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Review article

Assessing the risk of a clinically significant infection from a Microneedle Array Patch (MAP) product☆

Maria Dul[a,1], Mohammed Alali[b], Mahmoud Ameri[c,2], Matthew Douglas Burke[d,3], Christine M. Craig[e], Benjamin Paul Creelman[f], Lisa Dick[g], Ryan F. Donnelly[h], Michael N. Eakins[i], Collrane Frivold[f], Angus Harry Forster[j], Philippe-Alexandre Gilbert[k], Stefan Henke[l,4], Sebastien Henry[m], Desmond Hunt[n], Hayley Lewis[o], Howard I. Maibach[p], Jessica Joyce Mistilis[f], Jung-Hwan Park[q], Mark R. Prausnitz[r], David Kenneth Robinson[k], Carmen Amelia Rodriguez Hernandez[b], Charles Ross[j], Juyeop Shin[s], Tycho Joseph Speaker[t], Kevin Michael Taylor[u], Darin Zehrung[v,5,6], James C. Birchall[a,6], Courtney Jarrahian[f,*,6], Sion A. Coulman[a,*,6]

[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] ValSource, Inc., USA
[f] PATH, Seattle, USA
[g] Kindeva Drug Delivery, USA
[h] School of Pharmacy, Queen's University Belfast, Belfast, UK
[i] Eakins & Associates, USA
[j] Vaxxas Pty Ltd., Australia
[k] Bill and Melinda Gates Foundation, Seattle, USA
[l] Dr. Stefan Henke Pharma Consulting, Germany
[m] Micron Biomedical, Inc., USA
[n] United States Pharmacopeia, USA
[o] Zosano Pharma, USA
[p] Department of Dermatology, University of California San Francisco, San Francisco, CA, USA
[q] Department of Bionano Technology, Gachon University, Seongnam, Republic of Korea
[r] School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, GA, USA
[s] Raphas Co. Ltd, Republic of Korea
[t] AbbVie, Inc., USA
[u] University College London School of Pharmacy, British Pharmacopoeia Commission, UK
[v] PharmaJet, Inc., USA

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ABSTRACT

Microneedle Array Patches (MAPs) are an emerging dosage form that creates transient micron-sized disruptions in the outermost physical skin barrier, the stratum corneum, to facilitate delivery of active pharmaceutical ingredients to the underlying tissue. Numerous MAP products are proposed and there is significant clinical

☆ All authors are / were members of the Microneedle Array Patch Regulatory Working Group (MAP-RWG) and/or the Sterility Working Group (a sub-group that was initiated specifically to address the subject of this article). 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] Previously Zosano Pharma, USA.
[3] Previously Radius Health, Inc. USA.
[4] Previously LTS Lohmann Therapie-Systeme AG, Germany.
[5] Previously PATH, Seattle, USA.
[6] Co-last author.

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Sterility
Microbiological specification
Risk assessment

potential in priority areas such as vaccination. However, since their inception scientists have hypothesized about the risk of a clinically significant MAP-induced infection.

Safety data from two major Phase 3 clinical trials involving hundreds of participants, who in total received tens of thousands of MAP applications, does not identify any clinically significant infections. However, the incumbent data set is not extensive enough to make definitive generalizable conclusions. A comprehensive assessment of the infection risk is therefore advised for MAP products, and this should be informed by clinical and pre-clinical data, theoretical analysis and informed opinions.

In this article, a group of key stakeholders identify some of the key product- and patient-specific factors that may contribute to the risk of infection from a MAP product and provide expert opinions in the context of guidance from regulatory authorities. Considerations that are particularly pertinent to the MAP dosage form include the specifications of the finished product (e.g. microbial specification), it's design features, the setting for administration, the skill of the administrator, the anatomical application site, the target population and the clinical context. These factors, and others discussed in this article, provide a platform for the development of MAP risk assessments and a stimulus for early and open dialogue between developers, regulatory authorities and other key stakeholders, to expedite and promote development of safe and effective MAP products.

1. Introduction

The fabrication of micron-scale needles using mass manufacturing methods [53,66] initiated the development of a diversity of proposed microneedle-based products for drug delivery and sensing applications, predominantly in the skin [126,131]. Microneedle Array Patch (MAP) is a term used to describe microneedle-based delivery systems that integrate an active pharmaceutical ingredient (API), including drugs and biologics, within a product that is designed to temporarily disrupt the physical skin barrier (stratum corneum) at the site of application, to facilitate local delivery of the API [101].

MAPs are often sub-categorised based on their principal mechanism of action i.e. (i) coat and poke (coated MAPs), (ii) poke and dissolve (dissolvable MAPs) and (iii) poke and release (e.g., hydrogel-forming MAPs) [126]. Coated MAPs typically consist of inert microneedle structures, manufactured using materials such as stainless steel, silicon, titanium or a hydrophobic polymer. These devices are then coated with a pharmaceutical formulation, often in liquid form, that is dried on the surface to create the coated MAP. A range of manufacturing methods have been used to achieve this, including dip coating, inkjet coating, immersion coating, drop coating and spray coating [22,77,94,99,144,173]. Poke and dissolve and poke and release MAPs are typically manufactured using water-soluble materials such as hyaluronic acid, polyvinyl alcohol, polyvinyl pyrrolidone, polylactic/glycolic acid, carbohydrate compounds (e.g., chitosan, starch, carboxymethylcellulose and maltose) and naturally occurring polymers (e.g., silk fibroin and gelatin) [29,174]. In these proposed MAP products, the API is often incorporated within the matrix of the microneedle structure, but in poke and dissolve MAPs the cargo is released by dissolution in the biological fluid of the skin, and in poke and release MAPs the polymer swells and the cargo is released by molecular diffusion into the surrounding tissue [29]. Manufacturing methods include micro-molding, two-step casting processes, droplet-born air-blowing (also referred to as droplet extension), centrifugal lithography and/or photopolymerization [23,88,143].

