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Microarray Patch Packaging

An exploration of technical, usability, and general design considerations

MAPs for PrEP Project: Dissolving microarray patches (MAPs) for long-acting HIV and pregnancy prevention

PATH

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Abbreviations

AAMI	Association for the Advancement of Medical Instrumentation
ANSI	American National Standards Institute
APET	amorphous-polyethylene terephthalate
API	active pharmaceutical ingredient
ASTM	ASTM International
CFR	United States Code of Federal Regulations
CHW	community health worker
COC	cyclic olefin copolymer
CPP	cast polypropylene
CVMP	Committee for Medicinal Products for Veterinary Use
DIN	German Institute for Standardization
EC	European Commission
EMA	European Medicines Agency
EN	European Standard ratified by the European Committee for Standardization, European Committee for Electrotechnical Standardization, or ETSI
EtO	ethylene oxide
EU	European Union
EVA	ethylene vinyl acetate
FFS	form-fill-seal
GMP	Good Manufacturing Practice
HDPE	high-density polyethylene
HIPS	high-impact polystyrene
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
ISTA	International Safe Transit Association
LDPE	low-density polyethylene
MAP	microarray patch
MPT	multipurpose prevention technology
PA	polyamide
PC	polycarbonate
PCL	polycaprolactone
PE	polyethylene
PET	polyethylene terephthalate
PETG	polyethylene terephthalate glycol

Ph. Eur.	European Pharmacopoeia
PP	polypropylene
PrEP	pre-exposure prophylaxis
PS	polystyrene
PSI	pounds per square inch
RABS	restricted access barrier systems
USAID	United States Agency for International Development
US CFR	United States Code of Federal Regulations
USFDA	United States Food and Drug Administration
USP	United States Pharmacopeia
WHO	World Health Organization

Executive summary

Microarray patch (MAP) technologies are rapidly advancing for a variety of pharmaceutical and vaccine delivery applications. As with all pharmaceutical products, MAPs require packaging to provide protection, maintain safety and a suitable level of sterility, and promote usability and acceptability. As such, packaging strategy needs to be considered early and throughout MAP development. Primary requirements for MAP packaging include physical protection, moisture barrier, usability, and appropriate microbial protection.

This report describes the critical considerations for MAP packaging, including requirements, packaging configurations and components, sterility control, and usability and programmatic fit. This report is intended as a resource for MAP developers and manufacturers. A summary of packaging aspects and recommendations is listed in Table 1.

Table 1. Recommendations for MAP packaging.

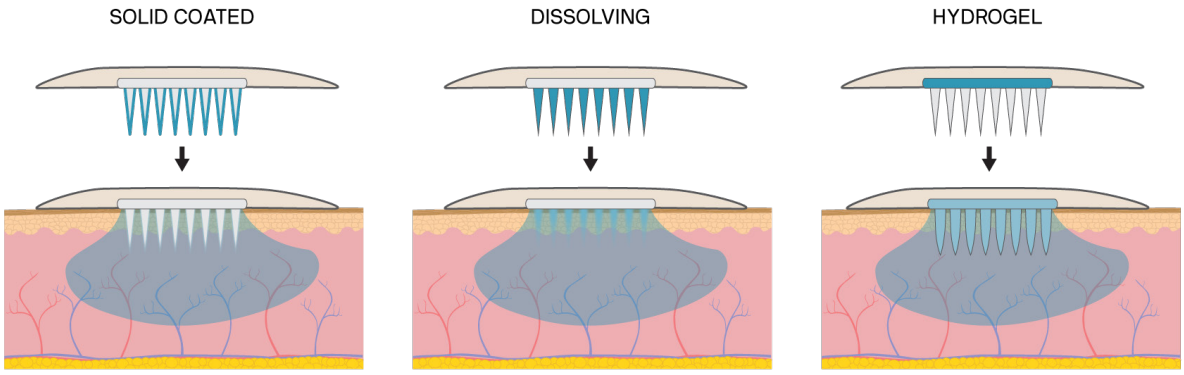
Category	Recommendations
Packaging configurations/ types	An integrated MAP delivery device can reduce packaging waste by lessening requirements for additional layers of packaging.
Materials selection	Due to the high moisture sensitivity of MAPs, low-permeability polymer-based films and aluminum foils, films, or sheets are recommended for their barrier properties.
Desiccants	The target active pharmaceutical ingredient dictates the packaging requirements; if the manufacturing process and/or selected packaging system does not provide sufficient moisture control, desiccants may be needed.
Adhesives and heat seals	Care must be taken to ensure any off-gas and/or heat from either the adhesives or adhesive sealing process does not adversely affect the MAP's active pharmaceutical ingredients.
Packaging assembly	For MAP products anticipating high-volume production, packaging solutions that are easily scalable, such as designs that use web-based production, should be prioritized.
Sterility control	Device requirements should determine the appropriate level of microbial protection. Sterility control planning is a priority during early development as it affects material selection and packaging assembly. Early assessment of the anticipated sterilization method should be conducted to ensure stability of a MAP is not compromised. For terminal sterilization, irradiation is likely to be the most compatible sterilization method for MAP packaging configurations. If deemed necessary, the full development and validation of aseptic processing systems can take years.
Usability	Failure modes and effects analysis and simulated use testing should be carried out with the MAP and its packaging early in the development process to aid in design decisions throughout development.
Programmatic	For development and refinement of packaging requirements appropriate for low- and middle-income countries, MAP developers should consult all potential stakeholders, from distributors and vendors to medical professionals and patients.
Environmental impacts	A MAP design that requires a minimal amount of packaging—preferably of recyclable material—while still providing suitable levels of protection, would help minimize environmental impact.
Supply chain	Overall package volume should be minimized for shipping and cold chain storage, without compromising usability and programmatic acceptability.
Packaging cost	Automating packaging can lower per unit cost and better maintain microbial protection. Easily automatable packaging configurations should be selected if high production volumes are expected. A delivery device integrated as the primary packaging for the MAP may be preferable for physical protection, as preformed trays increase cost and waste.

Abbreviation: MAP, microarray patch.

Introduction

Microarray patches (MAPs) consist of micron-scale projections that can painlessly penetrate the epidermis to deliver a pharmaceutical or a vaccine to the upper layers of skin. MAP types include solid coated, dissolving, and hydrogel arrays (shown in Figure 1). Due to the size and composition of the projections, they are generally fragile and moisture sensitive.

