds of volunteers, with no significant safety concerns [13]. This, in combination with encouraging clinical responses from microneedle-based products [14,15], exemplifies the potential of the technology and has stimulated international efforts [16] to develop capacity for large-scale manufacture of microneedle-based products in preparation for widespread clinical use [17]. Active lines of communication between regulatory authorities and individual microneedle product developers are therefore established, however the regulatory science [18,19] is immature and microneedle-specific guidance from internationally recognised regulatory authorities and pharmacopoeias is limited [20,21]. Established legislation, guidance and specifications for analogous dosage forms will undoubtedly inform the regulatory science of future microneedle-based products. However, this emerging dosage form possesses unique features that will necessitate innovations in the regulatory science and development of dosage-form specific guidance to ensure the quality, safety, and efficacy of products [21,22]. This article aims to contribute to this endeavour by identifying and addressing some of the fundamental elements of the relevant regulatory science, including how the dosage form is described, defined and categorised, and some important quality and safety considerations for future products.

Microneedle-based drug delivery systems that are designed for application to the skin are diverse, both in terms of their mechanism of action and their proposed clinical applications. A clear understanding of how a specific proposed microneedle-based product will be categorised is therefore an important first step that will determine the regulatory science and pathway for that product. When applied to the skin to create micron-sized disruptions for direct therapeutic effect, i.e. not used with an active pharmaceutical ingredient (API), microneedle-based products will likely be categorised as medical devices [20]. However, numerous proposed microneedle-based therapeutic products include an API, either as an integrated part of the product or as an accompanying formulation. These microneedle-based drug delivery systems are often sub-categorised based on their form and function [6,23,24] (Table 1). For regulatory purposes, the majority of proposed products within these sub-categories will be classified as combination products in the USA [25–27], Japan [28] and South Korea [29]. If the API is as an integrated part of a single entity (Table 1; coated, dissolving, hydrogel and pre-filled hollow microneedles) the product will likely be further classified as a single entity combination product. The API in these single entity microneedle-based combination products could be a drug or biological product (as defined by the FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER)).

Products that include more than one entity, e.g. solid or hollow microneedles to be used with an accompanying formulated API, are more likely to be classified as cross-labelled or co-packaged combination products, as defined by the FDA [25,27]. API-free devices and co-packaged or cross labelled microneedle-based products (or co-packaged medicinal products, as they are likely to be classified by EMA [30–32]) are outside the scope of this article.

This relatively simple description of how proposed microneedle-based drug delivery products may be categorised and classified

Table 1
Commonly used descriptions of sub-categories of microneedle-based drug delivery systems [24]. Coated, dissolving and matrix microneedles are the focus of this article.

Microneedle Form	Mode of Delivery	Description
Solid Microneedles	Poke and Patch	Microneedles mechanically disrupt the skin barrier (poke), to create physical conduits across the stratum corneum barrier. They are then removed. API is applied in a conventional dosage form (topical product) to the microneedle-treated skin.
Hollow Microneedles	Poke and Flow	Microneedles mechanically disrupt the skin and facilitate delivery of a liquid formulation into the skin via a hollow microneedle.
Coated Microneedles	Coat and Poke	Microneedles are coated with a formulation containing an API. On application they mechanically disrupt the skin barrier and remain in situ for a designated period, during which time the API is predominantly released by dissolution of the microneedle coating. The product is removed after a designated period.
Dissolving Microneedles	Poke and Dissolve	Microneedles manufactured using a water soluble or biodegradable matrix containing an API. On application they mechanically disrupt the skin barrier and remain in situ for a designated period, during which time the API is predominantly released by dissolution or degradation of the microneedle matrix. The product is removed after a designated period.
Matrix (Hydrogel-forming) Microneedles	Poke and Release	Microneedles manufactured using an insoluble (in water) microneedle matrix. On application they mechanically disrupt the skin barrier and remain in situ for a designated period, during which time the API is predominantly released by diffusion. The product is removed after a designated period.

provides context and guidance, however it is only indicative. Some microneedle-based products could possess features that correspond with more than one sub-category of microneedle-based drug delivery system (Table 1), and others may not be effectively described by any of the sub-categories. There are also regional differences in the requirements of different international regulatory authorities. For example, in the UK and European Union (EU), single entity combination products (as defined by the FDA) will likely be classified and regulated as integral medicinal products [30–33]. In Europe, the medical device (i.e., microneedle-based component of the product) that forms part of the single integral medicinal product may also be subject to a conformity assessment [32,34,35]. Developers are therefore encouraged to seek advice from the relevant regional regulatory authorities at an early stage of product development to confirm classification of their microneedle-based product and the associated regulatory requirements thereafter.

For clarity, this article aims to inform and establish aspects of the regulatory science for future microneedle-based products that combine the microneedle device and API (in solid or semi-solid form only) in a single entity and are designed for application to the skin (as exemplified and illustrated in Fig. 1). The API in these single entity microneedle-based combination products could be a drug or biological product such as a vaccine. A nomenclature and definition that could be used for regulatory purposes is proposed and rationalised for this sub-category of microneedle-based products. Their candidate critical quality attributes (CQAs) are also identified and discussed and innovations that may be required for test methods to demonstrate these CQAs are considered. A collaborative and consultative approach, involving numerous key stakeholders, has been adopted to promote an internationally informed and harmonised understanding, on which future regulatory guidance can be constructed. Elements of this article may also inform the regulatory science of other proposed microneedle-based medical products, e.g. those designed for application to other anatomical sites and/or use without an integrated API, however these closely-related products are not the focus of this work.

2. 'Forming', 'storming' and 'norming'

2.1. 'Forming' the regulatory working group

Informed development of the regulatory science of microneedle-based products will require collaborative input from a diversity of stakeholders. A Regulatory Working Group (RWG) [36] was established, under the remit of PATH's Center of Excellence [37], to provide expert opinion, informed by wider stakeholder consultation, on the regulatory science of microneedle-based dosage forms. The RWG is co-chaired by Cardiff University (CU) and PATH and comprises key stakeholders from the pharmaceutical industry (small and large organisations), academic institutions, national regulatory authorities, international pharmacopoeias and public health organisations, both governmental and non-governmental. A purposive recruitment strategy was used to ensure formation of a representative yet agile group that possessed expertise in microneedles for drug delivery and/or the development and regulation of medicines and medical devices. Founding members of the RWG contributed to and agreed the terms of reference for membership, which includes a declaration of potential conflicts of interest. The information that is provided in this article is a consensus opinion from this group and not a reflection of the personal views of individual members. CU and PATH are co-chairs of the RWG, and their primary role was to facilitate discussion, gather opinions, collate findings and disseminate results.

2.2. 'Storming' and 'norming'

The primary aims were iteratively created by co-chairs and members of the RWG. These aims were to (i) develop a proposed nomenclature

