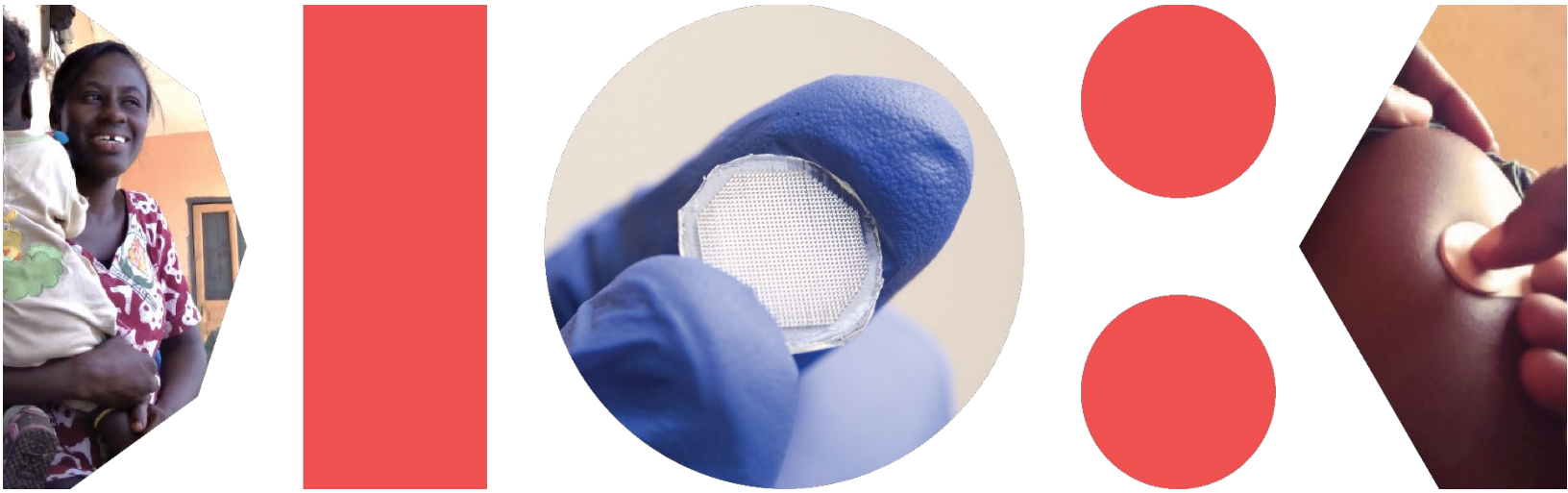
Advancing Long-Acting Levonorgestrel Microneedle Array Patches

Early Regulatory Insights to Guide Development



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Abbreviations

API	active pharmaceutical ingredient
AUC	area under the concentration-time curve
BMI	body mass index
BMD	bone mineral density
C_{max}	maximum observed serum concentration
C_{min}	minimum observed serum concentration
CQA	critical quality attribute
DMPA-IM	depot medroxyprogesterone acetate, intramuscular
DMPA-SC	depot medroxyprogesterone acetate, subcutaneous
EMA	European Medicines Agency
FIH	first-in-human
GLP	Good Laboratory Practice
HPLC-MS	high-performance liquid chromatography-mass spectrometry
ICH	International Council for Harmonisation
ISO	International Organization for Standardization
IUD	intrauterine device
IV	intravenous
LNG	levonorgestrel
MAP	microneedle array patch
MN	microneedle
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic
PLA	polylactic acid
PLGA	poly(lactic-co-glycolic acid)
RH	relative humidity
UK MHRA	United Kingdom Medicines and Healthcare products Regulatory Agency
US FDA	United States Food and Drug Administration
USP	United States Pharmacopeia

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1. Executive summary

Additional contraceptive options are needed to expand the availability, accessibility, and acceptability of long-acting contraception globally. Microneedle array patches (MAPs) are a novel drug delivery system with the potential to help address this need, and the Gates Foundation has funded several developers to advance their programs for levonorgestrel (LNG)-containing MAPs for long-acting contraception.

Regulatory guidance applicable to this novel delivery system is limited, and no drug-containing MAPs have been granted marketing authorization to date in any health area. To support the timely and streamlined development of long-acting LNG MAPs in the absence of regulatory precedent, PATH sought product-agnostic regulatory scientific advice from agencies recognized as operating at an advanced level of performance: the European Medicines Agency, the United Kingdom Medicines and Healthcare products Regulatory Agency, and the United States Food and Drug Administration.[1]

The scientific advice requests focused on specific chemistry, manufacturing, and controls topics, as well as nonclinical and clinical considerations for first-in-human (FIH) studies. This white paper summarizes the scientific advice received from the agencies and contextualizes its implications for advancing LNG MAP development. Key regulatory findings by topic area are as follows:

Product quality development

- Regulator feedback on microbial specifications suggested that a sterile product would reduce regulatory risk for late-stage development and emphasized the importance of a data-driven rationale to justify nonsterile specifications.
- Across agencies, there was broad agreement that MAP critical quality attributes should support demonstration of product quality, safety, stability, and manufacturing consistency throughout development.