MAP technology is a potentially revolutionary tool for future rapid mass vaccination strategies [108] and therefore there is strong motivation to expedite clinical translation of MAP products. However, the innate function of the skin is to provide a physical, biochemical and immunological barrier to exogenous insults, including the invasion of pathogens [127]. MAPs temporarily diminish the physical skin barrier at the site of application and therefore there is a hypothetical increase in the risk of microbial invasion and a subsequent infection. Assessing this risk is a key contemporary issue in the development of safe and effective MAP products for human use. Risk assessments are ideally informed by extensive clinical data, however human use of MAP products is curently limited to clinical trials [78]; there are no approved MAP products in routine clinical use. Therefore, at present an assessment of infection risk from a potential MAP product will also be informed by pre-clinical results, theoretical analysis and expert opinions.

This article aims to identify, and provide expert opinion o risk factors that are particularly pertinent, or exclusive, to the MAP dosage form, to assist developers, regulatory authorities and other stakeholders when appraising the risk of a clinically significant infection from a MAP product. The opinions shared in this document have been initiated and developed by discussions with members of the MAP Regulatory Working Group (RWG) [100] and the MAP Sterility Working Group (a sub-group that was initiated specifically to address this subject area), under the remit of PATH's Center of Excellence (CoE) for MAPs.

2. Assessing the risk of a clinically significant infection from a MAP product

Skin and soft tissue infections (SSTIs) are diverse in terms of their clinical presentation, severity and etiology, but all involve microbial invasion of the skin and underlying tissues [38,105]. Many SSTIs have minor clinical consequences. However, in the USA, SSTIs, such as cellulitis [129], account for approximately 10% of infections that necessitate hospital admission [102]. Clinically significant SSTIs are normally associated with physical insults to the skin barrier such as trauma, ulceration, inflammation or insect bites. Therefore, since inception of microneedle-based products, the scientific community has theorized and debated the potential of MAP-induced microbial invasion of the skin, either during MAP application (inoculation of the skin with a microorganism) or following its removal (invasion of microorganisms through MAP-induced micro-disruptions in the skin), and the likelihood of a MAP-induced clinically significant infection. For clarity, in this context a clinically significant infection is defined as being directly attributable to use of a MAP product (SSTI or systemic infection), diagnosed by a clinician and has health related consequences. It should not be confused with indicators of irritation at the site of MAP application such as erythema and swelling, which may be anticipated for some MAP products [67].

Proposed MAP products are diverse, in terms of their manufacturing methods, constituent materials, geometries, dimensions, APIs, microbiological specification, packaging and intended clinical applications. Multiple patient-related factors also contribute to the risk of infection, e.g., elderly age [90], obesity [60], edema [38], critical illness [21] and the immune status of the patient [140]. The theoretical risk of a clinically significant infection from a MAP is therefore multi-factorial and this necessitates an assessment of that risk for each proposed MAP product.

Construction of a risk assessment for a medicinal product, under the guiding principles of Quality by Design [171] and quality risk management [71], requires identification of the factors that contribute to the risk of harm (a clinically significant infection) from a particular hazard (microbial invasion into MAP treated skin), and an understanding of how these factors influence the likelihood (probability) and severity of the harm. All risk assessments are informed and supported by contemporary scientific knowledge and data.

Clinical experience with a product, or a closely related product, provides the most reliable probability data for risk assessment. Therefore,

clinical trials provide the most relevant data set for MAPs, and these describe thousands of MAP applications to hundreds of participants (National Library of Medicine [NLM], studies: NCT01674621 [112], NCT04064411 [118] (Radius Health); NCT00489918 [111], NCT02745392 [114], NCT03282227 [116] (Zosano Pharma); NCT02438423 [113] (Micron Biomedical); Australian New Zealand Clinical Trials Registry (Australia & New Zealand) ACTRN12618000112268 [7] (Vaxxas)). It is noticeable that none of these clinical trials have reported a SSTI at the site of MAP application. These trials include two 12-month multi-center Phase 3 studies (NCT04064411 [118], NCT03282227 [116]) for two different coated MAP products. Both studies evaluated self-administration outside the clinical setting either daily, for treatment of osteoporosis ([103], NCT04064411 [118]), or when required, for acute treatment of migraines ([83,109], NCT03282227 [116]). Two hundred and fifty two participants started the 12 month study for daily self-administered MAP (500 μm microneedles) treatment of osteoporosis, and two hundred participants completed the study, (NCT04064411 [118]); this equates to at least 73,000 MAP applications. In the acute treatment of migraine (NCT03282227 [116]) 5963 treatments were self-administered by 335 participants, with each treatment consisting of a double MAP (340 μm microneedles) application i.e. 11,386 MAP applications. Combined, these two clinical studies provide safety data on >80,000 MAP applications in >500 patients, and while mild to moderate treatment site reactions, e.g. erythema and swelling, were relatively common there were no reports of a MAP-induced infection. This safety data is encouraging, but the number of MAP products that have been examined and the number of applications to human participants remains relatively small (tens of thousands rather than millions), and so the absolute and relative risk of a MAP-induced infection remains unknown.