Figure 1. Types of microarray patches.



MAPs are in development for a variety of indications, including vaccine delivery, at-home treatment of migraines and osteoporosis, and many other applications. Because MAPs have the potential to be an easy-to-use and discreet delivery technology, they have been identified as having the potential to meet the needs of women and adolescents in low- and middle-income countries who are at greatest risk of HIV infection and unintended pregnancy, and who need acceptable products that provide both long-acting protection against HIV and contraception. In the future, self-applied MAP delivery systems for HIV pre-exposure prophylaxis (PrEP) and those serving as multipurpose prevention technologies (MPT) containing both PrEP and contraception could enhance acceptability, ease of use, and compliance compared to other PrEP strategies, thereby reducing risk of HIV infection and unintended pregnancy—especially among young women—and improving women's reproductive health.

This packaging report reviews MAP packaging requirements that are broadly applicable for all use cases, including MAPs intended to be used for HIV PrEP delivery and those used as an MPT in low- and middle-income countries.

Generic packaging definitions

Packaging is a crucial factor in the protection and safety of medical products. In addition to ensuring product stability, packaging contributes to a product's usability and acceptability. Because packaging impacts many design and testing aspects, it is best to start its development as soon as possible in the product's development. This report focuses on packaging considerations for MAPs as a category of combination products for delivery of pharmaceuticals and vaccines. This report draws guidance from US and European regulatory agencies and the World Health Organization (WHO)—all critical organizations for ensuring appropriateness for use in low- and middle-income countries.

WHO describes packaging as "the collection of different components […] which surround the pharmaceutical product from the time of production until its use."[1] Packaging containing a pharmaceutical

product must protect the product's quality and stability by preventing spoilage, tampering, or other damage; facilitate storage and transportation; and provide required labeling.

Regulatory bodies, including the United States Food and Drug Administration (USFDA), describe three types of packaging based on its proximity to the product:[2]

- **Primary packaging.** Primary packaging is that which is in direct contact with the device and/or drug and is intended to protect the product from contamination (both microbial and nonmicrobial), light, volatile gases (e.g., oxygen), moisture ingress, and loss of solvent. The degree to which these are of concern depends on the product and its intended use. Primary packaging also bears the necessary labeling for identification and use. Examples of primary packaging are a glass vial for a drug product or a blister pack for a pill.
- **Secondary packaging.** Secondary packaging, not in direct contact with the product, provides an additional layer of protection. However, secondary packaging is critical if it provides essential protection in addition to that provided by the primary container. For example, a foil pouch (enclosing a transparent plastic ampoule) might provide the necessary protection against light or moisture/gas ingress. Secondary packaging also serves as the final market presentation and contains the primary container or multiple primary containers in the case of multidose packaging. Common examples of secondary packaging include cartons or boxes that can provide additional mechanical protection. The volume and weight of secondary packaging are relevant characteristics used for assessing storage space requirements at the warehouse, transportation, and service delivery levels. Figures 2 and 3 depict examples of MAP primary and secondary packaging components.
- **Tertiary packaging.** Tertiary packaging provides additional protection against vibration, mechanical shock, stacking forces, and temperature during storage and transport of the product. Cardboard boxes and crates for global shipping are examples of tertiary packaging; they generally hold multiple secondary packaging units.

Figure 2. Examples of primary and secondary packaging for MAPs.

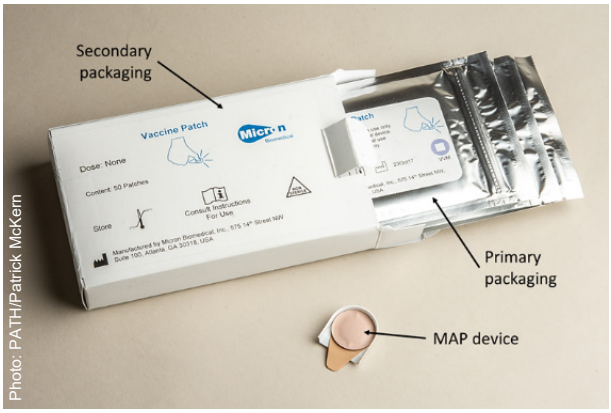


Figure 3. Examples of primary and secondary packaging for MAPs.

Abbreviation: MAP, microarray patch.

Because packaging plays a direct role in product stability and affects labeling, it is considered part of the device and/or drug system that it encompasses and is subject to the same quality assurance requirements as the pharmaceutical product itself. Packaging design and materials chosen must not have an adverse effect on the product (chemical reactions, leaching of packaging materials, absorption), and the product must not have an adverse effect on the packaging by changing its properties or affecting its protective function. Ultimately, packaging requirements are determined by relevant regulatory guidance

documents and standards, production process capabilities, storage requirements of the product, and the manufacturer's internal policies (safety, marketing, etc.). These requirements must be met throughout the intended shelf life of the product as defined by the manufacturer. All packaging requirements must be validated by the manufacturer and documented for submission to the regulatory authority when seeking market approval. Documentation also can be requested as part of review by international procurement agencies, as well as during manufacturer audits. For the entire packaging, approval by the authorities is mandatory.

Packaging suitability

As a sensitive combination product (i.e., a drug and delivery system), a MAP is likely to be vulnerable to deleterious effects of handling, the environment, and time. For this reason, packaging requirements for this class of product will likely be stringent, as the packaging must be shown to be both suitable and effective in performing its critical functions.

Regulatory authorities, including the USFDA and the European Medicines Agency consider packaging suitability for drugs and biologics in four general areas: protection, safety, compatibility, and performance. The design of the packaging system must be demonstrably suitable for the intended application in each of these areas.

All testing of packaging suitability should be implemented at the anticipated environmental extremes and durations of its life cycle (time of manufacture [lot release] through product disposal), as defined by its target product profile.