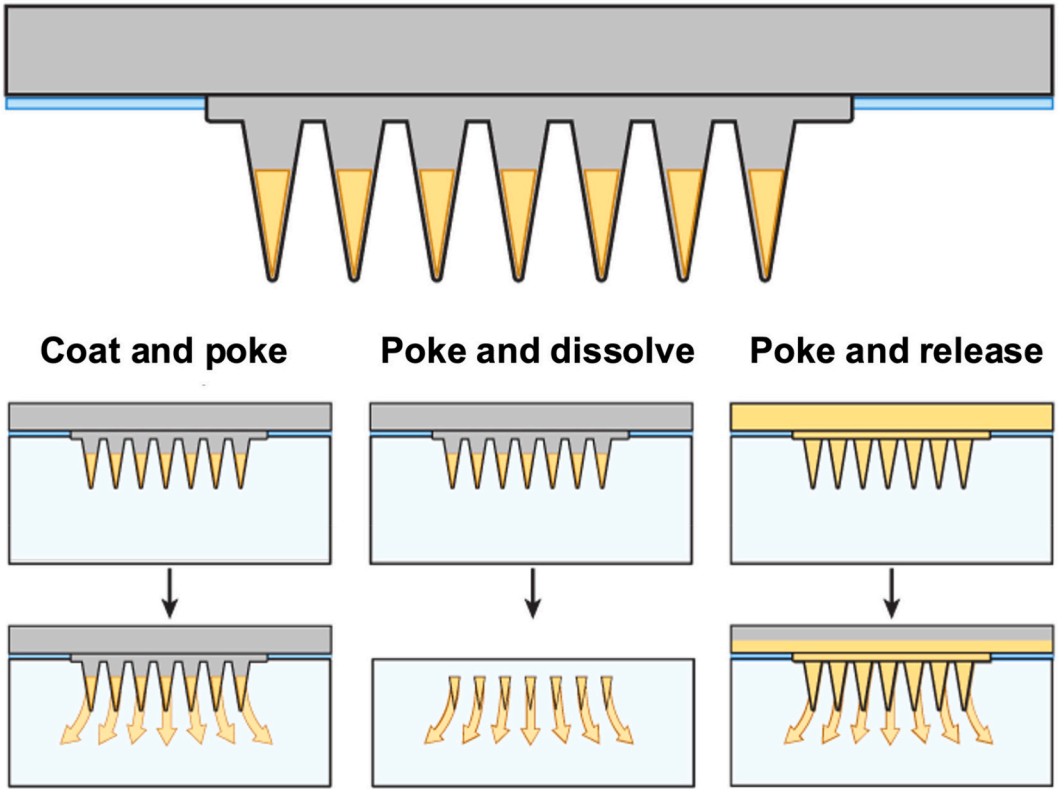

Fig. 1. An illustration of the sub-categories of microneedle-based products that combine the microneedle device and API (in solid or semi-solid form only), in a single entity. Adapted from Prausnitz MR. Annu Rev. Chem Biomol Eng. 2017;8:177–200 and reproduced with permission from the Annual Review of Chemical and Biomolecular Engineering, Volume 8 © 2017 by Annual Reviews, http://www.annualreviews.org

and definition for the dosage form, (ii) identify potential CQAs and (iii) determine which CQAs are unlikely to be exemplified using internationally recognised standardised test methods for other dosage forms. The working principles of the group were, and continue to be, informed by the principles of Quality by Design (QbD) [38]. The subsequent text, and Figs. 2 and 3, provide an overview of the collaborative and consultative brainstorming ('storming') and consensus normalisation ('norming') activities that were used to meet the aims.

One-to-one formal ($N = 18$) and informal discussions with RWG members and other key stakeholders were used to gather opinions on the key contemporary CMC (Chemistry, Manufacturing and Controls) related issues in the regulatory development of microneedle-based dosage forms. These wide-ranging discussions considered the scientific and regulatory vocabulary used to describe the dosage form, its potential CQAs and the associated test methods and specifications that would be required to demonstrate and/or control identified CQAs. All formal meetings were transcribed and used by the co-chairs of the RWG (CU and PATH) to inform the agenda of a one-day face-to-face inaugural RWG workshop.

The inaugural workshop (attended by 22 stakeholders that were either members of the RWG, employees of the co-chairing organisations or invited observers) consisted of activities designed, by the chairs of the RWG, to stimulate debate, inform thinking, harmonise understanding and prioritise key areas. Initial discussions were focussed on the vocabulary used to describe the dosage form and its categorisation for regulatory purposes. This was followed by activities to encourage discussion of the potential CQAs for the dosage form and the accompanying test methods that may need to be developed (either by major adaptations to established internationally recognised test methods, or the development of a bespoke test) to characterise these attributes. Key outcomes from the meeting were collated, communicated to members of the RWG and used to inform draft proposals related to the nomenclature, definition, CQAs and test methods for the dosage form. An online tool was then used to garner feedback from individual RWG members on these proposals and to inform iterative progression towards a consensus opinion (Figs. 2 and 3).

RWG consensus was followed by engagement and consultation with wider stakeholders, facilitated using synchronous interactions i.e. online polling tools [39] during presentations at major international conferences (*Microneedles & Transdermal Drug Delivery Systems Virtual Conference 2020 and The 6th International Conference on Microneedles 2020)* and asynchronous communication and consultation using a bespoke online survey that was available on the RWG's [36]. These activities provided additional insights, alternative opinions and corroborated the work of the RWG.

3. Nomenclature (label name) and definition

Transparent communication between regulatory authorities, developers and other stakeholders is a key facilitator in efficient regulatory

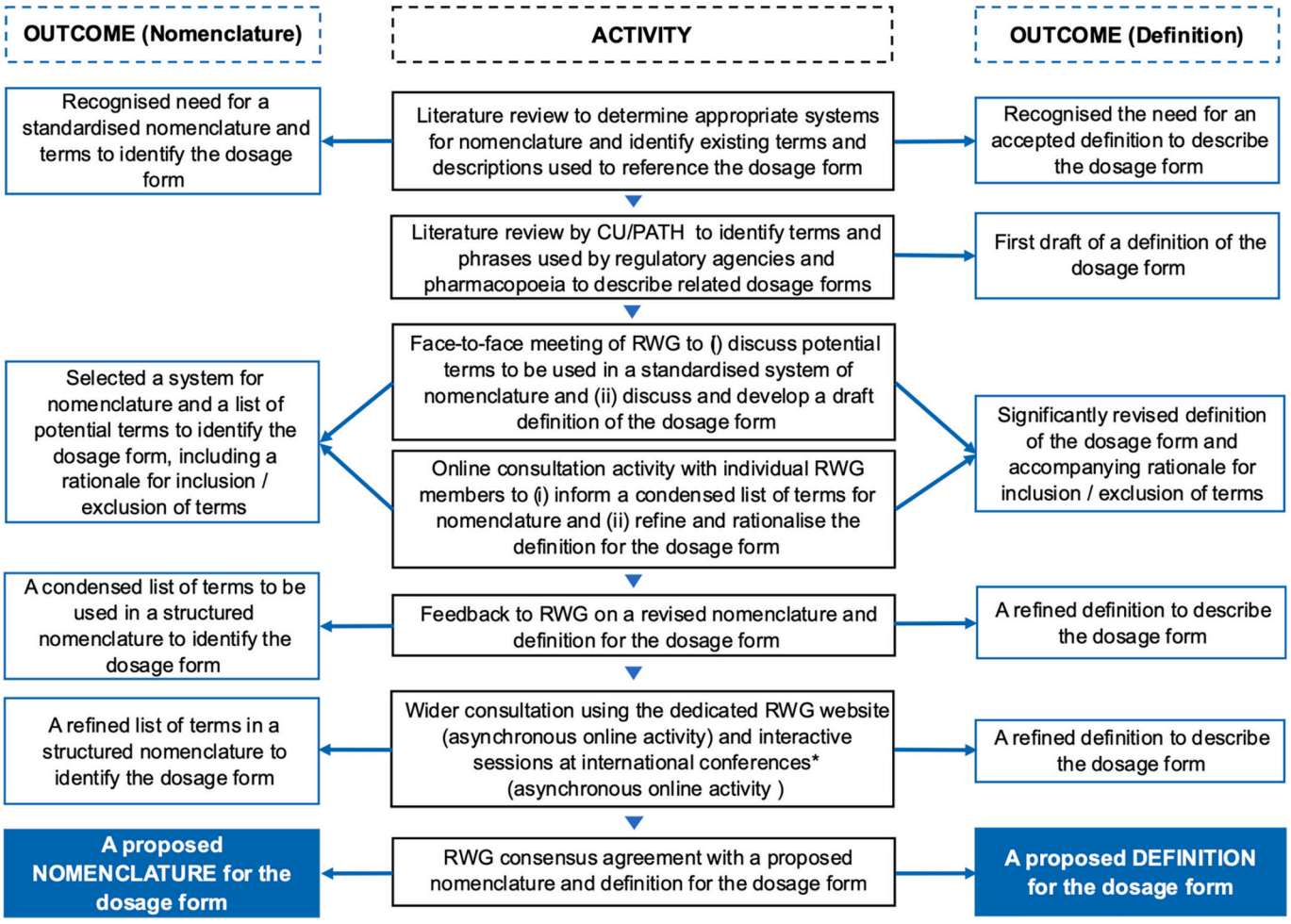

Fig. 2. An overview of activities and outcomes to summarise the process used to develop a proposed nomenclature and definition for microneedle-based products that combine the microneedle device and API (solid or semi-solid form only) in a single entity and are designed for application to the skin.
* *Consultation Activities took place at Microneedles & Transdermal Drug Delivery Systems Virtual Conference 2020 and The 6th International Conference on Microneedles 2020.*