Clinical data from analogous commercial products in widespread clinical use, such as transdermal patches (depending on the country of use or regulatory agency, this dosage form may be referred to as transdermal system), intradermal injections, other microneedle-based medical devices (e.g., hollow microneedle devices) and cosmetic procedures such as microneedling [26,58,95] may also be used to inform risk assessments. These products provide indicative data on safety but some fundamental differences to MAPs, e.g. cosmetic "microneedling" products can have needles that are >1 mm, result in caveated extrapolations.

The remainder of this article identifies key considerations, cites relevant materials and provides expert opinions to help and guide developers, regulators and other stakeholders, when assessing the risk of clinically significant infection from a MAP product. However, this article does not, and cannot, determine the acceptable level of risk for any particular MAP product. All medicinal products are associated with some degree of risk [71] and therefore, while a risk assessment that is focussed on patient safety, should aim to quantify the risk of infection from a specific MAP product, it must also be viewed in the context of a wider risk-benefit analysis. Such analysis would consider all stakeholders (e.g., the patient, the health care provider, the public, the pharmaceutical industry, the regulatory authorities) and all forms of risk (e.g., patient risks, public health risks, commercial risks, reputational risks to the technology or science more broadly) in the product specific scenario [46]. For example, to protect a healthy population in an emergency pandemic for a disease with high levels of mortality, the acceptable level of risk may be different than a treatment in a healthy subject for a self-limiting condition. As Baker suggests "*…there is general agreement that risks carrying a low probability of harm can be accepted if they can be justified, thus driving development efficiency and potentially shortening development times and increasing speed of product launch to the patients in need*" [9]. It is also important to recognise that risk is dynamic and is informed by contemporary scientific understanding and clinical evidence, and therefore all risk assessments should be considered 'live' documents.

3. Key considerations when assessing the risk of infection from a MAP product

An Ishikawa diagram (Fig. 1) has been iteratively developed by the authors of this article (members of the MAP RWG and/or the MAP Sterility Working Group) to identify relevant factors when assessing the risk of infection from a MAP product. Many of these factors are recognised and understood by the pharmaceutical industry and international regulatory authorities. However, some are particularly pertinent to the MAP dosage form and are therefore considered in more detail in this article.

3.1. Microbiological specification of the finished product; 'low bioburden' versus 'sterile' MAP products

The microbiological quality of a MAP product is a key consideration when assessing the risk of a clinically significant infection. Therefore, the microbiological specification that is assigned to a finished MAP product will be deemed a critical quality attribute (CQA), i.e., a feature of the finished product that should be within an appropriate limit, range, or distribution, to ensure the desired product quality [75]. Recent draft Food and Drug Administration (FDA) guidance for transdermal products states that *"transdermal drug delivery systems (TDS) designed with a physical mechanism to abrade or penetrate the skin, increase the potential for infections"* and *"During development manufacturers of such TDS should consider the risks and determine whether the TDS should be manufactured as sterile or with a bioburden level below that normally seen with TDS designs that rely on chemical permeation enhancers"* [46]. Like MAPs, wound care products are topically applied to a compromised skin barrier, albeit wound care products are typically used when the barrier is significantly more compromised than the micro-disruptions created by a MAP. FDA guidance for wound care products states "*if a wound-treatment product cannot be manufactured to be sterile, it should have a low bioburden*" [45].

MAP products will therefore likely be designated as either 'sterile' or 'low bioburden'. The latter of these terms considers acceptable bioburden (the number of colony-forming units per MAP) and objectionable microorganisms (those that can either cause illness or product degradation) for the product. Assignment of the most appropriate microbiological specification to a product, i.e., either sterile or low bioburden, will be informed by its own risk assessment, which should consider many of the factors identified in Fig. 1. The specific risks associated with bacterial endotoxin are also an important element of microbiological quality [49,76,166], however they are not considered in detail in this article.

Some MAP manufacturers have aligned their products with TDS, defined under United States Pharmacopoeia (USP) <1151> as "*A route of administration characterized by drug product application to the skin where the drug substance passes through the dermal layer with the intent to achieve a systemic effect*" [158]. These are non-sterile low bioburden products [46] that conform to USP ⟨1111⟩ and therefore have $<10^2$ aerobic organisms and $< 10^1$ yeasts/moulds per patch with no detection of either *Staphylococcus aureus* or *Pseudomonas aeruginosa* [154].

Other MAP manufacturers have adopted the USP <1> definition of a parenteral product for their finished MAP product [149]. USP <1> states *"Parenteral drug products include both injections and implanted drug products that are injected through the skin or other external boundary tissue, or implanted within the body to allow the direct administration of the active drug substance(s) into blood vessels, organs, tissues, or lesions"* [149]. These products must demonstrate an "*absence of viable microorganisms*", which is defined as a probability of generating no more than 1 non-sterile unit per 1 million units produced [37,160]. If this product classification is adopted, then the sterility of the product must be confirmed using appropriate methods described in Sterility tests USP <71> [161], and endotoxin limits must be established and tested as per USP <85> [147].

