Notes from stakeholder discussions about MAP CQAs. *This table communicates quality considerations that were identified and discussed in exploratory one-to-one discussions with key stakeholders (N > 20). The table provides a summary of the amalgamated notes that were recorded in these individual discussions. These discussions helped to inform and develop the MAP-RWG "White Paper" publication. These notes are not an exhaustive list and is not a consensus document from the MAP-RWG. Neither has the text been refined or peer reviewed. The document simply provides a publicly available record of notes that were taken from stakeholder discussions. It should not be used directly to define the Regulatory Science of MAPs, but it may provide material that helps to prompt discussion.*

BIOLOGICAL ATTRIBUTES	
Biocompatibility	**General Purpose:** ○ Need to determine the biological consequences of the interaction between the finished MAP product and the skin, during and after application. ○ The biocompatibility of individual materials that are used in MAP manufacture will inform a quality assessment. **In vivo or clinical considerations:** ○ Drug / excipient clearance from the skin may be different than other compartments e.g. sub-cutaneous fat. ○ Local minor skin reactogenicity during / after MAP application is anticipated due to the visible nature of the organ and its immunocompetence. **In vitro considerations:** ○ The biocompatibility standard for medical devices can be considered (ISO 10993 biocompatibility studies) for finished MAP products. ○ Test methods can be informed by those used in analogous products e.g. topical, transdermal, injectable or implant products. **Closely Related Attributes:** ○ drug purity / impurities / residual solvents; extractables / leachables; particulates

Delivered Dose	**General Purpose:** ○ The 'label claim' (or Assay) of a MAP product must be clear in terms of loaded dose and delivered dose. ○ Must ensure reproducibility of delivered dose within and between batches. ○ Validated *in vitro* methods are necessary to ensure this CQA in all batches of a finished MAP product and throughout its shelf life. ○ Bespoke validated *in vitro* test method development may be needed to exemplify delivered dose from a finished MAP product. ○ Pre-clinical and clinical development studies needed to verify and validate performance and quality control. ○ Tests and acceptance criteria of delivered dose established in the product specification should consider the use the finished MAP product i.e., including any associated applicator or auxillary equipment. **In vivo or clinical considerations impacting delivered dose:** ○ The method of MAP application (with or without and applicator; force and speed of application) and the wear time are important contributors to delivered dose; MAP application methods are often product specific. ○ Anticipated differences in MAP performance at different anatomical sites of application mean that products may be licensed for a specific anatomical site(s). ○ Must also consider dosing reproducibility between different patient populations e.g. paediatric versus adult. This may inform design of clinical trials. ○ Need to ensure that the MAP delivers the API to its intended target site in its intended form i.e. need to ensure an API is not inactivated/denatured during MAP manufacture, storage and use. **In vitro considerations:** ○ "Needle" morphology, puncture performance and dissolution are important contributors to delivered dose. ○ As part of an overall control strategy, consider the use of congruent tests ("needle" morphology, puncture performance, drug release / dissolution / disintegration and/or other attributes of a finished product if appropriately validated) and quality control methods (in process controls, process validation) as a surrogate quality control measure for delivered dose. ○ Different test methods and / or specifications are likely needed for different APIs e.g. vaccines versus conventional small drug molecules.

	○ Can measurement of the mass of API that remains on a MAP (i.e., in vitro residual drug) following its application to an appropriate skin surrogate (synthetic or biological) indirectly determine 'delivered dose', if appropriately validated and exemplified? ○ Ideally, routine *in vitro* tests to assure the quality of a finished MAP product should use non-biological tissue. ○ *In vitro* skin permeation tests using full thickness skin may be inappropriate for MAPs not designed for transdermal drug delivery. **Closely Related Attributes:** ○ assay; drug release / dissolution / disintegration; "needle" morphology / geometry; puncture performance; wear time; physical stability