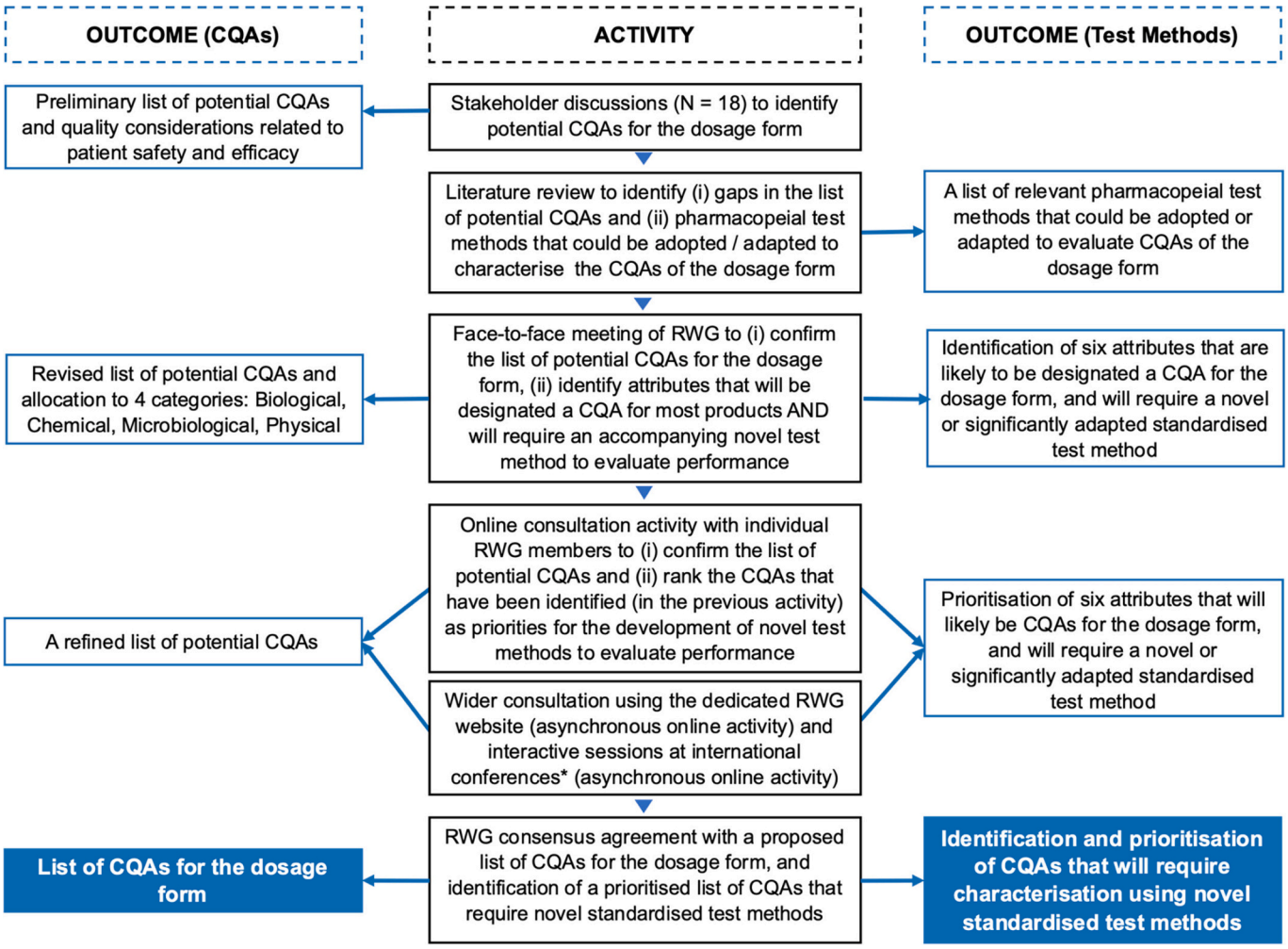

Fig. 3. An overview of activities and outcomes to identify the CQAs, and accompanying test methods, of microneedle-based products that combine the microneedle device and API (solid or semi-solid form only) in a single entity and are designed for application to the skin.
** Consultation Activities took place at Microneedles & Transdermal Drug Delivery Systems Virtual Conference 2020 and The 6th International Conference on Microneedles 2020.*

approval of high quality, safe and effective products. Therefore, the first step in the development of guidance and standards for microneedle-based dosage forms is to establish the scientific and regulatory vocabulary that is used to describe the dosage form. At present, a diversity of words and phrases have been used to identify microneedle-based technology (Supplementary Table 1) and to describe its features and functions. The RWG, in consultation with wider stakeholders, has therefore iteratively developed a proposed 'label name' for the dosage form (Table 2), using an established system of nomenclature, and an accompanying definition (Fig. 4). The following text describes this iterative development and provides accompanying rationale, which is integral to a shared understanding, future development and potential adoption by international regulatory authorities and pharmacopoeias.

3.1. Iterative development of a proposed nomenclature (label name)

A nomenclature to construct a 'label name' for the dosage form, for regulatory purposes, is described in Table 2. The configuration is informed by the United States Pharmacopoeia (USP) General Chapter ⟨1121⟩ Nomenclature, which states that a medicinal product would generally be described by the [DRUG] [ROUTE OF ADMINISTRATION] and [DOSAGE FORM] [40]. While this provides a structure for construction of a label name, international differences in the vocabularies of national/regional regulatory authorities mean that product developers should be cognisant of the requirements of the regulatory body in the specific territory where their product will be licensed.

Each word, or part of a word, in the proposed 'label name' for the dosage form has been selected to provide an accurate description using,

Table 2
A proposed nomenclature for microneedle-based products that combine the microneedle device and API, in solid or semi-solid form, in a single entity and are designed for application to the skin.

[ROUTE OF ADMINISTRATION]	[DOSAGE FORM] Part 1a	[DOSAGE FORM] Part 1b	[DOSAGE FORM] Part 2
Topical / Cutaneous / Intracutaneous / Intradermal / Transdermal / Other	**Microneedle**	**Array**	**Patch / System**
Route will be assigned based on the method of application, the anatomical locus of API deposition in the skin and the primary therapeutic target site. A new route may be appropriate for this innovative dosage form.	*Microarray is synonymous with "DNA microarrays" and so "microneedle array" provides a distinct and scientifically accurate description. Array may be considered superfluous by some regulatory authorities. Microprojection is an alternative if the term 'needle' is considered detrimental to the clinical acceptability of the dosage form.*		*This term is dictated by the requirements of the regulatory body in that territory e.g. "Patch" is used by EMA and "System" is used by FDA. Another term might be appropriate if the product varies from the defined dosage form (Figure 4).*

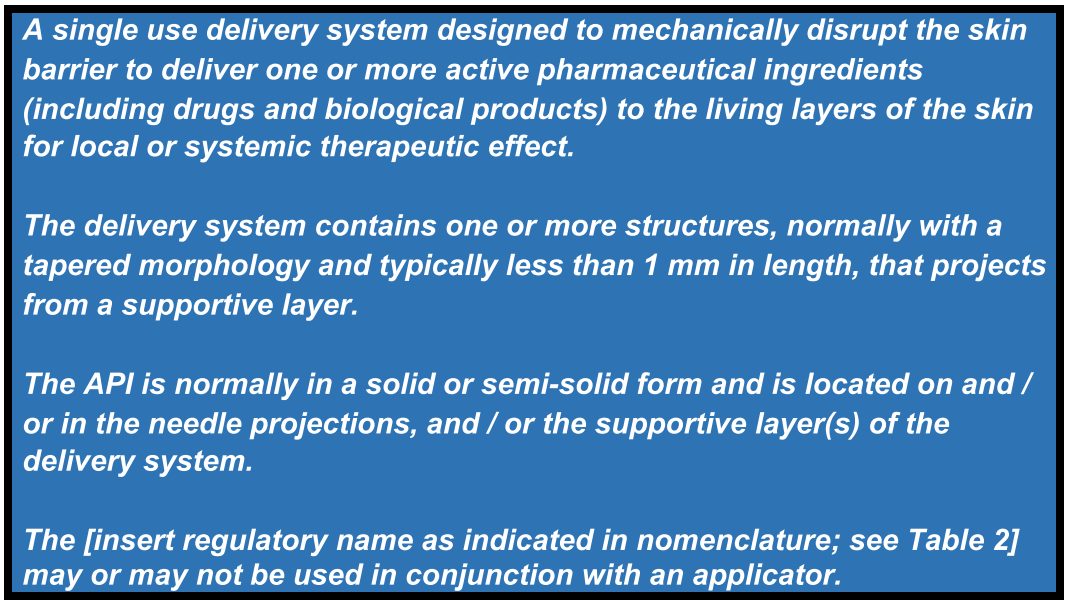

Fig. 4. A definition for microneedle-based products that combine the microneedle device and API, in solid or semi-solid form, in a single entity and are designed for application to the skin.

where possible, terms that are recognised by international regulatory authorities. The first word used in a label name should identify the API and thus will be product specific. However, the subsequent word, the [ROUTE OF ADMINISTRATION], has a finite number of internationally recognised terms for products applied to the skin: topical, cutaneous, transdermal, intradermal, intracutaneous and percutaneous. Selection of the most appropriate term to describe the route of administration is dictated by the anatomical site of application, the nature of the API i.e., drug or biological product, and the intended target site i.e., on, in or through the skin.