The USP contains numerous chapters addressing bioburden in both non-sterile and sterile products, as well as sterility, bacterial endotoxin and pyrogen tests (see Table 1). General chapters (USP <60> Tests for *Burkholderia cepacia* complex [153], USP <61> Microbial enumeration tests [155] and USP <62> Tests for specified microorganisms [156]) provide helpful guidance on how microbiological activity can be measured and controlled (by manufacturing methods and/or terminal sterilisation techniques) to ensure the finished product meets its

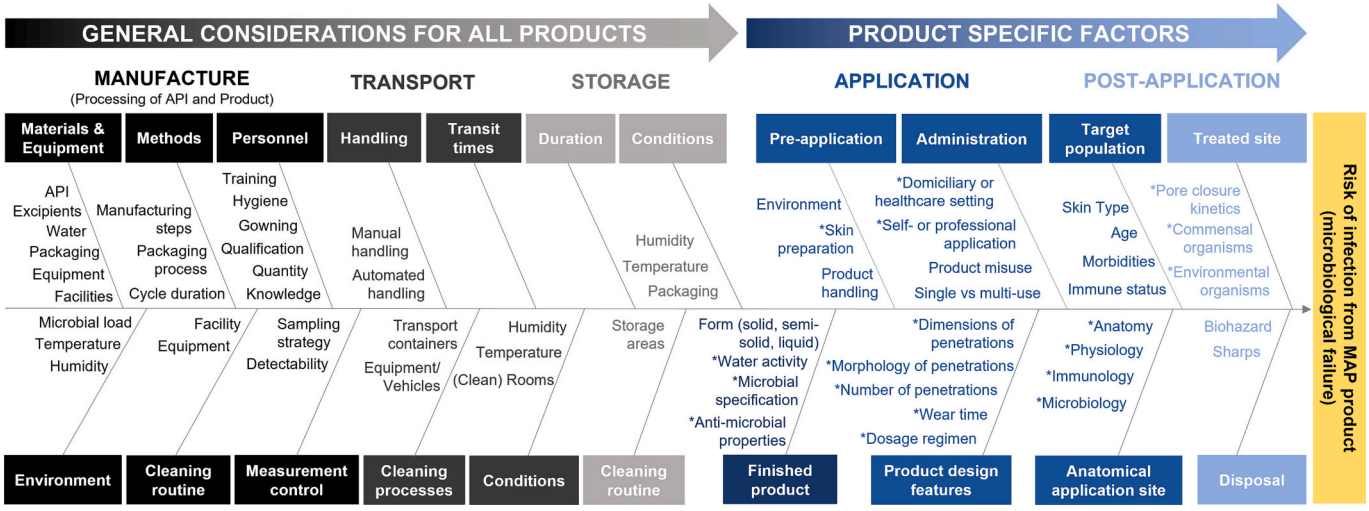

Fig. 1. Key considerations when assessing the risk of infection from a MAP product.
This Ishikawa diagram, developed by members of the MAP RWG and/or the MAP Sterility Working Group, summarises some of the key considerations when assessing the risk of infection from a MAP product. Factors highlighted with an asterisk (*) have been identified as particularly relevant, either because they are exclusive to the dosage form or are particularly pertinent to MAP products. These specific factors are discussed in this article.

microbiological specification. USP references are used in this article to exemplify the requirements and test methods, but similar tests are published in international pharmacopoeias, and many are subject to harmonization. For instance, there are relevant European Pharmacopoeia (PhEur) texts: Sterility (2.6.1) [43], Microbial enumeration of non-sterile products: microbial enumeration tests (2.6.12) [40], Microbial examination of non-sterile products: test for specified microorganisms (2.6.13) [41], Bacterial endotoxins (2.6.14) [39], Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use (5.1.4) [42], and these are harmonized with the USP and Japanese Pharmacopoeia (JP). Industry guidance from the Korean Ministry of Food and Drug Safety (MFDS), related specifically to microneedle products, is also aligned; the specifications and sterilisation methods of sterile products must be established, and non-sterile products should be associated with an explicit specification and a microbial limit test, unless it's absence can be justified [104].

The FDA Pharmaceutical Microbiology Manual [47] provides a helpful supplement to the USP for pharmaceutical microbiology testing and includes antimicrobial effectiveness testing, microbial examination of non-sterile products, sterility testing, bacterial endotoxin testing, particulate matter, device bioburden and environmental monitoring testing. Many of these microbiology-associated tests accompany product release, however it is important to recognise that demonstrable control over bioburden during MAP manufacture through the microbiological specification of raw materials and/or control of the manufacturing environment, for both low bioburden and sterile products, should be used to promote microbiological quality [74].

If all factors are equal, other than the microbiological specification of the finished product, then a sterile MAP product has a lower risk of causing a clinically significant infection than a low bioburden product. Several terminal sterilisation methods have been evaluated for MAPs [8,85,86,91,98,142], but many proposed MAP products will not tolerate terminal sterilisation because of incompatible constituent materials, e.g., a labile API or excipient [8,89,98]. Aseptic MAP manufacture provides another route to a sterile product, although this can be technically and fiscally challenging [64] and so for any MAP product, a cost analysis may help to understand the impact of the microbiological specification on the cost of manufacture and cost of goods.