CHEMICAL ATTRIBUTES	
Assay	**General Purpose:** ○ Likely to be a CQA for all finished products. ○ Need to measure the dose in the finished product to ensure the label claim has been met. **In vivo or clinical considerations:** **In vitro considerations:** ○ Existing standardised testing methods are likely to be adopted for most MAP products. ○ Small doses may present technical challenges and necessitate multi-product testing. **Closely Related Attributes:** ○ chemical stability
Chemical Stability	**General Purpose:** ○ Chemical stability depends on the nature of the API. ○ Must demonstrate that the API is stable over the shelf-life of the product. ○ Chemical stability will, in part, be determined by storage conditions, water content and potential interactions with MAP excipients. ○ Potential degradation products need to be identified, quantified and characterised to determine potential deleterious effects. **In vivo or clinical considerations:** **In vitro considerations:** ○ A chemical stability programme must evaluate the finished product (within its packaging) at a range of temperatures and humidity.

	○ A minimum expectation would be to use those temperatures and humidities defined by established ICH requirements for analogous pharmaceutical products. ○ Chemical stability should also be determined when the finished product is removed from its packaging; product stability in ambient conditions over its period of use must be assured. ○ Small doses may present technical challenges and necessitate multi-product testing. **Closely Related Attributes:** ○ assay; biocompatibility; container closure system / packaging; water content
Content Uniformity	**General Purpose:** ○ There may be significant differences in quality considerations between different categories of MAP products e.g. coated MAPs may not be designed to have uniform content with a single unit. ○ Important to assure content uniformity for individual dosage units (MAP to MAP) and batches, but is needle-to-needle uniformity a CQA? **In vivo or clinical considerations:** **In vitro considerations:** ○ Content uniformity for a single MAP product is challenging due to the micro- dimensions and doses of products. ○ USP Chapter *<905> Uniformity of Dosage Units* provides guidance on how to evaluate the content uniformity of individual dosage units, i.e. MAP to MAP. This is not applicable to dosage forms for 'cutaneous administration'. ○ Weight variation is included in USP test *<905> Uniformity of Dosage Units*, and may provide a more appropriate alternative assay for finished MAP products? ○ The mass of API might be too small to enable content uniformity testing on a needle-to-needle basis. ○ Other parameters may provide more appropriate indicators of needle-to-needle content uniformity in a finished MAP product e.g. the dimensions of the coating on a coated MAP product. ○ The content uniformity of materials used to manufacture MAPs will likely contribute to in-process controls.

	Closely Related Attributes: ○ delivered dose; drug release / dissolution / disintegration
Drug Release / Dissolution / Disintegration	**General Purpose:** ○ API release must be exemplified for all MAP products as it is a key determinant of bioavailability. ○ A dissolution test must identify potential batch-to-batch and within batch variations to ensure finished products are within specification. ○ A dissolution test must discriminate between the dissolution properties of different MAP products. ○ Batch-to-batch uniformity of a finished MAP product will be likely required. **In vivo or clinical considerations:** ○ The relationship between in vitro and in vivo (human) drug release / dissolution / disintegration needs to be characterised for MAP products. **In vitro considerations:** ○ MAP products may need to be categorised into rapid acting (seconds / minutes) or sustained release (tens of minutes / hours / days) products to enable distinctive dissolution specifications that are aligned to their label claims i.e. a single value (rather than a 'profile') could be used for a rapid acting product to indicate the dose of API released after X seconds/minutes (where X is the stated 'wear time' for the finished product), whereas a more conventional dissolution profile may be appropriate for a sustained release MAP product. ○ For a single finished MAP product unit, existing pharmacopeial dissolution test methods will typically result in low masses of drug in relatively high volumes of dissolution media, thus preventing robust quantitative detection of some APIs. ○ Adaptations to existing pharmacopeial dissolution test methods is more favourable than development of a 'new' dissolution test. ○ Adaptations may include modifications to equipment and/or optimisation of key parameters e.g. dissolution media and agitation. ○ In-process manufacturing controls and material specifications will help to assure reliable dissolution from a MAP product. **Closely Related Attributes:** ○ assay; content uniformity; delivered dose; wear time