Topical is a broad term used to describe products that are administered "to a particular spot on the outer surface of the body" [41]. This includes the skin but also includes other targets such as the eye, nose and ear. Topically applied drug products include, but are not limited to, creams, gels, ointments, pastes, suspensions, lotions, foams, sprays, aerosols and solutions. In Europe, administration of a medicinal product to the skin for local effect is also described as ***cutaneous*** [42]. Examples of products that are classified as cutaneous formulations include solutions, foams, emulsions, sprays and patches e.g. Qutenza® 179 mg cutaneous patch (as classified by the EMA) [43], where the target site for the API is local, i.e. cutaneous nociceptors in the skin epidermis and dermis. ***Transdermal***, i.e. administration of the API "through the dermal layer of the skin to the systemic circulation by diffusion" [41] is a common route of delivery for patch formulations. ***Intracutaneous*** has been used to describe direct administration into the skin, for products such as the Bacille Calmette Guérin (BCG) vaccine [44] and ***intradermal*** describes targeted administration of a drug or vaccine into the dermis layer of skin. Intradermal is typically used to describe injection by a needle and syringe using a skilled method of administration called the Mantoux technique [45]. This route of administration may be an appropriate description for hollow microneedle-based delivery systems. Examples of products that use the intradermal route of delivery include Fluzone® Intradermal Quadrivalent, BCG Vaccine AJV and Adcortyl® Intradermal Injection. ***Percutaneous*** is defined by the FDA as, "administration through the skin" and has been used to describe administration of the BCG vaccine by application of a single-use multiple puncture (thirty-six, 1 mm long needles) device to an area of skin that has been pre-treated with a topically applied liquid vaccine [46]. It has also been used to describe medical devices that traverse the skin to access another body site e.g. Percutaneous Transluminal Coronary Angioplasty (PTCA) Catheters [47].

The method of application, the anatomical locus of API deposition (stratum corneum, viable epidermis, papillary dermis, reticular dermis) and the location of the primary therapeutic target are important considerations when assigning a route of delivery to a product. Intradermal is currently used to describe commercially available products that deliver an API into the dermis for local effect, but these are typically invasive products that target the reticular dermis and deliver the payload as a liquid bolus. Therefore, this term does not accurately describe many proposed microneedle-based products, which aim to mechanically disrupt the most superficial layer(s) of skin (stratum corneum and/or viable epidermis) in a minimally invasive fashion, to facilitate localised delivery of an API following topical application, for local or systemic effect. Topical/cutaneous (local effect) or transdermal (systemic effect) may therefore be more appropriate terms to describe the route. However, although some topical/cutaneous products are applied to damaged skin, and some contain chemical penetration enhancers, an alternative term may be deemed necessary to describe the microneedle-induced mechanical disruption of superficial skin layer(s) that facilitates API delivery. Intracutaneous has been used to describe some proposed microneedle-based products, but this is often synonymous with intradermal, and therefore may not provide appropriate distinction. The innovative nature of a microneedle-based dosage form may necessitate new understandings of an existing term, or development of new terms e.g. "trans-/intra-epidermal or epicutaneous", to effectively describe the route of delivery. Importantly, the term that is selected to describe the route of delivery could have implications on the regulatory requirements for a product, e.g. the microbiological specification, and so must be carefully considered by stakeholders in the preclinical and clinical development of single entity microneedle-based combination products.

A word or phrase will also be needed to identify the [DOSAGE FORM]. The term 'patch' is used by the EMA and MHRA to describe flexible preparations intended for application to unbroken skin, for delivery of an API to or through the skin, for local (cutaneous patches) or systemic (transdermal patches) effect, over an extended period of time [42]. They are single-dose preparations, manufactured to dimensions that are dictated by their intended use. In Europe the term 'patch' may therefore be applicable to numerous proposed microneedle-based products. However, as previously acknowledged, there are regional

disparities in the terms that are used by regulatory authorities to describe dosage forms. For example, the FDA uses "topical" when the EMA may use "cutaneous", and the FDA uses "system" while the EMA refers to a "patch". This can result in regional differences in the label name for the same product e.g. the Qutenza® (capsaicin) topical system (FDA) and the Qutenza® 179 mg cutaneous patch (EMA); NEUPRO (rotigotine) transdermal system (FDA) and the NEUPRO 4 mg/24 h transdermal patch (EMA). It is also important to note that there is a spectrum of proposed microneedle-based drug delivery systems within the sub-categories described in Table 1. For example, some proposed dissolving microneedle-based systems deposit biodegradable micron-sized particles in the skin following removal of the patch, for sustained release applications [48,49]. Additional or alternative words may therefore be needed to describe some of the proposed delivery systems.

When used alone, 'patch' or 'system' do not identify the distinguishing feature of the dosage form i.e. mechanical disruption of the skin barrier at the micron scale using projections that are normally tapered. In the case of microneedle-based products, the name of the dosage form is therefore likely to consist of more than one word. There is precedent for this e.g. inhalation products that are used for pulmonary drug delivery have an additional term that sub-categorises the dosage form (inhalation aerosols, inhalation powders, inhalation sprays, inhalation solutions and inhalation suspensions). Similar nomenclature is

Table 3
A summary of the rationale for terms and phrases that have been used to define the MAP dosage form.

Proposed term / phrase	Rationale
"single use"	*Contemporary proposed products are applied once, whether it be for acute or chronic use. Therefore, "**single use**" is currently appropriate but should a multi-use product be developed, then this may be amended.*
"delivery system" designed to	*The term "**delivery system**" differentiates it from products that could be used for diagnostic purposes.*
"mechanically disrupt"	*"**Mechanically disrupt**" differentiates the dosage form from other methods that may be used to disrupt the skin barrier, either chemically or physically.*
"skin barrier"	*Whilst this dosage form is also being developed for application to other anatomical sites, this definition is focussed on its application to the "**skin**". Application to another organ would require a different definition, as it would be associated with a different patient safety profile.*
to "deliver" one or more active pharmaceutical ingredients	*The term "**deliver**" differentiates the dosage form from products that may be developed for diagnostic applications.*
"active pharmaceutical ingredients (including drugs and biological products)"	*A range of drugs and biological products, most commonly vaccines, have been formulated in proposed products.*
to the "living layers of the skin"	*The FDA uses this term in guidance for "microneedling" products. It refers to all living cells and tissues in the skin, below the stratum corneum.*
for local or systemic "therapeutic effect"	*The term **"therapeutic effect"** is intended to capture both medicinal treatments and vaccines.*
The delivery system contains "one or more structures"	***"one or more"** maintains the design space, permitting dosage forms to be developed with any number of microneedles.*
"normally with a tapered morphology"	*A 'needle-like' morphology was considered as a term, but this could exclude a structure that was shaped more like a blade. Therefore, "**tapered**" is proposed as a "catch all" term. The word "**normally**" has also been used to accommodate atypical configurations.*
"typically less than 1 mm in length"	*The dosage form is often defined as containing structures that are "**less than 1 mm**". Whilst this is typical, there may be dosage forms that have structures that are longer than 1 mm but with a restricted depth of penetration. Therefore, the expression **"typically"** has been used. Comments from MAP-RWG members indicated that the depth of penetration, rather than the length of the tapered projection, best defines the dosage form.*
projects from a "supportive layer"	*A **supportive layer** is currently present on all proposed configurations of the dosage form. This differentiates the dosage form from single needles with micron dimensions that are used for procedures such as the injection of materials into single cells.*
The API is "normally in a solid or semi-solid form"	*Current proposed configurations of combination products include the API formulation in a "**solid or semi-solid form**", but a liquid formulation within the product is conceivable. The term "**normally**" accommodates this potential variation.*
"located on and / or in the needle projections, and / or the supportive layer(s) of the delivery system"	*The sentence is intended to clearly identify the dosage form as a single entity combination product, as described by the FDA. It differentiates the product from a two-component delivery system e.g. a hollow microneedle (device) and a solution for injection (medicinal product).*
"may or may not be used in conjunction with an applicator"	*There is a diversity of proposed products, both with and without applicator devices, and therefore this broad definition ensures product design is not constrained.*

also used for nasal drug products e.g. nasal sprays, nasal solutions, nasal aerosols, and nasal powder dosage forms [50].