There is currently no requirement for MAP products to be sterile, and so a microbial risk assessment for a given product may determine that a low bioburden MAP is safe and effective for patients in that specific case. A requirement to make all MAP products sterile would likely lead to product development failures. Failure to realise a MAP product that has potentially lifesaving health benefits is itself associated with risks, both to the individual patient and the wider public. When assigning a finished product specification of either low bioburden or sterile to a MAP product, it is therefore important to consider the absolute and relative magnitudes of the risk of a clinically significant infection from a low bioburden product, compared to a sterile product, and to frame this within the context of other product-, patient- and population-specific factors to determine if the risk is acceptable. This will include a wider risk-benefit analysis when assessing product quality [44], i.e., risks to the population (public health risks), technology (reputational risk of failure) and pharmaceutical industry (commercial risk).

Table 1
A list of current USP Microbiological Tests [145–148,150–157,159–162].

Microbiological Tests for Non-Sterile Products	General Microbiological Tests	BET, Pyrogens and Sterility Tests
USP <60>, <61>, <62>, <1111>, ⟨1112⟩, <1115>	USP <51>, ⟨1113⟩, <1116>, <1227>, <1229.3>	USP <71>, <85>, <151>, <161>, <1211>

3.2. *Water activity of the finished product*

The water content of a pharmaceutical product has implications for chemical and mechanical stability of the API and other quality attributes linked to the physical stability of the formulation, e.g., coating adhesion and structural rigidity. However, in a non-sterile dosage form it also has ramifications for microbiological safety; the presence of water in a low bioburden product could theoretically promote microbial growth during manufacture or storage and therefore should be considered when assessing the infection risk from a MAP product. Established pharmacopoeial tests [163], which rely on the Karl Fisher Reagent, have been widely used to determine the water content of formulations. These test methods, when used appropriately, determine the total water content, i.e., bound (hydrates) and unbound (adsorbed) water. This is key to chemical stability but is only indicative for microbiological safety.

The more relevant measure is water activity (referred to as aw), which is defined as “the ratio of vapor pressure of water in the product to vapor pressure of water at the same temperature" [146]. It is an established measure in the food industry, to prevent microbial spoilage of foodstuffs [137], and provides an indication of the freely available water in the product that can potentially support microbial growth [133,134,146]. Different water activity thresholds support the microbial growth of

different microorganisms and therefore the water activity specifications for pharmaceutical products are informed by the identity of the microorganisms of concern [146]. For example, a water activity of 0.97 is required to support the growth of *Pseudomonas aeruginosa* whilst a lower water activity, 0.86, will support *Staphylococcus aureus* [146]. Therefore, when assessing the risk of microbial spoilage of a MAP product, it is important to consider water activity in the context of the identities of the objectionable pathogens for that product.

In a sterile MAP product, the water activity of the final product is unlikely to form part of a risk assessment for infection; if a MAP product is effectively packaged and stored to maintain a sterile specification, then the absence of microorganisms negates the risk of microbial growth during storage. However, water activity is a key consideration when assessing the potential for microbial spoilage of a non-sterile MAP product [46], and will contribute to the microbial limits testing program and release specifications for the final product [30,72,73]. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q6A specifies testing procedures and release criteria for non-sterile drug products based on the properties of the dosage form, and identifies the dryness of the product as a key consideration when determining the microbial limits acceptance criteria and testing [73]. If the water activity of the final product is low (a value of >0.75 is needed to support bacterial growth and > 0.61 to support fungal growth), products can benefit from self-preservation [46,133] and this may be reflected in the microbiological specification of the non-sterile product. For example, a topical cream has a water activity of 0.97 and, therefore the microbial testing strategy includes total aerobic microbial count, total combined yeast and mould count, and the absence of *Pseudomonas aeruginosa* and *Staphylococcus aureus* (identified as the greatest potential contaminants). However, a topical ointment has a water activity of 0.55 and so the risk of contaminants is reduced, resulting in a reduced microbial testing limit strategy [146]. Some MAP products with low (<0.60) water activity values may therefore be at less risk of microbial spoilage during storage and could benefit from reduced microbiological controls [46].

Water activity is a particularly pertinent consideration for MAPs that use aqueous constituent materials or manufacturing processes, but this must be considered in the context of other product- and patient-related parameters, including the environmental conditions (e.g., temperature, humidity) during their storage and use. It is also likely to inform MAP development (e.g., material selection and formulation), manufacturing methods (e.g., drying processes), primary and secondary packaging, the potential use of desiccants and the shelf life of the finished product (e.g., in stability protocols as described in ICH Q1A [72], including microbiological shelf-life stability testing). However, although the USP Chapter <922> Water activity [164], provides guidance on measuring water activity in pharmaceutical products, which is often achieved using dew point chilled mirror technology [48], published evidence of water activity testing in MAPs is limited [68]. Future studies need to identify and validate equipment and methods that can accurately measure the water activity of MAP products and determine how this measure will influence the microbiological specification of a MAP product.