Protection

Packaging must protect the MAP for the entire duration of its shelf life—including transport, storage, handling, and use. The requirements for protection are determined by the specific MAP design and formulation and may include characteristics such as physical/mechanical, moisture, gas, and light protection. Typically, increasing the level of protection robustness is associated with an increase in cost; therefore, the degree of protection should be calibrated to only what is necessary to meet the packaging requirements. Primary packaging is responsible for maintaining appropriate microbial protection and cleanliness, and for providing protection from external elements. Secondary packaging provides physical protection for the primary package. Due to the fragility of MAP microprojections, it is anticipated that the primary packaging will also require physical protection, in addition to microbial and cleanliness protection (including moisture and gas ingress protection).

Testing to confirm protection

Packaging protection is verified during the product development process through integrity testing. Testing should evaluate both physical integrity (i.e., protection from nonviable particulates and external forces) as well as sterility (i.e., protection from microbial contamination). Testing the degree of light, gas, and moisture ingress may also be important depending on the specific sensitivity of the MAP. Packaging must also be assessed for its ability to protect the product during transport and must account for the effects of pressure, vibration, and physical handling.

Relevant testing standards*

Integrity testing

- USP <71> Sterility Tests.
- USP <671> Containers—Performance Testing.
- USP <788> Particulate Matter.
- ASTM F1886 Package Integrity (Visual Inspection).
- ASTM F1929 Package Integrity (Dye Penetration).
- ASTM F2391-05, F2228 Package Integrity (Tracer Gas).
- ASTM F2338 Package Integrity (Vacuum Decay).
- ASTM 2096 Package Integrity (Pressurization).
- ASTM D3078 Determination of Leaks in Flexible Packaging by Bubble Emission.
- ASTM 2096 Detecting Gross Leaks in Medical Packaging by Internal Pressurization (Bubble Leak Test).

Transport and storage

- ASTM D4169 Performance Testing of Shipping Containers.
- ASTM D4332 Conditioning Container, Packages, or Packaging for Testing.
- ISTA 3A Series Tests.

Stability

- ICH Quality Guidelines: Q1A–Q1F Stability.
- ASTM F1980 Accelerated Aging of Sterile Barrier Systems for Medical Devices.

Safety

Packaging materials must be both safe for users to interact with, as well as able to safely interact with the contained liquid and not compromise its efficacy.

Testing to confirm safety

An extractables study identifies and quantifies compounds that could be extracted from packaging materials when subjected to a variety of solvents or harsh conditions (e.g., elevated temperatures). A risk assessment can then determine if the nature and quantity of any compounds found in the packaging materials are within acceptable limits. The assessment should include an examination of any coatings and laminates under consideration, as well as secondary packaging, labeling materials, adhesives, dyes, and inks. To aid in the risk assessment, information may be available from the packaging material supplier, who can give permission to reference a regulatory master file that has been submitted to a regulatory authority.

* The standards cited in this report, with the following abbreviations in their names, were developed by the following corresponding organizations: ANSI//AAMI, American National Standards Institute/Association for the Advancement of Medical Instrumentation; ASTM, ASTM International; DIN, German Institute for Standardization; EMA/CVMP, European Medicines Agency/Committee for Medicinal Products for Veterinary Use; EN, European Standard ratified by the European Committee for Standardization, European Committee for Electrotechnical Standardization, or ETSI; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; EN ISO: ISO standard adopted by the European Union; IEC, International Electrotechnical Commission; ISO, International Organization for Standardization; ISTA, International Safe Transit Association; USP, United States Pharmacopeia; Ph. Eur., European Pharmacopoeia; US CFR, United States Code of Federal Regulations; UFDA, United States Food and Drug Administration; USP, United States Pharmacopeia; WHO, World Health Organization.

Relevant testing standards

General

- WHO Technical Report Series, No. 902, *Annex 9: Guidelines for Packaging of Pharmaceutical Products*.
- EMA/CVMP/205/04: Guideline on Plastic Immediate Packaging Materials.
- ICH Quality Guidelines: Q1A–Q1F Stability; Q5A–Q5E: Quality of Biotechnological Products.
- USP <1663>, USP <1664>.
- Ph. Eur. Section 3. Materials and Containers.
- USFDA Guidance for Industry: *Container Closure Systems for Packaging Human Drugs and Biologics*.
- ISO 11607 Packaging for Terminally Sterilized Medical Devices.
- USP <659> Packaging and Storage Requirements.
- USP <1031> Biocompatibility of Materials.
- USP <1177> Good Packaging Practices.

Materials and extractables

- ISO 10993 Biological Evaluation of Medical Devices.
- USP <87>, <88> Biological Reactivity Tests.
- USP <85> Bacterial Endotoxin.
- USP <151> Pyrogens.
- USP <661> Containers—Plastic (Materials of Construction and Packaging Systems).
- Ph. Eur. 3.1.7, 3.1.14, and 3.2.

Child resistance

- EN ISO 8317 for Reusable Packaging.
- EN 862 for Non-Pharmaceutical Packaging.
- DIN EN 14375 for Pharmaceutical Products.
- US CFR § 1700.20.

Compatibility

Packaging materials must not cause unacceptable physical or chemical interactions with the MAP that compromise the dosage or quality (potency, strength, or purity) of the product.

Testing to confirm compatibility

The potential for adverse interactions should be assessed through a leachables study. A leachables study (using the actual dosage form) or stability test can be conducted to identify and quantify the actual compounds that leach from the primary packaging into the dosage form. It should be noted that compounds, such as inks or dyes present in secondary packaging or labeling, should also be assessed if the primary packaging is permeable (as is the case for many plastics).

Relevant testing standards

- ICH Quality Guidelines: Q1A–Q1F Stability.

Performance

Packaging performance generally refers to any functionality of the packaging that is not related to safety, compatibility, or protection. For example, performance of a glass vial may refer to the ability of the stopper to be punctured multiple times without generating unacceptable levels of particulates, or the ability of a squeeze tube to be used as a consistent dosing mechanism. Consideration should therefore be given to the ease with which the packaging can be opened to minimize use difficulties, potential use errors, and the chance of injury or damage to the product resulting from excessive force. In the case of a MAP product where the primary packaging could also be the delivery device, it will have significant impact on performance-related functionality and may require incorporating labeling into the packaging to assist the user in its correct use.

Testing to assess performance

User studies that assess critical tasks such as label comprehension and opening of the packaging should be conducted to evaluate the potential of product damage or user harm, as per IEC 62366-1 (Application of Usability Engineering to Medical Devices). An example of a standardized performance test for a pouch or lidded tray could include peel force testing per ASTM F88.