Numerous words have been used to describe the structures used to mechanically disrupt the skin (Supplementary Table 1), but the term "microneedle" provides a simple and technically accurate description that is extensively used in the published literature. In addition, "array" could describe the multiplicity (>1) of projections that are associated with nearly all proposed microneedle-based drug delivery products and differentiates from the "micro-needle" that is used in medical science for cell manipulations such as artificial insemination. "Microneedle Array Patch" (MAP) is therefore a proposed label name for the dosage form (Table 2) and will be used throughout the remainder of this article, accepting that regional divergences mean that in a regulatory submission to the FDA, for example, it may be referred to as a 'Microneedle System'. The proposed nomenclature (Table 2) provides a platform for a shared understanding, but a flexible structure to accommodate the diversity of proposed microneedle-based products and the contemporary vocabulary of the presiding regulatory authorities and international pharmacopoeias.

3.2. Iterative development of a proposed definition

A nomenclature must be accompanied by a definition that accurately describes the dosage form. The definition must use precise vocabulary and unambiguous phrasing, whilst maintaining a flexible design space that can accommodate the diversity of potential MAP products. A proposed definition of the MAP dosage form (Fig. 4) has therefore been iteratively developed through conversation and consultation. Terms and phrases have been carefully selected, or omitted, for specific reasons and therefore, to promote transparency, the definition is accompanied by a rationale for these inclusions or exclusions (Table 3). Regional differences may result in modifications to the definition, akin to the nomenclature, but the proposed definition provides a template to facilitate a shared understanding of the dosage form.

A distinctive feature of all MAP products is their ability to mechanically disrupt the outermost non-living skin barrier, the stratum corneum, to facilitate passage of an API to the viable epidermis and/or dermis. This is the fundamental identifying feature of a MAP dosage form (Fig. 4) and is aligned to FDA guidance on microneedling products [20], which classifies products based on "(i) needle length and arrangement and whether the specifications facilitate penetration into living layers of the skin, (ii) needle sharpness and whether that facilitates penetration into living layers of the skin and (iii) degree of control of manual or motorised microneedling products over the movement of needles and depth of penetration into living layers of the skin". The dimensions and architecture of the tapered sub-millimetre structures that typically characterise a MAP product and its method of application are important determinants of a product's ability to overcome the stratum corneum barrier. However, ultimately, if a product does not physically compromise the integrity of the outermost non-living skin barrier, i.e., the stratum corneum, then the product is not a MAP product.

3.3. Consultation, corroboration, and consensus

In stakeholder consultation exercises at two international conferences, which were focused on microneedle technology, 83 people from fifteen different countries provided feedback on their level of agreement with the terms and phrases used in both the proposed nomenclature ($N = 80$) and definition ($N = 68$) for the dosage form. A Likert scale, from 1 (Strongly Disagree) to 5 (Strongly Agree) was used to indicate a level of agreement. As indicated in Supplementary Fig. 1, there was general agreement with the terms used in the label name i.e. Microneedle (mean score 4.3, median 5, mode 5), Array (mean score 3.7, median 4, mode 5) and Patch/Delivery System (mean score 4.1, median 5, mode 5), and the proposed definition (mean score 4.1, median 4, mode 4).

Consultation exercises also enabled stakeholders to provide qualitative written feedback on the proposed nomenclature and definition. The most common alternatives to the proposed nomenclature (Table 2) replaced the term "microneedle" with "microprojection" or "microarray". Microprojection is used widely in the published literature [51,52] and is not inappropriate, but it provides no inference of a tapered structure. Microarray is also widely cited, often within the term microarray patch [53,54]. However, "microarray" does not indicate any protrusion and is an established term in scientific and medical vocabulary to describe a lab-on-a-chip genetic testing method [55]. Therefore, its inclusion in the 'label name' of a medicinal product could cause confusion, particularly if the MAP product was designed to deliver a nucleic acid cargo e.g. an RNA vaccine. The consensus opinion of the MAP-RWG was that "Microneedle Array" provides a technically accurate and unambiguous term for technical nomenclature.

The proposed alternatives to the word "microneedle" are predominantly motivated by a desire to omit the term "needle", as it may conjure images of a conventional injection with a hypodermic needle and, by association, negative connotations related to pain, bleeding and "needlestick" injury. For some potential end-users, the term 'micro*needles*' may therefore provide a barrier to use [56–58]. The word "needle" may also result in a perception of 'sharps' risk from a product and this could have consequences for their transport, storage and/or disposal. However, "microneedle" provides a technically accurate description of the distinguishable physical feature of the dosage form that facilitates mechanical disruption of the stratum corneum. There is therefore a conflict between the most appropriate technical term for regulatory nomenclature, in which descriptions should be accurate and unambiguous, and the descriptive vocabulary that is most suited to end-users. A term such as microprojection may provide an alternative intermediate, but it is important to recognise that the 'label name' of any medicinal product does not preclude the adoption and promotion of other terms to describe the product to patients, healthcare practitioners and the public. Existing examples of this include the use of acronyms (e.g. "IUDs" to describe intrauterine devices), the emergence of informal names (e.g. "the pill" to describe daily combined hormonal contraceptive tablets, or "the coil" to describe an intrauterine device), the omission of elements of the label name (e.g. "inhaler" is used to describe a "metered dose inhaler"), the continuation of outdated terms (e.g. "patch" is sometimes used to describe a topical or transdermal "system") or adoption of the proprietary name of a landmark product to describe all products in class (e.g. "Botox" to describe all botulinum toxin type A products). In a more recent example, COVID-19 vaccinations are often identified by their manufacturer e.g. "Pfizer/BioNTech vaccine", "Moderna vaccine" or "Oxford/AstraZeneca vaccine". It is crucial that the label name and definition of microneedle-based dosage forms do not jeopardise the success of future clinical products. Therefore, developers and regulators are encouraged to think carefully about the terminology that is used to market MAP products, ensuring the vocabulary used in communications is carefully considered and informed by potential users, both patients and clinicians. The first clinically approved MAP product(s) will likely set precedent, and therefore the words used to describe the most clinically advanced MAPs are a particularly important consideration. Future work should develop user-informed vocabulary to identify the dosage and describe its function to patients and the public.

4. Developing MAP products under the quality by design framework; identifying and prioritising MAP critical quality attributes (CQAs)

MAP product development should be guided by the principles of Quality by Design (QbD) i.e. "a systematic approach to development, that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and quality risk management" [59]. A QbD framework [60] will typically define a quality target product profile (QTPP) and use this to identify the critical quality attributes (CQAs) of the finished product to ensure its

safety and efficacy [59,61–63]. CQAs are attributes of a pharmaceutical product that are critical to its safety, efficacy and quality. They could be a physical, chemical, biological, or microbiological property, and should be associated with a validated test method that can demonstrate an appropriate limit, range or distribution, that assures product quality for that specific attribute [59].

Manufacture of the product takes place in a pharmaceutical quality system that should also recognise key relationships between the product's CQAs, its component materials (critical material attributes) and the processes (critical process parameters) used to manufacture that product. Continuous improvement and control strategies are emphasised in the manufacture of products within this QbD framework, which informs the design space and promotes production of quality pharmaceutical products.

4.1. Identifying common critical quality attributes of MAP products

Comprehensive MAP QTPPs will be product specific. However, the proposed definition of a MAP (Fig. 4) communicates universal features and functions that will result in elements of a QTPP that are applicable to most MAP products. Construction of a QTPP for a MAP product should be informed by previously published examples of MAP QTTPs [64–67] and established guidance for analogous dosage forms e.g. Transdermal Delivery Systems (TDS) [68,69].

Common features of a MAP (Fig. 4) that are intrinsic to safety and efficacy will result in CQAs that are common, potentially ubiquitous, to all MAP products. Identifying and understanding these attributes, and the associated validated test methods, will play a key role in MAP product development and quality assurance. Interactions with MAP-RWG members and wider stakeholders (Fig. 3) identified and categorised (Biological, Chemical, Microbiological and Physical) CQAs that could be relevant to MAP products (Table 4). Many of these CQAs are synonymous with other dosage forms and are well understood. However, some CQAs are unique to the dosage form or particularly pertinent to MAPs. Therefore, while discussions with key stakeholders about quality considerations have been wide-ranging (notes available at microneedleregulatory.org), our activities have identified and explored the MAP CQAs for which traditional developmental programs, control strategies, and test methods are likely to be challenging.

Table 4
A list of potential Critical Quality Attributes (CQAs) for a MAP product. For simplicity, each CQA has been categorised as Biological, Chemical, Microbiological or Physical (some CQAs might fall under more than one category). This is not an exhaustive list and will be product specific.