3.3. The dimensions, morphology and quantity of microneedle penetrations created by a MAP product

If all other factors are equal, a MAP product that penetrates to a greater depth in the skin is, by definition, more invasive. However the relationship between the depth of MAP penetration and the risk of a clinically significant infection is unknown. While there is some rationale to associate the risk of a clinically significant infection with the depth, width, morphology and frequency of microneedle-induced skin barrier insults, the relative importance of each (or any) of these parameters, is unknown. It would be prudent not to assume simple proportional linear relationships, e.g., if all other factors are equal, doubling the length of microneedle penetration does not mean infection risk doubles for the MAP product. Rather, there may be "thresholds" for infection risk that correlate with the biological architecture and/or immune competence of the stratified target tissue. For example, if a microneedle protrudes into a specific skin compartment or sub-compartment (e.g., viable epidermis, basement membrane zone, papillary dermis or reticular dermis) it may be associated with a greater risk of infection (local or systemic) for the patient. Alternatively, it may be a simple dichotomous relationship whereby the depth of puncture at the micron scale is irrelevant, and what is important is whether the stratum corneum barrier has been breached or whether the immunocompetent viable epidermis has been traversed. It is also worth noting that while MAPs aim to disrupt the physical skin barrier, they do not negate the immunological barrier. To the contrary, proposed MAP vaccines aim to exploit the skin's immunocompetence.

It is also important to recognise that while the number, dimensions, and architecture of the micron-sized disruptions that are created in the skin barrier may influence the likelihood of microbial invasion, these parameters must not be directly inferred from the characteristics of the MAP product. For example, a MAP possessing 600 μm microneedles that penetrate partially into the skin is not necessarily "more invasive" than a MAP product with microneedles that are 300 μm in length, which penetrate fully into the skin; it depends on the actual penetration depth. Partial penetration of the microneedle length into the skin has been frequently observed in both laboratory models [106,120,141] and human studies [28]; MAP penetration is acknowledged to be influenced by numerous factors, including the width of individual microneedle projections, the sharpness of microneedle tips, the number of microneedle projections, their spacing on an array, the mechanical properties of the needles, coating of the protrusion and the application parameters e.g. force and speed [2,5,11,32,33,55,87,93,96,97,120,123,169]. Patient-related factors (considered in section 3.6), such as the biomechanical properties of the skin at the application site will also contribute to the dimensions and architecture of MAP-induced skin micro-disruptions [69,80]. Therefore, it is the puncture efficiency of a MAP product (the number of individual needles on a MAP product that effectively penetrate the viable skin tissue) and the dimensions and morphology of the microchannel that is created in the skin that should inform any judgement about how invasive a MAP product is, and the impact this may have on the risk of a clinically significant infection.

At present there is no *prime facie* evidence of a correlation between infection risk and the dimensions and frequency of micro-insults created by existing MAP products. Early *in vitro* laboratory studies using Silescol® membranes and porcine skin suggested that microbial penetration across a microneedle-treated (280 μm long microneedles) membrane was significantly less than that of a hypodermic needle treated membrane [34]. Some stakeholders have also highlighted the established and accepted use of invasive medical interventions such as injections [36] and surgical procedures [135], and the relative safety of microneedling procedures [26,58], as indicators of MAP safety. Ear piercing [14] and tattooing [124] have also been cited as examples of non-medical procedures that compromise the skin barrier and are in widespread use on a daily basis.

However, while there is some analogy between these examples and MAP application, there are notable differences related to the safety requirements of the non-medical procedures, the depth of penetration (often the milli- or centi-metre scales) and the ethics associated with the different interventions. For example, a personal decision to pierce a body part and a government programme to vaccinate a large proportion of the population are associated with different levels of acceptable risk. Therefore, it may be more appropriate to draw parallels between MAPs and analogous medicinal or medical products, such as transdermal patches, medical microneedling procedures using sub-millimetre microneedle projections [58] or wound care dressings [3,84], and to use emerging data from MAP clinical trials to provide indicative evidence of safety.

3.4. MAP wear times, dosing regimens and restoration of the physical skin barrier

The duration of MAP application (wear time) and the dosing regimen determine the length of time that a MAP device is *in situ*. Vaccination of

healthy subjects is the dominant proposed therapeutic application for MAP products [78] and this is likely to require few administrations (potentially one) and minimal wear times (seconds to minutes). For example, the Quality Target Product Profile for a measles rubella MAP vaccine indicates a maximum wear time of 5 min and an optimal wear time of <1 min [168]. Other MAP products propose chronic treatment regimens requiring extended wear times of minutes [175], tens of minutes [6] or hours [1]. Extended wear times and more frequent dosing may be associated with a greater risk of a clinically significant infection from a MAP product. However, laboratory studies examining application of high density MAPs (250 μm projections at a density of 10,000 / cm^2) [63], or frequent and prolonged application of MAPs (600 μm projections applied for 24 h at weekly or bi-weekly intervals over a period of 3–5 weeks) [165] indicate typical pore lifetimes of <24 h, potentially as low as 6 h, with minimal deleterious effects on barrier function or local cell metabolism.

Human skin barrier repair following MAP application has also been inferred in clinical studies by histamine challenge tests at the application site [63] or changes in electrical impedance and/or trans-epidermal water loss (TEWL), predominantly following application of sterile stainless-steel placebo microneedles [10,18,61,62,65,82,107,121,122]. These studies, with up to hundreds of healthy volunteers, typically <65 years old, have examined a diversity of microneedle device designs (between 10 and 100 individual microneedles, with lengths of 180 μm to 800 μm) and indicate that the barrier may be restored in humans in just hours for devices that are least invasive [61], but may take days for MAPs with longer needles and/or more microneedle projections [10,18,61,62,65,82,107,121,122].