Drug Purity / Impurities / Residual Solvents	**General Purpose:** ○ This attribute is dictated more by the materials than the specific dosage form. ○ Many materials used in MAP products are well characterised and used previously in pharmaceutical products. ○ Polymer-based MAPs will need to evaluate residual monomers. ○ Novel materials will necessitate enhanced scrutiny. **In vivo or clinical considerations:** **In vitro considerations:** ○ Existing established standardised testing methods are likely to be adopted for most MAP products. ○ Impurity limits should be established as part of standard impurity control for finished MAP products (and intermediates). ○ Small quantities of impurities may present technical challenges and may necessitate multi-product testing. ○ Learnings from analogous products are likely to guide testing and specifications. **Closely Related Attributes:** ○ assay; biocompatibility; chemical stability
Extractables / Leachables	**General Purpose:** ○ Need to establish an interaction profile between the different materials used in a MAP product e.g. the API, formulation, delivery system and applicator device. ○ The majority of materials used in MAP products are well characterised and have been combined previously in pharmaceutical / medical products. ○ Novel materials will necessitate enhanced scrutiny. **In vivo or clinical considerations:** **In vitro considerations:**

	○ Physical contact points between the formulated API and the delivery system need to be established. ○ Existing standardised testing methods are likely to be adopted for most MAP products. ○ Learnings from analogous products are likely to guide testing and specifications. **Closely Related Attributes:** ○ biocompatibility; chemical stability; container closure system / packaging; physical stability
Identity	**General Purpose:** ○ Need to be confident of API identity. **In vivo or clinical considerations:** **In vitro considerations:** ○ Existing standardised testing methods are likely to be adopted for most MAP products. ○ Small doses may present technical challenges and necessitate multi-product testing. **Closely Related Attributes:** ○ assay
Polymorphisms	**General Purpose:** ○ In some MAP products, the form of the API (amorphous / crystalline) may change following manufacturing and / or during storage. ○ Polymorphisms could change a range of MAP attributes including the bioavailability of the API. **In vivo or clinical considerations:** **In vitro considerations:**

	○ Need to consider the potential for crystallisation and / or phase separation, as observed in some transdermal patches. ○ Existing standardised testing methods are likely to be adopted for most MAP products. ○ Small doses may present technical challenges and necessitate multi-product testing. **Closely Related Attributes:** ○ chemical stability; delivered dose; drug release / dissolution / disintegration; mechanical strength; physical stability
Water Content	**General Purpose:** ○ Water content includes bound and unbound ('free') water. ○ This will be an important attribute for the majority of MAP products, regardless of their design. ○ The water content may be polymer dependent. **In vivo or clinical considerations:** **In vitro considerations:** ○ Water content should be monitored over the stability period as it can have an impact on numerous other MAP attributes. ○ Water content should be characterised during the lifetime of a product i.e. during manufacturing (in-process control), following storage of the finished product in its packaging and following removal of the MAP from its primary packaging. ○ Low quantities may necessitate water content measurements in small batches of MAPs rather than single dosage units? **Closely Related Attributes:** ○ chemical stability; container closure system / packaging; mechanical strength; microbiological specification; physical stability; puncture performance; water activity

MICROBIOLOGICAL ATTRIBUTES	
Microbiological Specification	**General Purpose:** ○ Finished MAP products will be designated as either low-bioburden or sterile products (Dul et al. 2023). ○ The microbiological specification has a significant impact on manufacturing methods and costs. ○ A risk-assessment should be made to determine the microbiological specification of a MAP product. This is discussed in detail in Dul et al. 2023. **In vivo or clinical considerations:** ○ Clinical safety data is emerging (Phase 3 clinical trials in tens of thousands of users) but a significant data set (millions of users) is currently unavailable for the MAP dosage form. **In vitro considerations:** ○ Existing guidance and directives on the test methods and limits that are appropriate for the specification should be adopted / adapted for finished MAP products. These are summarised in Dul et al. 2023. **Closely Related Attributes:** ○ container closure system / packaging; water activity; water content
Particulates	**General Purpose:** ○ Particulates level will need to be controlled and will likely be a CQA for MAPs. **In vivo or clinical considerations:** **In vitro considerations:**