MAP Critical Quality Attributes

Biological	Chemical	Microbiological	Physical
Biocompatibility	Assay	Microbiological Specification including adventitious agents and endotoxins	Adhesion
Delivered Dose	Chemical Stability	Particulates	Container Closure System / Packaging
	Content Uniformity	Water Activity	Mechanical Strength
	Drug Release / Dissolution / Disintegration		"Needle" Morphology
	Drug Purity / Impurities / Residual Solvents		Physical Stability
	Extractables / Leachables		Puncture Performance
	Identity		Wear Time
	Polymorphism		
	Water Content		

4.2. Prioritising MAP CQAs that will require innovative standardised test methods and/or control strategies

Adoption or minor adaptation (apparatus, conditions, protocol and/or specifications) of established validated compendial tests is the preferred, and most pragmatic, option to demonstrate and/or control the CQAs of finished MAP products. Supplementary Table 2 identifies some established quality control test methods that may be relevant to MAP products. However, MAPs have unique principal features and functions that will likely necessitate the development and validation of novel test methods and control strategies to assure the CQAs of finished MAP products. Novel test methods may include major adaptations to established compendial methods for analogous dosage forms, or the development of a bespoke method that is exclusive to a MAP. A prioritisation exercise with MAP-RWG members therefore identified MAP attributes that would likely (i) be a CQA (based on the potential severity of patient harm if quality was not assured) for the majority of MAP products (Fig. 5A: x-axis) and (ii) require a new test method (Fig. 5A: y-axis) to characterise and demonstrate/control the CQA, either because a standardised test method currently does not exist, or test methods for analogous dosage forms are deemed unsuitable. This information was captured using a prioritisation matrix (Fig. 5A), where MAP attributes were assigned to a quadrant based on their (i) "criticality" (x-axis) and (ii) "priority" (y-axis) for test method development.

Six attributes were assigned to the top right quadrant i.e., deemed both critical and a priority (Fig. 5A). These are delivered dose, dissolution, mechanical strength, needle morphology, physical stability and puncture performance. An online ranking exercise with members of the MAP-RWG ($N = 16$) further prioritised these six attributes (Fig. 5B). Delivered dose was identified as the MAP CQA that would benefit most from development of a validated standardised test method ($N = 12$ ranked it as highest importance), followed by puncture performance ($N = 5$ ranked it as second) and dissolution ($N = 6$ ranked it as second). Consultation with the wider MAP community confirmed delivered dose and puncture performance as priorities for test development (Fig. 5C). These three priority CQAs are intrinsically linked to the principal function of the dosage form, as defined in the proposed definition of a MAP (Fig. 4), i.e., mechanical disruption of the skin barrier (*puncture performance*) and subsequent release of the therapeutic cargo (*dissolution/drug release*) to deliver a therapeutic dose (typically sub-milligrams) to the target site (*delivered dose*). It is therefore the MAP's distinctive method of drug delivery, compared to other pharmaceutical dosage forms, that necessitates the development of novel validated *in vitro* test methods to assure the quality of finished products.

Test methods to evaluate the quality of a finished pharmaceutical product should ideally be relatively simple (accessible, robust, cost-effective apparatus and analytical equipment), reproducible (synthetic material preferred to biological samples), representative (informed by the nature of the CQA in clinical use) and valid (*in vitro in vivo* correlation (IVIVC)). The primary purpose of these standardised test methods is to ensure the quality of finished pharmaceutical products (within batch and between batches), enable direct comparison to other products within the same dosage form and ensure performance of the product over the duration of its specified shelf life, i.e., during transport, storage and use. Compendial tests may also have a role in the pre-clinical development of pharmaceutical products. However, it is important to recognise that they do not replace *in vitro* and *in vivo* biorelevant laboratory models, which typically form the foundation of rational pre-clinical development of pharmaceutical products. It is also important to recognise that quality control tests on a finished product are not the only determinant of product quality, which is typically supported by a dossier of data from pre-clinical development and a robust control strategy for materials and manufacture to ensure that a product meets its

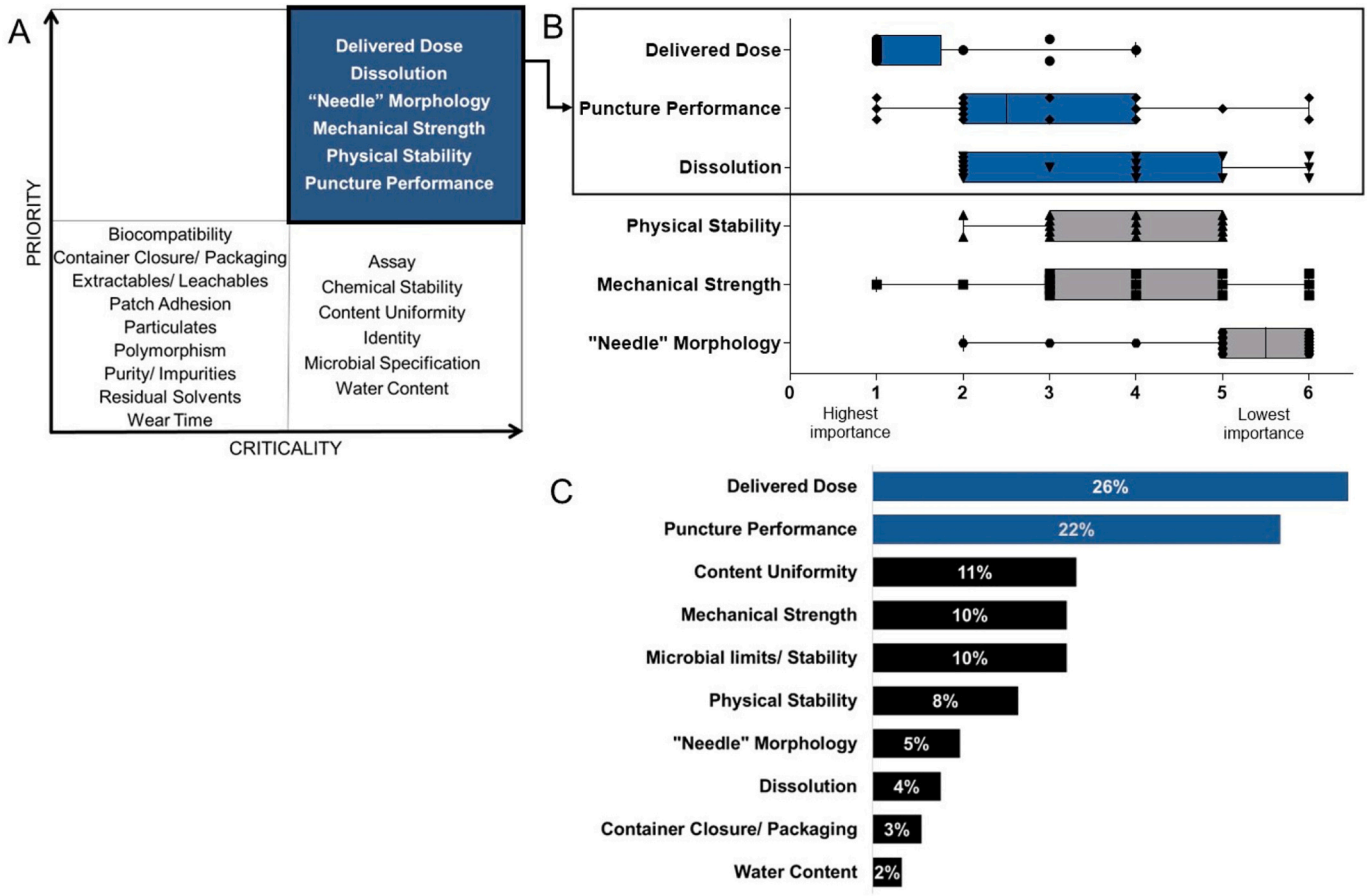

Fig. 5. (A) A prioritisation matrix to determine MAP attributes that would likely be deemed a CQA ("criticality") and would benefit most from an established MAP-specific quality control test ("priority"). Six priority attributes were identified (top right quadrant). (B) The results of a ranking exercise, performed by members of the MAP-RWG ($N = 16$), to assign a level of importance to the "priority" CQAs for MAPs. (C) Results from ranking exercises, performed *during two international microneedle conferences (Microneedles & Transdermal Drug Delivery Systems Virtual Conference 2020 and The 6th International Conference on Microneedles)* ($N = 66$), to assign a level of importance to the "priority" CQAs for MAPs. Blue = high priority CQAs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

specifications.