Other product-related factors may also influence the lifetime of MAP induced micro-disruptions. This includes occlusion of the treatment site [61], the application procedure and specific APIs that can modify pore closure times [18]. Intended deposition of materials in the skin, or unintended deposition of microneedle structures / fragments from a defective product, may also have an impact on barrier repair, and this emphasises the importance of an appropriate and comprehensive quality assurance testing regimen.

Recent studies have examined patient-specific factors and indicate that the kinetics of 'pore closure' are comparable at different proposed MAP application sites (the forearm, upper arm, abdomen and buttock) [121] but differ in patients with different ethnic/racial backgrounds [122] and for those over 65 years old [82]. The relationship between skin recovery time and the risk of infection is poorly understood. A simple assumption would be that MAP products associated with faster skin recovery will be associated with a reduced risk of infection from an invading environmental or commensal microbe. However, this does not quantify the risk or consider the complexity and diversity of environments, e.g., aerobic versus anaerobic, in which different microorganisms proliferate. Data from MAP studies in human volunteers is therefore needed to better understand the relationship between skin recovery and the risk of infection.

3.5. Antimicrobial APIs

MAP products containing antimicrobial agents have been proposed for the treatment of SSTIs [79], to promote wound healing [12,50], to overcome biofilms [170] and to prevent microbial contamination of the MAP product or treatment site [24,52]. APIs that have been incorporated into MAP products include gentamicin sulfate [57], chloramphenicol [170] and amphotericin B [172], and excipients that have been included to prevent microbial spoilage or reduce the risk of a MAP-induced infection include zinc oxide and silver coatings [25,56], silver nanoparticles [52,56], polymer coatings [17] and encapsulated anti-microbial agents [15,16,56]. Some authors have suggested that inclusion of an antimicrobial agent such as these could, in some instances, render the MAP product "self-sterilising" [52].

Incorporation of antimicrobial agents in a MAP product and the development of formulations that resist microbial contamination have therefore been proposed as a strategy to reduce the hypothetical risk of infection, albeit dependent on the identity of the antimicrobial agent, its concentration, and the target microbe(s). However, it is difficult to evaluate the value of such strategies as the 'baseline' risk of infection, if any, from MAP products is unknown. There are also concerns that inclusion of antimicrobial agents in topical products, such as a MAP, could have a deleterious effect on the protective microbiota of 'healthy' skin or could promote antimicrobial resistance. For vaccine products, cross-reactivity, other negative effects related to vaccine immunogenicity, and potential antigen and API incompatibilities are also significant considerations. Therefore, at present, whilst the inclusion of an antimicrobial agent in MAP formulations to reduce the likelihood of a MAP-induced infection is a theoretical possibility, it is less well understood than established formulation strategies (e.g., inclusion of preservatives), and manufacturing controls that aim to minimise the bioburden and water activity of MAP products.

3.6. The anatomical application site, the setting and the patient

The heterogeneity of the skin barrier at different anatomical skin sites, in terms of its permeability [13,31,92,136,139,167], architecture [51,81,132], biomechanical properties [138] and endogenous microbiota [59], could result in intra- and inter-individual differences in the extent of skin barrier disruption and the kinetics of skin repair [121,122]. Other patient-related factors that influence the immunological [119] and physical [35,125,128] competence of the skin barrier [20] include the age of the patient, their immune status [4,130], general health and whether the tissue at the proposed application site is diseased or injured. Therefore, MAP products will likely be designed and licensed for application to specific named body site(s), e.g., the forearm, deltoid, abdomen, thigh and buttock have been proposed as MAP application sites, and accompanying risk assessments should be specific to that product.

The designated setting for MAP application (healthcare setting or domiciliary environment) and the identity of the administrator (self-administration, non-skilled administration, or administration by a healthcare worker) are also considerations when assessing infection risk. Safety data from Phase 3 studies that examined self-administration of MAPs in the domiciliary setting (described in Section 2) is encouraging but the relative importance of these factors on infection risk remains unknown. Human factor studies to understand how potential users interact with MAP products, including applicators, patient information leaflets and packaging, in an authentic user environment will help to inform an assessment of infection risk.

The skin is also a potential pathogen source. Human skin is home to a diverse but organised population of microbes, including bacteria, fungi and viruses [20,27], whose composition depends on the physiology of the skin site [20,59]. These resident microbial communities are predominantly protective, typically existing in a mutualistic relationship with the healthy human to prevent colonization of the skin by pathogens [19]; indeed, some commensal organisms are now being investigated as a therapeutic in a concept called 'bacteriotherapy' [110]. Changes to the skin microenvironment can induce pathogenicity in previously mutualistic commensal bacteria [27]. The impact of MAP-induced micro-disruptions on the behaviour of commensal microorganisms is currently unknown.

Tissue preparation prior to administration often accompanies invasive medical and non-medical procedures, such as injections [36], surgical procedures [135], ear piercing [14], and tattooing [124], to reduce the risk of infection. However, whilst this is beneficial in some scenarios [54], in a healthy population swabbing the skin surface with an antimicrobial does not reduce the risk of infection from a medical injection [70]. Therefore, numerous health organizations, including the WHO, advise that unless the skin is visibly dirty, disinfecting the skin (alcohol swabbing) is unnecessary prior to medical injections [36]. Skin swabbing may therefore be unnecessary prior to application of a minimally invasive MAP product to a healthy volunteer at a 'visibly clean' application site.