Testing will depend on specific functionality of the packaging and could include a combination of bench-based and user-based evaluations (i.e., usability evaluations to identify use errors associated with packaging functionality and bench testing for pouch opening peel strength to ensure packaging is both properly sealed and easily opened).

Relevant testing standards

- ASTM D3330 Method for Peel Adhesion of Pressure-Sensitive Tape.
- ASTM F88 Seal Strength of Flexible Barrier Materials.

Sealing

- Norm: DIN 55409-1: Seal strength, flexible packaging, peelable
  The test parameters of this test method can be adjusted especially for the testing of flexible packaging material, such as pouches and bags.
- Norm: DIN 55409-2: Seal strength, stable and rigid packaging, peelable
  The test parameters of this test method can be adjusted especially for the testing cap/top/cover sealing of blisters, shells, pods, or cups.
- *Guidance on Labelling and Packaging in Accordance with Regulation (EC) 1272/2008* (Version 4.2).
- *Guidance on Harmonized Information Relating to Emergency Health Response – Annex VIII to CLP* (Version 4.0).
- European Parliament and Council Directive 94/62/EC on Packaging and Packaging Waste.
- Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on Classification, Labelling and Packaging of Substances and Mixtures, Amending and Repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

MAP industry guidance

PATH's MAP Center of Excellence established a Regulatory Working Group[3] with the aim of defining the regulatory pathway for MAPs to aid in clinical translation of the technology class. Chaired by PATH and Cardiff University, this group includes experts in both commercial and academic MAP and vaccine development and representatives from national regulatory authorities and public health agencies. The

Regulatory Working Group has identified critical quality attributes of the technology class, including several that pertain to packaging, and relevant guidance for assessing appropriate MAP packaging materials and design.[4]

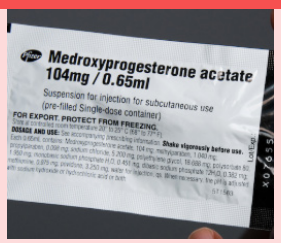
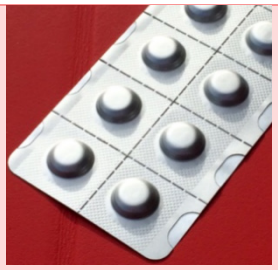
Packaging configurations

Because of its flexibility as a platform technology and broad range of potential use cases, MAP technologies are being proposed with many different packaging configurations. Configuration variables—such as packaging types, delivery device integration, and multidose formats—all may affect supply chain logistics, cost-effectiveness, and waste volumes, which will be discussed in later sections.

Packaging types

Primary packaging types potentially appropriate for use with MAPs are described in Table 2.

Table 2. Primary packaging types.

Type	Description	Typical materials used	Images
Pouch	Flexible, heat-sealed pouch with two or more layers. Can be premade for low-volume production (requires only sealing machine) or made in-line directly from roll stock for high-volume production (requires automated packaging equipment). Can be combined with other packaging types to achieve necessary protection.	CPP, foil, PE, PET	
Stamped container	Preformed, stamped metal cup allows for MAP (and, potentially, delivery device mechanism) to be stored in a container with strong barrier properties while providing more mechanical protection than a simple foil pouch overwrap.	Aluminum alloys	
Form-fill-seal	While not yet optimized for MAPs, FFS technology is common as pharmaceutical packaging. The base layer is thermoformed into collapsible blisters to accommodate bulky contents. Provides less physical protection than thermoformed (rigid) tray. Not well suited for low-volume production, as it is typically produced on high-volume machinery. Blister packaging is an example of FFS. This strategy could be used for storing MAP single-dose cartridges that are used with reusable applicators.	COC, EVA, PA, PE, PP	 Used under Creative Commons license.

Type	Description	Typical materials used	Images
Thermoformed tray with peel-top lid	Preformed plastic rigid tray with die-cut lid. Provides more physical protection but not as well suited for high-volume production as other packaging types. Trays are more costly than pouch or FFS style packaging due to the more complex logistics of automating a non–roll stock material.	Tray: PC, PE, PP, PE, PETG, APET, HIPS, COC Lid: foil, coated polyolefin non-woven materials	

Adapted from: Fuente J, Bix L. Medical device packaging. In: Yam KL, eds. *The Wiley Encyclopedia of Packaging Technology*. 3rd ed. Hoboken, NJ: John Wiley & Sons, Inc.; 2009:713–727.

Abbreviations: APET, amorphous-polyethylene terephthalate; COC, cyclic olefin copolymer; CPP, cast polypropylene; EVA, ethylene vinyl acetate; FFS, form-fill-seal; HIPS, high-impact polystyrene; MAP, microarray patch; PA, polyamide; PC, polycarbonate; PE, polyethylene; PET, polyethylene terephthalate; PETG, polyethylene terephthalate glycol; PP, polypropylene

Applicator/indicator integration

Delivery of many MAP products will likely require a delivery device, such as an applicator (mechanism for providing sufficient administration force and/or velocity to MAP) or an indicator (mechanism for confirming to the user when they have applied enough force), to aid in application. These components could either be integrated directly into the MAP design or packaged separately (potentially as a reusable device). A delivery device could also be designed to function as the MAP's primary packaging, thus decreasing the overall packaging waste. Depending on the size of the delivery device, this could significantly increase the product's overall supply chain volume. This, however, must be evaluated in the context of the anticipated use case to determine its ultimate impact on the total cost of delivery. Examples of MAP indicators and applicators are shown in Figure 4.

Figure 4. MAP indicators and applicators.

(A)	(B)	(C)	(D)

(A) Georgia Tech MAP indicator (MAP with indicator mounted in plastic tray; foil overwrap not shown); (B) Vaxxas MAP applicator (integrated, stamped container providing physical, light, moisture, and gas packaging protection); (C) Corium MAP applicator; (D) Zosano MAP applicator (packaged separately from MAP).

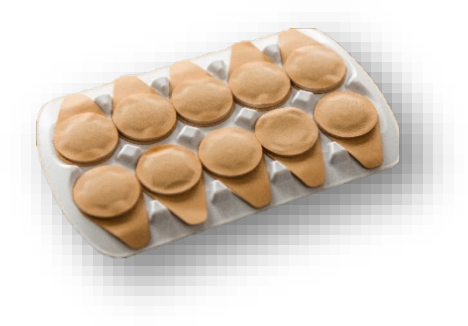
Abbreviation: MAP, microarray patch.