4.2.1. Delivered dose

Delivered dose is one of the most important CQAs to confirm throughout the lifecycle of any pharmaceutical product, and therefore a comprehensive control strategy from early product development through expiry of the finished product is essential, particularly for a new delivery system such as a MAP. Numerous biorelevant test methods are used in pre-clinical development of proposed MAP products to evaluate this CQA, and these predominantly rely on biological skin models. Early pre-clinical studies often use *ex vivo* models (excised skin) to quantify the locally delivered dose. In these models delivered dose can be determined directly by API extraction from the MAP treated skin area but this is often technically challenging or impossible. More commonly, delivered dose is inferred by mass balance i.e. the measured mass of API in the MAP after application is combined with the measured mass that is detected in surface swabs of MAP treated skin and this is subtracted from the initial loaded dose. Indirect quantification is often combined with visual confirmation of successful microneedle-mediated disruption of the stratum corneum (determined by topical staining of the treated tissue and/or transverse imaging of the skin by optical coherence tomography). These methods, in conjunction with the pharmacodynamic responses and/or pharmacokinetic data (e.g. plasma levels), are often used to evaluate delivered dose *in vivo*. Biorelevant pre-clinical tests, widely described in the published literature, are crucial to rational pre-clinical product development but they do not provide a simple reproducible method to evaluate delivered dose in finished MAP products. A validated *in vitro* quality control test to measure delivered dose from a finished MAP product does not exist. This was identified during the MAP-RWG ranking exercise as highly desirable (Fig. 5B).

The technical challenge of a single all-encompassing test to evaluate delivered dose from any MAP product is, in part, challenged by the diversity of proposed MAP designs and delivery mechanisms. However, it is not always necessary to have a single comprehensive test method for a CQA, and instead the quality of the finished product may be assured by test methods and in-process controls for contributory attributes. For most MAPs, delivered dose is a direct result of mechanical disruption of the stratum corneum (puncture performance) and drug release in the skin (drug release/dissolution), and therefore uncoupling these attributes to create two simplified robust validated *in vitro* tests could provide a control strategy to help assure delivered dose from a MAP. In addition, the materials and learnings from development of these two test methods could establish a platform for future rational development of the more technically challenging 'delivered dose' test for a MAP, i.e. an amalgamation of MAP puncture performance and drug release/dissolution tests.

4.2.2. Puncture performance

Mechanical disruption of the stratum corneum is a fundamental feature of a MAP (Fig. 4) and therefore "puncture performance" will likely be a CQA for all MAP products. If a MAP is not able to physically disrupt the barrier as intended, and specified, the product will not be

efficacious. Hypodermic needles are an analogous dosage form that relies on puncture to facilitate delivery of an API. However, hypodermic needle puncture is at the millimetre to centimetre scale and therefore is visibly confirmed by a skilled administrator. 'Puncture tests' [70] that are used to assure the quality of hypodermic needles therefore do not determine a needle's ability to create a puncture. Instead, they examine the nature of the puncturing event to ensure that needle puncture is associated with minimal pain and tissue damage. These tests typically employ a force gauge and motorised test stand to measure the force needed for the needle to puncture a synthetic substrate, e.g. silicone, and the drag force on the needle as it transitions through the substrate. This provides information related to needle sharpness and the surface quality of the needle (e.g. absence of needle burrs) and is used to help predict/demonstrate the smoothness of needle insertion into the biological tissue, rather than to confirm puncture per se.

Unlike hypodermic needles, MAPs are responsible for almost imperceptible micron scale disruption of the outermost skin barrier. Therefore, the primary outcome of a puncture performance test for a finished MAP product is not to characterise the process of needle insertion, but to determine if a MAP has been able to mechanically disrupt the stratum corneum barrier. Key parameters in the development, optimisation and validation of a MAP puncture performance test will include the properties of the substrate material (biological or synthetic) to be punctured, the apparatus, the protocol and the analytical method used to measure puncture performance. The outcomes of a MAP puncture performance test(s) could include a discrete quantitative measure of puncture efficiency (i.e., the percentage of microprojections that have punctured the substrate following application), a determination of puncture depth and/or characterisation of the pattern of punctures. Such outcomes would then inform the acceptance criteria of the product specification for a MAP, e.g., 95 ± 5 % puncture efficiency.

Any standardised puncture performance test that is developed for a finished MAP product must accommodate the diversity of potential MAP designs. This includes different approaches to MAP application; some proposed products are designed to be manually administered using finger/thumb application and others use bespoke applicators to control the force, speed and/or duration of MAP application. Flexibility in the design of apparatus and protocols will therefore be an important feature of any future standardised test. Acknowledged differences in the skin physiology (including architecture and biomechanics) of target populations (e.g. adult, elderly or paediatric) at different anatomical application sites (e.g. deltoid, wrist, abdomen) must also be recognised and reflected in modifiable test parameters, and associated specifications, that ensure IVIVC. However, although a standardised *in vitro* MAP puncture performance test should be informed by *in vivo* data and can potentially contribute to development of a MAP product, its primary purpose is to ensure quality of the final product, i.e., it does not replace biorelevant *ex vivo* and *in vivo* tests that are essential to pre-clinical MAP development.

MAP puncture performance is also influenced by other measures of product quality, including the morphology, dimensions and organisation of the microneedle projections (e.g. length, shape, sharpness, needle-to-needle spacing), their physical stability (i.e. their integrity pre-application) and their mechanical strength during application. These CQAs, also prioritised by the MAP-RWG (Fig. 5B), could also contribute to a holistic control programme to assure the quality of a finished MAP product during transport, storage and use. High-magnification inspection tools, both during and after manufacture, and established material testing methods that are used for other pharmaceutical and non-pharmaceutical products, e.g. axial and sheer fracture tests, will therefore be important contributors to the suite of test methods and specifications that helps to assure puncture performance of a MAP product.

4.2.3. Drug release/dissolution

Following disruption of the living layers of skin (puncture performance), a MAP product must release its API in a bioavailable form (in most cases a solubilised form) to achieve therapeutic effect. This could be a multi-step process and is determined by the physicochemical properties of the API, its formulation, and the type of MAP [71]. For coated MAPs, release of the API is typically facilitated by relatively rapid dissolution of a solid-state API formulation in the aqueous skin environment. Relatively thin (nano- or micro-meters) coatings of soluble materials on the surface of an inert insoluble microneedle projection can result in direct dissolution of the API in seconds. For less soluble formulations and/or thicker coatings, the dissolution kinetics may be slower and therefore drug release may be preceded by separation of the coating formulation from the microneedle projection, either during insertion or removal of coated microneedle projections. Temporary solid state, or even semi-solid state, fragments of a formulated API in the skin may be considered akin to the disintegration process that precedes dissolution in oral dosage forms [71].

For dissolving MAPs, the kinetics of drug release in the biological environment are typically governed by dynamic relationships between fragmentation of the microneedle (by physical or chemical stimulus), degradation of the formulation and/or dissolution of the formulation (including the API). *In situ*, a deteriorating solid three-dimensional microneedle architecture and its interaction (chemical and physical) with the aqueous biological environment can result in complex multifactorial mechanisms of drug release. A range of parameters will contribute to this process and these are typically characterised and optimised in the development of potential MAP products, in conjunction with learnings from analogous formulations and dosage forms. However, the principal outcome for most MAP products in all sub-categories, is to release a soluble form of an API(s) in the aqueous skin environment. A simple validated dissolution test that can capture the kinetics of drug release is therefore likely to be a key component of control strategies that are used to ensure the quality of finished MAP products.

The aim of a dissolution (drug release) test on a finished MAP product is to characterise the kinetics of API release in a manner that enables identification of potential batch-to-batch and within-batch variations, thus ensuring product quality [71]. However, characterising dissolution in a single MAP product, which may contain sub-milligram quantities of an API is challenging. The relatively high volumes of dissolution media and the requirement to submerge the entire dosage form in the most widely used Basket (Apparatus 1) or Paddle (Apparatus 2), dissolution tests does not suit the low doses and relatively fragile micron-scale features of a MAP. Therefore, significant adaptations of these dissolution test methods (apparatus, materials, protocols and/or specifications) or exploration of less commonly used, but internationally recognised, dissolution apparatus may be required for MAP products e.g. flow-through cell (Apparatus 4). It may also be necessary to develop a novel test method that does not submerge the dosage form and instead characterises drug release at the point of contact between the MAP and an aqueous semi-solid [72,73]. Another complication is the significant differences in release kinetics of proposed MAP products i.e. API release in seconds versus months. For dissolution tests, it may therefore be appropriate to categorise the MAP product based on its release kinetics (e.g. 'rapid' versus 'sustained') and use specific test methods and/or specifications for these categories. In the forthcoming years the increasing volume of pre-clinical and clinical data from MAP products, combined with innovations in analytical equipment, will hopefully help to establish a simple validated dissolution test(s), and accompanying specifications, that are suitable for MAP products.