While parallels and hypotheses are important at this stage of MAP development, the risk of a MAP-induced infection resulting from a microorganism that originates from the skin surface or external

environment is currently unknown. Clinical studies have started to evaluate the impact of the patient / patient sub-groups (NCT03207763 [115], NCT03332628 [117]) on the infection risk from a MAP product, however more clinical data is required to determine the importance, or not, of factors such as the anatomy of the application site, the physical environment and the skin microbiota. For example, future clinical trials using sterile MAP products (assumed to harbour no pathogens) could provide data to determine the likelihood, severity and or cause of a MAP induced infection from an environmental or commensal pathogen.

4. Conclusion

Micron-scale disruption of the physical skin barrier by MAP products is associated with a potential hazard (microbial invasion of the skin) that could result in patient harm (a clinically significant infection), but the likelihood and nature of this harm is currently unknown. The absence of MAP-induced infections in published clinical trials involving thousands of MAP applications to hundreds of patients, and the relative safety of analogous procedures such as medical microneedling, does not discourage MAP development. However, the limited data set (thousands rather than millions of MAP applications to humans) and the relatively low incidence of MAP-induced infections (no infections recorded after tens of thousands of MAP applications in Phase 3 clinical studies) means that the probability of a MAP-induced infection is unlikely to be quantified until an approved MAP product is in widespread clinical use and evaluated under robust systems for pharmacovigilance. The diversity of proposed MAP products complicates this further. Therefore, at present, MAP developers must assess the risk of infection from their specific MAP product and use this, alongside a robust suite of pre-clinical and clinical data, to justify their product design and specifications in active dialogue with the appropriate regulatory agencies.

This article identifies and provides expert opinions on some of the key product- and patient-specific factors that should contribute to an assessment of infection risk from a MAP product (Fig. 1). The parameters relate to product quality (e.g., the origin and quality of raw materials, process parameters during manufacture or the product packaging), product design and clinical utility, and includes the much-discussed microbiological specification of the MAP product which, at present, could be justified as either low bioburden or sterile, depending on the holistic risk assessment of that product. This article does not consider all risks e.g., public health risks, commercial risks and reputational risks, nor does it determine the acceptable level of risk, which is specific to the product and clinical context. Most importantly, this article provides a shared understanding, a platform for the development of risk assessments for MAP products and a stimulus for early and open dialogue between developers, regulatory authorities and other key stakeholders, in lieu of extensive clinical data, to expedite and promote development of safe MAP products.

Disclaimer

The views and opinions expressed in this report are those of the authors and do not necessarily reflect the official position of their organizations.

CRediT authorship contribution statement

Maria Dul: Conceptualization, Investigation, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Mohammed Alali:** Conceptualization, Investigation, Writing – review & editing. **Mahmoud Ameri:** Conceptualization, Investigation, Writing – review & editing. **Matthew Douglas Burke:** Conceptualization, Investigation, Writing – review & editing. **Christine M. Craig:** Conceptualization, Investigation, Writing – review & editing. **Benjamin Paul Creelman:** Conceptualization, Investigation, Writing – review & editing. **Lisa Dick:** Conceptualization, Investigation, Writing – review & editing. **Ryan F. Donnelly:** Conceptualization, Investigation, Writing – review & editing. **Michael N. Eakins:** Conceptualization, Investigation, Writing – review & editing. **Collrane Frivold:** Conceptualization, Investigation, Writing – review & editing. **Angus Harry Forster:** Conceptualization, Investigation, Writing – review & editing. **Philippe-Alexandre Gilbert:** Conceptualization, Investigation, Writing – review & editing. **Stefan Henke:** Conceptualization, Investigation, Writing – review & editing. **Sebastien Henry:** Investigation, Writing – review & editing, Conceptualization. **Desmond Hunt:** Conceptualization, Investigation, Writing – review & editing. **Hayley Lewis:** Conceptualization, Investigation, Writing – review & editing. **Howard I. Maibach:** Conceptualization, Investigation, Writing – review & editing. **Jessica Joyce Mistilis:** Conceptualization, Investigation, Writing – review & editing. **Jung-Hwan Park:** Conceptualization, Investigation, Writing – review & editing. **Mark R. Prausnitz:** Conceptualization, Investigation, Writing – review & editing. **David Kenneth Robinson:** Conceptualization, Investigation, Writing – review & editing. **Carmen Amelia Rodriguez Hernandez:** Conceptualization, Investigation, Writing – review & editing. **Charles Ross:** Writing – review & editing, Conceptualization, Investigation. **Juyeop Shin:** Conceptualization, Investigation, Writing – review & editing. **Tycho Joseph Speaker:** Conceptualization, Investigation, Writing – review & editing. **Kevin Michael Taylor:** Conceptualization, Investigation, Writing – review & editing. **Darin Zehrung:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing. **James C. Birchall:** Conceptualization, Funding acquisition, Investigation, Project administration, Visualization, Writing – review & editing. **Courtney Jarrahian:** Conceptualization, Funding acquisition, Investigation, Project administration, Visualization, Writing – review & editing. **Sion A. Coulman:** Conceptualization, Funding acquisition, Investigation, Project administration, Visualization, Writing – original draft, Writing – review & editing.

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.

Data availability

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

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