Multidose packaging

Multidose packaging (multiple MAPs within the same primary container) may be an option for some products, such as those intended for use in very high-throughput delivery scenarios (mass vaccination campaigns). An example of a multidose presentation is shown below in Figure 5. This packaging strategy can reduce the per-dose supply chain volume as well as the overall packaging waste, and may reduce cost of manufacturing. However, maintaining appropriate moisture and gas barriers, microbial protection,

and physical protection for the remaining MAPs once the packaging has been opened will be challenging; additional testing will be necessary to validate the duration of stability after opening under intended use conditions. The risk of wasting MAPs due to the inability to use all doses within the labeled time frame of the multidose container, and the risk of inadvertently delivering an ineffective or compromised MAP due to storage in an open primary container, must be weighed against the potential advantages of the multidose presentation.

Figure 5. An example of a multidose microarray patch packaging prototype.



Packaging design components

Labeling

Package labeling plays an important role in communication of information. A MAP's labeling should communicate the trade name, identity of the product, indications for use, dose volume, route of administration, lot number, the date of manufacture, expiration date, country of origin (where applicable), the manufacturer and their place of business and contact number, and the storage, transport, handling, and/or use conditions under which the product is to be stored and handled. For a separately packaged delivery device, the labeling must include the name of the compatible product, the date of manufacture, the manufacturer and place of business, whether the product is sterile, whether it is single use, as well as instructions and warnings. The specification of storage conditions should indicate limits for exposure to temperature, humidity, and light where appropriate, as these can alter the ability of the packaging to protect the product. USP chapter <7> describes these requirements in detail. Some dosage forms or articles have mandatory labeling statements that are described in the US CFR (e.g., 21 CFR 801, 21 CFR 201.320, and 21 CFR 369.21) and in the European Union Medical Device Regulation 2017/745.

Care should be taken to ensure that removing secondary packaging will not result in separating the product from key information, such as product identity or essential instructions for use. For this reason, if a packaging strategy allows the primary packaging to be separated from a common secondary package without compromising the primary packaging, the primary packaging should contain all the necessary labeling, as they are likely to be separated from the secondary packaging and product literature prior to use.

Materials selection

Packaging material plays a significant role in the product's protection as well as the compatibility of various sterilization methods dictated by the target level of microbial protection. If the sterility control approach (see below) determined for the packaging strategy is terminal sterilization (product subjected to a sterilization procedure after sealed in primary packaging), the selected material should be chosen in

compliance with ISO 11607-1 Packaging for Terminally Sterilized Medical Devices. Table 3 lists material categories usable in packaging for MAPs. For products packaged aseptically (packaged in a fully isolated environment to ensure sterility of product), the packaging is required to maintain sterility of the product.

Table 3. General categories of materials used in MAP packaging.

Medical-grade material category	Example(s)	Performance	Gas/moisture ingress protection	Most applicable sterilization methods
Bonded polymer filament	Tyvek	Polymer sheet made up of randomly laid HDPE fibers. Porosity allows for sterilization methods requiring permeability of packaging, while still maintaining an effective barrier to microorganisms. More resistant to tearing and punctures than paper but also more costly and requires moisture ingress protection.	Minimal	Dry heat, gas, irradiation
Polymer film/tray	Polyethylene (PE, HDPE, LDPE, PET, PETG); PP; polystyrene (PS, HIPS); vinyl	Polymers offer a large range of flexibility and opacities but typically are susceptible to moisture and gas permeation (some varieties are better than others).	Variable	Gas, irradiation (not appropriate with PP)
Low-permeability, polymer-based film	COC	Clear polymer that is stronger than PP or PE and a better moisture barrier. Noted to have low levels of extractables.	Moderate	Gas, irradiation
Aluminum	Aluminum alloys	Most reliable form of moisture, gas, and light ingress protection. Often augmented with other layers to allow for heat sealing and physical protection of the foil/sheet integrity.	Strong	Dry heat, gas, irradiation

Adapted from: Industrial Specialties Mfg. & IS MED Specialties website. Plastics sterilization compatibility page. https://www.industrialspec.com/resources/plastics-sterilization-compatibility/. Accessed December 14, 2020.

Abbreviations: COC, cyclic olefin copolymer; EVA, ethylene-vinyl acetate; HDPE, high-density polyethylene; HIPS, high-impact polystyrene; LDPE, low-density polyethylene; MAP, microarray patch; PE, polyethylene; PET, polyethylene terephthalate; PETG, polyethylene terephthalate glycol; PP, polypropylene; PS, polystyrene.

Desiccants

Desiccants are packaging materials that can help protect moisture-sensitive products, such as MAP microprojections, by absorbing water vapor contained in the packaged space. Desiccants can be used in conjunction with moisture-barrier packaging to ensure low moisture environments and thus allow MAPs with high moisture sensitivity to remain effective throughout their shelf life.

Desiccant materials may include silica gel, molecular sieve, activated carbon, calcium sulfate, calcium oxide, and clays. These materials can be contained within capsules, sachets, or embedded in the primary packaging film or within a layer of polymer laminate walls.[5] The parameters shown in Table 4 should be considered when selecting desiccant formats.

Table 4. Desiccant properties relevant to microarray patch.

Parameter	Effects
Target shelf life	Selected desiccant and packaging should allow product to reach target shelf life.
Headspace within packaging	Headspace volume—the unfilled volume in the sealed packaging—can contain moisture; increased headspace may require additional desiccant.
Packaging moisture barrier properties	Selection of more-impermeable packaging material may allow for reduction of desiccant.
Initial water content of drug product	If the drug product contains residual moisture, this may affect the relative humidity inside the packaging, and additional desiccant can be used to finish drying.
Minimizing relative humidity or maintaining initial relative humidity	Desiccants can be selected to minimize the relative humidity or can maintain a target relative humidity range to prevent drying out.

Packaging and desiccant systems should be tested in controlled temperature and humidity conditions to verify that the systems meet shelf-life requirements. Relevant standards include: USP Chapter <659> Packaging and Storage Requirements, USP Chapter <670> Containers—Auxiliary Packaging Components, USP Chapter <671> Containers—Performance Testing, and ISO 15378:2017 Primary Packaging Materials for Medicinal Products.