However, it is important to acknowledge that a dissolution test for a finished MAP product should not be used in isolation to ensure quality. Congruent test methods will be used to inform the drug product specification (e.g. dissolution, assay, content uniformity, and microscopic observation of individual needles). These should be combined with in-process controls (e.g. ensuring uniformity of the liquid drug formulation during manufacture and controlled loading of a formulation in or on microneedles) and developmental and stability data to demonstrate a

validated manufacturing process (e.g. manufacture controls to ensure a uniform coating) that produces a consistent MAP product.

4.2.4. Identifying and understanding all MAP CQAs

Delivered dose, puncture performance and drug release have been identified by stakeholders as priority MAP CQAs for the development of novel test methods and specifications, to ensure quality. However, this should not detract from, or devalue, other attributes that may be critical for the dosage form or individual MAP products. Physical stability, mechanical strength and needle morphology were also identified as CQAs of the MAP dosage form that are likely to benefit from the development of novel quality control test methods and specifications (Fig. 5A: top right quadrant of the matrix). For some MAP sub-categories and individual products these attributes will be particularly pertinent. For example, mechanical strength may be a significant consideration for some dissolving MAPs but not for stainless steel coated MAPs. Innovation in test method development and transparent dissemination of new understandings is therefore encouraged for all potential MAP CQAs, to help inform the regulatory science of the emerging dosage form and expedite clinical translation of safe and effective MAP products.

Other attributes, such as the microbiological specification of a MAP, were assigned to the bottom right quadrant of the matrix (Fig. 5A). This indicates that the microbiological specification will be a CQA for most MAP products, but it is likely to be assured using existing test methods. However, there has been considerable debate in the scientific community regarding the most appropriate microbiological specification to assign a MAP (low bioburden or sterile) and the likelihood of a MAP-induced clinically significant skin infection. In response to this, a parallel workstream identified the factors to consider when assessing the risk of a clinically significant infection from a MAP product. This includes product- and patient-related considerations, and is the subject of a separate publication [13].

MAP attributes that were assigned to the bottom left quadrant (Fig. 5A), were considered less 'critical' for the MAP dosage form. However, while there are commonalities in proposed MAP products (Fig. 4), there is also notable diversity in their constituent materials, form and function. Therefore, the broad categorisation of CQAs for the dosage form (Fig. 5A: top right quadrant of the matrix) should not downplay other attributes, which for some MAP products will be critical. It is also important to acknowledge that MAPs facilitate delivery of APIs and excipients into a compartment of the body (viable epidermis and dermis) that may not have been accessible previously using established topical or injectable dosage forms. At this stage in MAP development this necessitates product specific QTPPs and accompanying risk assessments, which are informed by scientific extrapolations from analogous products (e.g. wound dressings, topical products, transdermal patches and injectables), comprehensive pre-clinical studies and an expanding clinical trial data set. However, the rapidly expanding data set across the breadth of different proposed MAP products encourages future work to explicitly define MAP sub-categories and identify the CQAs, critical process parameters (CPPs) and/or critical materials attributes (CMAs) that may be exclusive to, or particularly pertinent for, these sub-categories.

5. Conclusions

The regulatory science of microneedle-based dosage forms that deliver APIs into the viable layers of skin is relatively immature; no clinically approved single entity MAP products have set precedent, and explicit guidance from regulatory authorities and the international pharmacopoeias is predominantly limited to microneedle device products [20]. This seminal publication, informed by discussion and consultation with numerous stakeholders, aims to guide development, stimulate debate, and advance the regulatory science of single entity microneedle-based combination products. It proposes a definition for this innovative dosage form (Fig. 4), a flexible nomenclature based on the requirements of internationally recognised regulatory authorities (Table 2), and guidance on its likely categorisation under current legislation (e.g., a "combination product" by the FDA). Adoption of a shared vocabulary and harmonised understanding will not only promote continued growth of this dosage form, but also aid in efficient communication between developers and international regulatory authorities. However, further work is required to understand and define the most appropriate vocabulary, i.e. terms and phrases, for potential user groups (patients, the public and practitioners).

Potential MAP CQAs have also been identified and considered, with an emphasis on three attributes (delivered dose, puncture performance and drug release) that will be assigned as critical for most MAP products and are likely to need new or highly adapted test methods to characterise. Innovation is encouraged to provide methods and specifications that can help assure the quality of finished MAP products. However, quality tests alone do not ensure production of safe and effective commercial MAP products. A comprehensive package of robust control strategies for processes and the product, which is informed by scientific knowledge, data (pre-clinical and clinical) and risk assessment, must be established in an environment of continuous improvement.

This publication aims to harmonise current understanding and provide a platform for development of future guidance. It is not an exhaustive list for regulatory submissions and does not capture potential international divergences in regulatory requirements. MAP developers are therefore encouraged to initiate early dialogue with the relevant regulatory authorities to align expectations and identify the most appropriate pathway to regulatory approval of products. Future work should explore geographical differences in regulatory science, particularly in those LMICs with target end-user populations, and address issues related to the diversity of proposed MAP applicator systems, their transport, safe disposal, biocompatibility and, importantly, the relationship between MAP products and their end-users.

Supplementary data to this article (i.e. Supplementary Figure 1, Supplementary Table 1 and Supplementary Table 2) can be found online at https://doi.org/10.1016/j.jconrel.2024.11.056.

Disclaimer

This document does not necessarily represent the views of the author's respective company or organisation, nor the policies or guidelines of those companies or organisations, nor the funding bodies. The narrative provides a consensus view from the MAP-RWG that is framed within established regulatory guidance and current thinking as of the date of publication.

CRediT authorship contribution statement

Maria Dul: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Conceptualization. **Mohammed Alali:** Writing – review & editing, Investigation, Conceptualization. **Mahmoud Ameri:** Writing – review & editing, Investigation, Conceptualization. **Matthew Douglas Burke:** Writing – review & editing, Investigation, Conceptualization. **Benjamin Paul Creelman:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Lisa Dick:** Writing – review & editing, Investigation, Conceptualization. **Ryan F. Donnelly:** Writing – review & editing, Investigation, Conceptualization. **Michael N. Eakins:** Writing – review & editing, Investigation, Conceptualization. **Collrane Frivold:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Angus Harry Forster:** Writing – review & editing, Investigation, Conceptualization. **Philippe-Alexandre Gilbert:** Writing – review & editing, Investigation, Conceptualization. **Stefan Henke:** Writing – review & editing, Investigation, Conceptualization. **Sebastien Henry:** Writing – review & editing, Investigation, Conceptualization. **Desmond Hunt:** Writing – review & editing, Investigation, Conceptualization. **Hayley Lewis:** Writing – review & editing, Investigation,

Conceptualization. **Jessica Joyce Mistilis:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Jung-Hwan Park:** Writing – review & editing, Investigation, Conceptualization. **Mark R. Prausnitz:** Writing – review & editing, Investigation, Conceptualization. **David Kenneth Robinson:** Writing – review & editing, Investigation, Conceptualization. **Carmen Amelia Rodriguez Hernandez:** Writing – review & editing, Investigation, Conceptualization. **Juyeop Shin:** Writing – review & editing, Investigation, Conceptualization. **Tycho Joseph Speaker:** Writing – review & editing, Investigation, Conceptualization. **Caroline Strasinger:** Writing – review & editing, Investigation, Conceptualization. **Kevin M.G. Taylor:** Writing – review & editing, Investigation, Conceptualization. **Darin Zehrung:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **James C. Birchall:** Writing – review & editing, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Courtney Jarrahian:** Writing – review & editing, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Sion A. Coulman:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

Prausnitz is an inventor of patents, founder/shareholder of companies, and consultant to companies developing MAP technologies. This conflict of interest is managed by the Georgia Institute of Technology. Coulman and Birchall are inventors of patents. This conflict of interest is managed by Cardiff University. Ryan Donnelly is an inventor of patents that have been licensed to companies developing microneedle-based products and is a paid advisor to companies developing microneedle-based products. The resulting potential conflict of interest has been disclosed and is managed by Queen's University Belfast. The companies had no role in the design of the manuscript, in the collection, analyses or interpretation of the various studies reviewed, in the writing of the manuscript or in the decision to publish.

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Data availability

No data was used for the research described in the article.

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