	○ Particulates limits should be taken into consideration as it is in other dosage forms. **Closely Related Attributes:** ○ biocompatibility; chemical stability; container closure system / packaging
Water Activity	**General Purpose:** ○ A measure of the 'free water' in the product that is available for microbial growth. ○ An important attribute for MAPS that are designed to be thermostable. ○ The chemical stability, mechanical strength, microbiological specification and physical stability of a MAP product will be determined, in part, by its water activity. ○ Need to understand the relationship between the water activity of MAP products and their stability (chemical, physical and microbiological). **In vivo or clinical considerations:** **In vitro considerations:** ○ USP method (<922>) could be adopted / adapted to determine the water activity of MAP products, although accurate measurements in a single micron scale MAP will be challenging. **Closely Related Attributes:** ○ chemical stability; container closure system / packaging; drug release / dissolution / disintegration; mechanical strength; water content

PHYSICAL ATTRIBUTES	
Adhesion	**General Purpose:** ○ MAP product dependent i.e. many proposed MAPs do not have an adhesive. ○ MAPs with an adhesive need to be secured in place for the wear time. ○ There is extensive experience in the use of adhesives to secure medical and medicinal products to the skin surface. **In vivo or clinical considerations:** ○ The target population should be considered. **In vitro considerations:** ○ An adhesion test is only required if an adhesive is used to secure the MAP product to the skin. ○ Established standardised adhesion tests for transdermal patches (tack test, removal type test, peeling test) should be adopted for finished MAP products. ○ A 'cold flow assessment' is also likely to be appropriate for products that use an adhesive to secure the MAP to the skin. **Closely Related Attributes:** ○ delivered dose; wear time
Container Closure System / Packaging	**General Purpose:** ○ There is a range of container and packaging options for MAP products and extensive experience of their use with pharmaceutical and medical products. ○ The container closure system / packaging should ensure the product cannot be physically damaged during transport / storage. This is a particularly important consideration for the micron-sized needle projections of a MAP product. ○ The humidity in the packaging will be an important consideration for many MAP products. **In vivo or clinical considerations:**

	In vitro considerations: ○ Established materials and packaging designs should be adopted where possible. ○ A desiccant could be included in the package to control humidity, potentially in the wall of the container. **Closely Related Attributes:** ○ chemical stability; extractables / leachables; microbiological specification; particulates; physical stability; water content
Mechanical Strength (" Needle" and / or baseplate)	**General Purpose:** ○ Mechanical failure of the product during storage, transport and use must be avoided. ○ Mechanical failure could be a result of bending, buckling or fracture of individual microneedle projections or physical damage to the baseplate. ○ The flexibility / stiffness of the "microneedle support" may be important for some products. **In vivo or clinical considerations:** ○ The specification of a product will be influenced by the force of application used for the specific product and the potential use of an applicator. **In vitro considerations:** ○ Materials texture analysers and force testing machines are typically used to test this attribute in other pharmaceutical and medical products. ○ Testing of mechanical strength might require measurement of both sheer stress and compression. ○ Some tests may use a "skin model" as part of their methodology. ○ The mechanical strength may not be uniformly distributed e.g. incorporation of an API in / on the tip of the needle could change the mechanical strength in this region. ○ The end point could be measured by visual inspection of the product and / or a feature of a force-displacement profile. This could be linked to "needle" morphology / geometry characterisation.

	○ Mechanical strength could be characterised as part of the pre-clinical package and inferred in the final product based on the control of CMAs and CPPs. This may, or may not, replace finished product testing if appropriately validated and exemplified. **Closely Related Attributes:** ○ "needle" morphology / geometry; physical stability; puncture performance; water content
" Needle" Morphology / Geometry	**General Purpose:** ○ "Needle" morphology and geometry must facilitate skin puncture. ○ The level of inspection needs to be considered; one needle on one MAP in a single batch is probably insufficient, but all needles on all manufactured MAPs may be excessive. **In vivo or clinical considerations:** **In vitro considerations:** ○ Measured parameters could include needle dimensions e.g. height and base width, geometry / tip sharpness and the spacing of multiple needles in an array. ○ A visual inspection system could be used to provide "in line" quality control during manufacture and / or a finished product specification. ○ It may be possible (but not necessarily required) to do 100% visual inspection in an automated "in line" quality control. ○ In a coated microneedle product, it will be important to consider morphology before and after coating. ○ "Needle" morphology / geometry (combined with mechanical strength) could potentially be used as an indicative / surrogate measure of puncture performance, if appropriately validated and exemplified. **Closely Related Attributes:** ○ delivered dose; mechanical strength; physical stability; puncture performance