Depending on the active pharmaceutical ingredient (API), oxygen scavengers may be needed to maintain shelf life by rendering the internal space oxygen free. Like some desiccant formats, oxygen scavengers are typically contained within a sachet and usually are comprised of iron powder and sodium chloride. Oxygen scavengers work best in conjunction with packaging that has low oxygen permeability. During packaging design and testing, oxygen scavenger considerations include packaging headspace, packaging gas permeation, and leakage through the packaging closure or defects. Other effects of oxygen scavengers include off-gassing and slight odors.[6]

Adhesives and heat seals

Adhesives can be used to close openings in the packaging materials, allowing for the filling of large gaps, bonding dissimilar materials, and forming a hermetic seal. As with desiccants, packaging adhesive selection is dependent on environmental considerations, shelf life, packaging materials, packaging geometry, sterilization method, biocompatibility, and user requirements.

Adhesive options with low permeability include acrylic polymers, cyanoacrylates, vinyl acetate/vinyl chloride copolymers, and polyvinylidene chloride. These options can have differing viscosities, cure times (often light-curable), strength properties (dependent on bonding substrates), and temperature resistances.

As an alternative to using adhesives, heat sealing forms a sterile closure by welding one or more thermoplastics together. Common medical device packaging applications are sealing foils or films to thermoformed plastic trays. As with adhesives application, factors in heat sealing include temperature, dwell time, pressure, material choice, and sealing system technology (such as impulse, ultrasonic, radio frequency, etc.). Care must be taken to ensure the heat does not adversely affect the MAP's APIs.

Applicable test categories include performance, stability, integrity, seal strength, and biocompatibility. The relevant tests are governed by standards shown in Table 5. Typical seal strength requirements allow intended users to peel open the packaging while still providing enough resistance to maintain sterility and barrier properties, and preventing tampering or children from accessing the contents.

Table 5. Package seal tests.

Test category	Tests	Applicable standards
Performance	Vibration and drop testing, compression testing, climate conditioning, concentrated impact testing, bridge impact testing, altitude testing	ASTM D4169, ASTM D880, ASTM D5265, ASTM D6344, ISO 4180, ISO 12048, ISTA 3A
Stability	Aging	ASTM F1980
Integrity	Dye penetration, bubble leak	ASTM F1929, ASTM F3039, ASTM D3078, ASTM F2096
Seal strength	Peel test, seal width measurement	ASTM F88
Biocompatibility	In vitro cytotoxicity, sensitization, irritation/intracutaneous reactivity, pyrogenicity, genotoxicity, systemic toxicity	USP Class VI, ISO 10993

Abbreviations: ASTM, ASTM International; ISO, International Organization for Standardization; ISTA, International Safe Transit Association; USP, United States Pharmacopeia.

Relevant failure modes categories include the following:[7]

- Adhesive failure between the substrate and the adhesive typically due to lack of surface preparation.
- Cohesive failure within the adhesive, which can be caused by increased adhesive thickness, insufficient bonding time, or lack of curing light penetration.
- Structural failure within the substrate near the bond, which is instigated by stress concentrations in the bond proximity, resulting in seal creep, wrinkles, and channeling.

Packaging process

Packaging assembly

The packaging assembly approach depends on the selected packaging materials, sterilization methods, and quantity of devices within the secondary packaging. Polymer, foil, or coated paper rolls can be used for web-based assembly, and more rigid plastics and foils can be used for tray-based assembly with a flexible lidding. If the MAP or integrated delivery device has a structural feature to mechanically protect the MAP microprojections, a film-based overwrap could be acceptable; otherwise, a tray will likely be needed.

Web material is typically provided on rolls and is formed, die-cut, and sealed via automation. Sealing parameters need to balance seal strength and integrity with ease of opening. Trays are either formed inline from sheet or roll material or introduced into the assembly line as preformed products. Tray designs need to take into account desired clarity, impact resistance, ability to stack and de-nest trays, snap features that secure the product, and finger holes for product removal. Considerations for processing line development include that materials entering the packaging line will have to be aseptically handled and in a format compatible for throughput optimization.

Sterility control

Ensuring an acceptable low-bioburden environment within the primary packaging requires both a low particulate presence and low biological contamination. To ensure a low particulate presence, primary package assembly should take place in a clean-room environment. Currently, skin patches intended for transdermal delivery are packaged in a class 8 clean room, which is defined by the number and size of

particles allowable in the space by ISO 14644-1 Cleanrooms and Associated Controlled Environments—Part 1: Classification of Air Cleanliness by Particle Concentration and ISO 14644-2 Part 2: Specifications for Testing and Monitoring to Prove Continued Compliance With ISO 14644-1. Therefore, it is anticipated that a MAP will require, at a minimum, the same level of controls. If feasible, based on the API, a MAP should be terminally sterilized. There are several terminal sterilization techniques available for use with medical devices, but only a few are appropriate for MAPs due to their potential susceptibility to moisture and heat and possible negative effects on the API. These techniques are outlined in Table 6.

Table 6. Comparison of select sterilization methods described in USP 36 <1229>.

Sterilization method	Agent(s) and parameters	Typical application(s)	Benefits	Limitations
Irradiation	Gamma (typical), electron beam, X-rays, microwaves, visible light	Non-porous packaged devices	Faster than other methods. Does not require biological indicators due to the accuracy of dose measurement and correlation to microbial destruction.	Known to affect the physical characteristics of polymers and can cause them to yellow. Validation required to prove irradiation sufficiently penetrates packaging.
Gas sterilization (by direct contact)	EtO, ozone, chlorine dioxide, hydrogen peroxide	Polymers, non-pressure-rated equipment, type I glass syringe barrels (BD Hypak SCF™)	Good for sterilizing temperature-, pressure-, or moisture-sensitive materials and equipment.	Toxic residuals; long cycle time; high cost; penetration; nature and quantity of packaging materials can significantly affect the process. EU GMP notes method as last resort. Requires porosity in packaging to allow for direct contact with product.

Adapted from: Singer DC, Agalloco J. *Stay Ahead of the Curve—An Update on Sterility Assurance Topics in the USP*. Burlington, MA: Institute of Validation Technology Network; January 10, 2013. https://www.ivtnetwork.com/article/stay-ahead-curve%E2%80%94-update-sterility-assurance-topics-usp#.

Abbreviations: EtO, ethylene oxide; EU, European Union; GMP, Good Manufacturing Practice.

BD Hypak SCF is a trademark of Becton, Dickinson and Company.

Dry heat and steam sterilization require temperatures exceeding 120°C. Thus, due to the typical temperature and moisture sensitivity of MAPs, these methods are not recommended. Additionally, if the MAP's packaging must provide ingress protection from gas or moisture, then permeation-based gas sterilization techniques will not be appropriate. An integrated packaging configuration has more restrictive sterilization requirements, as the process must be applicable to both the MAP and the delivery device. A separate packaging configuration could allow for more flexibility in sterilization methods, as each unit will have its own primary package and can be processed separately. For a separately packaged applicator, porosity-based gas sterilization methods are only appropriate for the delivery device if its design allows for gas penetration to all internal surfaces. Inclusion of secondary packaging in the sterilization process can reduce post-sterilization packaging steps but may further reduce the number of applicable sterilization methods (e.g., ethylene oxide can be impeded by cardboard-based secondary packaging).

Aseptic processing

If terminal sterilization methods could potentially damage the API, device, or packaging, aseptic processing may be necessary depending on the sterility requirements defined by the manufacturer's target product profile. In this situation, the MAP device and packaging components are sterilized prior to

microneedle coating or molding, drying processes, and sealing of the primary container. These steps are performed in an environment designed to minimize the risk of microbial and nonviable particulate contamination.

Considerations for aseptic processing include sterilization methods for the MAP and packaging components and their effects on material selection; clean-room design and maintenance; air quality maintenance; environment monitoring; automation; material transfer systems and material flow; and personnel training and evaluations. Mock-up studies and risk assessments can provide crucial feedback in the system design and protocol generation. If raw materials, such as aluminum rolls (for forming or die-cutting), are introduced into the aseptic system, the materials need to be sterilized and double-bagged. Novel aseptic production and packaging systems can take years to develop and validate.

Material handling, including that of packaging materials, by personnel can be a major source of contamination. Machine encapsulation systems (i.e., isolators and restricted access barrier systems [RABS]), can address this issue. Isolators are fully sealed, allowing for manipulation via glove ports, half-suits, and/or automation. While isolators are fully sealed, over-pressurized during operation, and have automated decontamination systems, RABS can be opened for process intervention, have more operational flexibility, and usually need manual decontamination. Gowning and environmental monitoring costs are higher for RABS than for isolator systems since RABS operation requires an ISO 5 environment and isolators need ISO 8. A RABS is often used when a clean room is already available and does not need to be considered for the calculation of the investment.

Packaging design usability and programmatic fit

Usability

Human factors and usability should be considered in packaging design. As per ISO 62366 Application of Usability Engineering to Medical Devices and ANSI/AAMI HE75 Human Factors Engineering—Design of Medical Devices, user interactions include transport, storage, installation, operation, and disposal. Furthermore, these activities need to be viewed in context of the MAP's likely scenarios of use. For example, vaccine campaigns may require rapid administrations by a medical provider within a short period of time, whereas for other applications, the device may be self-administered by a user at home.

To aid design decisions, failure modes and effects analysis (known as FMEA) as well as simulated use testing, should be carried out with the MAPs and its packaging. These user studies should include actual stakeholders to gauge usability and acceptability. Individual packaging components should inherently guide the user workflow and prevent user errors (i.e., a tray underneath the MAP should include features to discourage premature contact with the microprojections).

As MAP devices are a new technology, to aid in correct use, warnings, instructions, and other indicia should be included in the packaging (e.g., printed on inserts, lidding films, and/or cartons). Such instructions and labels should be written in consideration of the intended audience. For some use cases, it may be preferable for instructions or labels to be attached to the applicator or indicator itself, in which case, wraparound or folded labels are possible solutions. Graphical, instead of written, instructions may be advantageous for ensuring users with low literacy are successful in using a MAP product.

Packaging should allow for ease of opening; enable ergonomic handling (especially for intended users that may be older and/or have disabilities); and prevent tampering, reuse, and child misuse. Examples of such features include tamper-evident labels or seals, tear notches, disposal directions, and minimum and maximum seal strengths.

Programmatic

Several programmatic implications have been identified that will be important to the packaging design of a MAP. All stakeholders—including distributors, vendors, medical professionals, and patients—interact with the MAP and its packaging in different ways, including storage, sale displays, administration, and disposal. MAP developers should consult stakeholders for packaging requirements and feedback. Some questions include:

- Do these stakeholders accept the device and packaging in these interactions?
- What are the cultural perceptions of the device and packaging—are the materials perceived as appropriate for a medical device or as cheap and unreliable?
- Can the packaging be easily stored in bulk with traditional logistics and stock management systems?
- Can users access barcodes and labels on the packaging for traceability?
- Are packaging components sufficiently labelled for choking or suffocation hazards?

MAP development efforts should explore these questions with interviews to understand stakeholder perceptions throughout the packaging design process.

Environmental impacts

Disposal methods for uncontaminated packaging include recycling, landfill, incineration, and pit burning—with pit burning being the most common method in low-resource settings. Materials that contain chlorine, such as polyvinyl chloride, are not recommended for incineration because they release toxic dioxins and furans into the environment, which can cause adverse health effects.[8] Therefore, it is recommended that packaging materials be selected that will mitigate the production of these gasses.

Clinics that do not have access to incinerators or pit burning locations are likely to manage waste disposal via burial. Secondary and tertiary packaging that biodegrades over time (i.e., not foil and most plastics) and has a low volume will decrease the required waste stream capacity, personnel, and infrastructure (utilities, fuel, maintenance, etc.) required for disposal.[9] However, the use of foil may be necessary due to its barrier properties. Thus, MAP developers should weigh competing design drivers carefully and solicit country feedback on packaging. Recycling individual components as segregated waste may be a sustainable option. Volume of waste should be kept to a minimum. For secondary packaging, packing density should also be optimized to lower perceived wastefulness.

Packaging design (with necessary instructions) may be selected to provide used, contaminated MAP products a storage container after use and before disposal in a biohazard container or incinerator.