Physical Stability	**General Purpose:** ○ Physical stability is an important parameter to establish and exemplify the shelf-life of a MAP product. ○ Pre-clinical studies need to demonstrate that the physical integrity of the finished product is maintained up to the point of application i.e. following transport, after storage at different temperatures and humidity, and following removal from the packaging. ○ Physical stability of the final product should be established after subjecting it to the same transport conditions that would be expected in routine clinical use. **In vivo or clinical considerations:** **In vitro considerations:** ○ Pharmacopeial friability tests measure the reduction in mass for a product, but for MAPs the mass may be too small to measure. Multiple dosage units will be required in such a test. ○ Vibration and impact challenge tests may provide more relevant test methods than friability tests, based on the likely MAP products will be packaged. ○ "Needle" morphology / geometry characterisation, before and after a stability program, could be linked to physical stability. ○ Other considerations include: tip damage, detachment of needles and detachment of coating (for coated MAPs). **Closely Related Attributes:** ○ delivered dose; "needle" morphology / geometry; mechanical strength; puncture performance

Puncture Performance	**General Purpose:**
	○ MAP product by definition (Dul et al. 2024) has to mechanically disrupt ("puncture") the skin barrier.
	○ Puncture performance is key to MAP performance, but an established validated and internationally recognised puncture performance test method does not exist for finished MAP product.
	○ A bespoke MAP puncture performance test must consider the test method, apparatus and materials, including the identity of any skin mimics / surrogates.
	○ Puncture performance specifications need to be established:
	  ○ Is a quantitative measure of the absolute depth and / or width of MAP "puncture" (in micrometers) required?
	  ○ Should a MAP puncture performance test provide a more qualitative measure of puncture i.e. whether the MAP is able to puncture one or more layers of a biological or synthetic material (akin to puncturing the stratum corneum and / or viable epidermis and / or the papillary dermis and / or reticular dermis)?
	○ A finished product specification may include limits for puncture efficiency i.e. the proportion of needles that 'puncture' a material in a validated puncture performance test.
	  ○ Is there a minimum accepted value for the puncture efficiency of the dosage form or is it product specific?
	  ○ What is an acceptable limit for a puncture performance specification e.g. +/- 5% of the final product specification?
	○ Could "needle" morphology (which could be an in-process control) and mechanical strength (could batch test the finished product) provide a surrogate indicator of puncture performance for a finished MAP product, providing these two attributes correlate with pre-clinical data?
	○ Could puncture performance and drug release / dissolution / disintegration be used as a surrogate indicator of delivered dose when testing a finished MAP product, if appropriately validated and exemplified.
	
	In vivo or clinical considerations:
	○ Puncture performance is also linked to the application method; force, speed and duration of application are important.
	○ MAP products are typically designed for a specific anatomical application site(s) and therefore licensed products are likely to be approved for application at those named anatomical sites.
	○ The puncture performance of a MAP product may not translate between different anatomical application sites.
	
	In vitro considerations:

	○ The shape, sharpness and needle-to-needle spacing are key attributes that influence the puncture performance. ○ A placebo product should not be used to demonstrate puncture performance, particularly in coated MAP products i.e. the finished product must be tested. **Closely Related Attributes:** ○ delivered dose; mechanical strength; “needle” morphology / geometry; physical stability
Wear Time	**General Purpose:** ○ The wear time should be specified. ○ A range of wear times have been proposed for MAP products. **In vivo or clinical considerations:** **In vitro considerations:** ○ Pre-clinical testing should provide evidence for the wear time. ○ Determined by pre-clinical studies. ○ Should be used to inform tests of other attributes, such as patch adhesion and delivered dose. **Closely Related Attributes:** ○ delivered dose; drug release / dissolution / disintegration; adhesion