Supply chain

A product's impact on the supply chain is determined by its total storage volume and weight, as well as the complexity of shipping requirements. For MAP products requiring cold chain storage, the packaging will have an increased impact on the supply chain cost. Additionally, separate packaging of a MAP and its applicator device will increase logistical challenges and the risk of mismatch of supplies at the point of use. An integrated packaging configuration for the MAP and its indicator or applicator could result in less total volume per device and simplified procurement logistics. However, if the formulation must be stored in the cold chain, the size of the integrated applicator or indicator is an important consideration.

Packaging cost considerations

Two key components of packaging production cost are the packaging materials and the degree of packaging automation and labor required. Their relative contribution to the final cost depends on the production volume.

Packaging material can either be sourced as lower-cost, film-based stock material (such as foil, etc.) that is incorporated into the final packaging during an automated packaging procedure, or as higher-cost, preformed packaging (such as premade pouches or thermoformed trays) that typically require off-site production and transportation to the final packaging location. Highly automated packaging processes, although a more costly initial investment, have lower labor costs and more reliable manufacturing, leading to a lower total packaging cost per unit for high production rates.

The choice of packaging type ultimately determines the ease of automation. Pouch-based packaging is well suited for all degrees of automation, as premade pouches can be used in a manual process to avoid the capital investment required for a fully automated packaging line, but can easily be scaled to higher levels of automation to achieve low-cost, high-volume production. If, however, trays are necessary to provide additional physical protection of the product, achieving automation would be more costly, as this is a more logistically complex packaging operation due to material handling.

Recommendations

Below is a summary of recommended packaging practices for categories covered in this report.

Packaging configurations/types

- An integrated MAP delivery device can reduce packaging waste and lessen requirements for further packaging.

Materials selection

- Due to the high moisture sensitivity of MAPs, low-permeability polymer-based films and aluminum foils, films, or sheets are recommended for their barrier properties.

Desiccants

- The target API dictates the packaging requirements. If the manufacturing process and/or selected packaging system does not provide sufficient moisture control, desiccants may be needed.

Adhesives and heat seals

- Typical seal strength requirements allow intended users to peel open the packaging while still providing enough resistance to maintain sterility and barrier properties, and preventing tampering or children from accessing the contents.
- Care must be taken to ensure any off-gas and/or heat does not adversely affect the MAP’s active pharmaceutical ingredients.

Packaging assembly

- For MAP products anticipating high-volume production, packaging solutions that are easily scalable, such as web-based designs, should be prioritized.

Sterility control

- Device requirements should determine the appropriate level of microbial protection.
- Sterility control planning is a priority during early development, as it affects material selection and packaging assembly.
- Early assessment of the anticipated sterilization method should be conducted to ensure stability of a MAP is not compromised.
- For terminal sterilization, irradiation is likely to be the most compatible sterilization method for MAP packaging configurations.
- If deemed necessary, the full development and validation of aseptic processing systems can take years.

Usability

- Failure modes and effects analysis, as well as simulated use testing, should be carried out with the MAPs and its packaging to aid in design decisions throughout development.

Programmatic

- For packaging requirements gathering and feedback, MAP developers should consult stakeholders—from distributors and vendors, to medical professionals and patients.

Environmental impacts

- A MAP design that requires a minimal volume of packaging—preferably of recyclable material—while still providing suitable levels of protection, would have the lowest environmental impact.

Supply chain

- Overall package volume should be minimized for shipping and cold chain storage, without compromising usability and programmatic acceptability.

Packaging cost

- Automating packaging can lower per unit cost and better maintain sterility.
- Easily automatable packaging configurations should be selected if high production volumes are expected.
- A delivery device integrated as the primary packaging for the MAP may be preferable for physical protection, as preformed trays increase cost and waste.

Conclusions

For pharmaceutical products, packaging plays a large role in maintaining the product performance over its intended shelf life. Early consideration and testing of a product's packaging system contributes to ensuring compatibility with the final product. To inform system design decisions that affect packaging selection, the various packaging configurations for a MAP delivery system should be considered according to their impact on product considerations, such as manufacturing complexity, programmatic acceptability, and environmental impact.

References

[1] World Health Organization (WHO). *Annex 9: Guidelines on Packaging for Pharmaceutical Products*. Geneva: WHO; 2002. Technical Report Series, No. 902. https://digicollections.net/medicinedocs/#d/s19638en.

[2] United States Food and Drug Administration (USFDA). *Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics*. Silver Springs, MD: USFDA; 1999. https://www.fda.gov/downloads/drugs/guidances/ucm070551.pdf.

[3] Microneedle Array Patch Regulatory Working Group website. https://www.microneedleregulatory.org/. Accessed December 14, 2020.

[4] Microneedle Array Patch Regulatory Working Group website. Critical quality attributes page. https://www.microneedleregulatory.org/critical-quality-attributes-cqas.html. Accessed December 14, 2020.

[5] Williams D. *Choosing in-wall desiccants for solid tablets and capsules.* TricorBraun website. Thought leadership page. https://www.tricorbraun.com/insights/thought-leadership/choosing-in-wall-desiccants-for-solid-tablets-and-capsules/. Accessed December 14, 2020.

[6] Mitsubishi Gas Chemical America, Inc. *Pharmaceutical Stability Products*. New York, NY: Mitsubishi Gas Chemical America; n.d. http://ageless.mgc-a.com/Pharmaceutical%20Stability%20Products%20Catalog.pdf.

[7] Müller N. *Medical device adhesives: specifications and failure modes. Medical Product Outsourcing*. November 2, 2017. https://www.mpo-mag.com/contents/view_online-exclusives/2017-11-02/medical-device-adhesives-specifications-and-failure-modes/

[8] Emmanuel J, McRae G, Mahmoudi F. *Environmentally Responsible Management of Health Care Waste with a Focus on Immunization Waste.* Washington, DC: Health Care Without Harm; 2002. http://www.bvsde.paho.org/bvsacd/cd48/reponsible.pdf.

[9] World Health Organization (WHO). *Safe Management of Wastes from Health-Care Activities*. 2nd ed. Geneva: WHO; 2014. https://www.who.int/water_sanitation_health/publications/safe-management-of-wastes-from-healthcare-activities/en/.