Nonclinical program

- Regulatory agencies generally considered the proposed nonclinical program, including a non-Good Laboratory Practice (GLP) pharmacokinetic (PK) study and abbreviated GLP toxicology study in minipigs, to be adequate to support FIH studies, while recommending additional considerations aligned with the intended duration of use (e.g., the duration of the toxicology study).
- The agencies were supportive of the proposed strategy in which select aspects of biocompatibility testing, consistent with International Organization for Standardization (ISO) 10993, would be conducted prior to the FIH study, with the remainder deferred until later in product development.

Clinical program

- Regulators agreed that the proposed FIH study objectives of safety, tolerability, and pharmacokinetics were appropriate, while noting that study design considerations may evolve as the product design and key scientific questions are refined.
- Inclusion of appropriate control groups (e.g., placebo MAP), when feasible, was encouraged to support the interpretation of safety and tolerability findings.

Reference product

- Regulators highlighted the importance of early alignment on the regulatory strategy for reference products and potential bridging approaches.

Disclaimer: The perspectives presented in this white paper are nonbinding and reflect the views of individual regulators. They do not represent the official positions of any consulted agencies.

2. Background and introduction

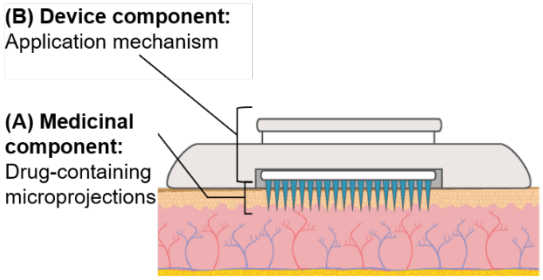
Although access to contraception and the range of available contraceptive options have expanded in recent decades, an estimated 164 million individuals globally still had an unmet need for contraception in 2021.[2] Unmet need is driven by a variety of factors; however, for some individuals, available and accessible contraceptive methods may not adequately align with their preferences, circumstances, or health needs.[3] As such, expanding the contraceptive method mix through the development of novel technologies has the potential to reduce unmet need. Levonorgestrel (LNG)-containing microneedle array patches (MAPs) represent one such long-acting contraceptive method currently in development.

MAPs are a novel delivery system in preclinical and clinical development for human therapeutic and prophylactic use. Long-acting contraceptive MAPs, specifically LNG-containing MAPs, are in early phases of development and have the potential to help address a global unmet need for contraception. However, regulatory guidance applicable to MAPs is limited, and currently, no drug-containing MAPs have been granted marketing authorization for any health area. To support the development of long-acting contraceptive MAPs in the absence of regulatory precedent, PATH, a global health nonprofit organization, received funding from the Gates Foundation, to seek product-agnostic advice from regulators ahead of first-in-human (FIH) studies. PATH sought scientific advice from three regulatory agencies—European Medicines Agency (EMA), United Kingdom Medicines and Healthcare products Regulatory Agency (UK MHRA), and the United States Food and Drug Administration (US FDA)—on product quality considerations for LNG MAPs, as well as nonclinical and clinical aspects relevant to FIH studies. This white paper summarizes the feedback from the agencies' regulatory experts and highlights key considerations for developers advancing LNG MAP products toward clinical trials in support of future marketing authorization applications.

Regulatory agencies were approached for scientific advice based on predefined selection criteria, including regulatory jurisdiction with respect to contraceptive MAP developers, the agency's maturity level, the timeline for the provision of scientific advice and fees, and available information on whether a product-agnostic guidance approach would be accepted by the agency. Based on their ranking across all key criteria, the following regulators and scientific advice pathways were selected: the Innovation Task Force (ITF) for EMA, scientific advice for UK MHRA, and the Critical Path Innovation Meeting (CPIM) for the US FDA. For the US FDA, the CPIM request was rerouted to a Type C meeting after internal US FDA discussions.

Scientific advice was received from the three regulatory agencies between February 3 and April 27, 2026, through either virtual meetings (EMA ITF) or written responses (UK MHRA and US FDA). The consultations were intentionally positioned as product-agnostic and designed to generate regulatory insights applicable across all LNG MAP developers, regardless of the specific composition or characteristics of individual products. Consistent with this objective, the scope of the consultations was limited to the medicinal component of the dissolving MAP platform delivering LNG over six months and did not include the device or application mechanism (Figure 1). Nevertheless, since LNG MAPs are drug-device combination products, developers must also consider the regulatory framework for their device components in the jurisdictions where they intend to develop and market their products. Therefore, as part of future product-specific scientific advice meetings, developers should seek device-specific regulatory advice, as appropriate, during development.

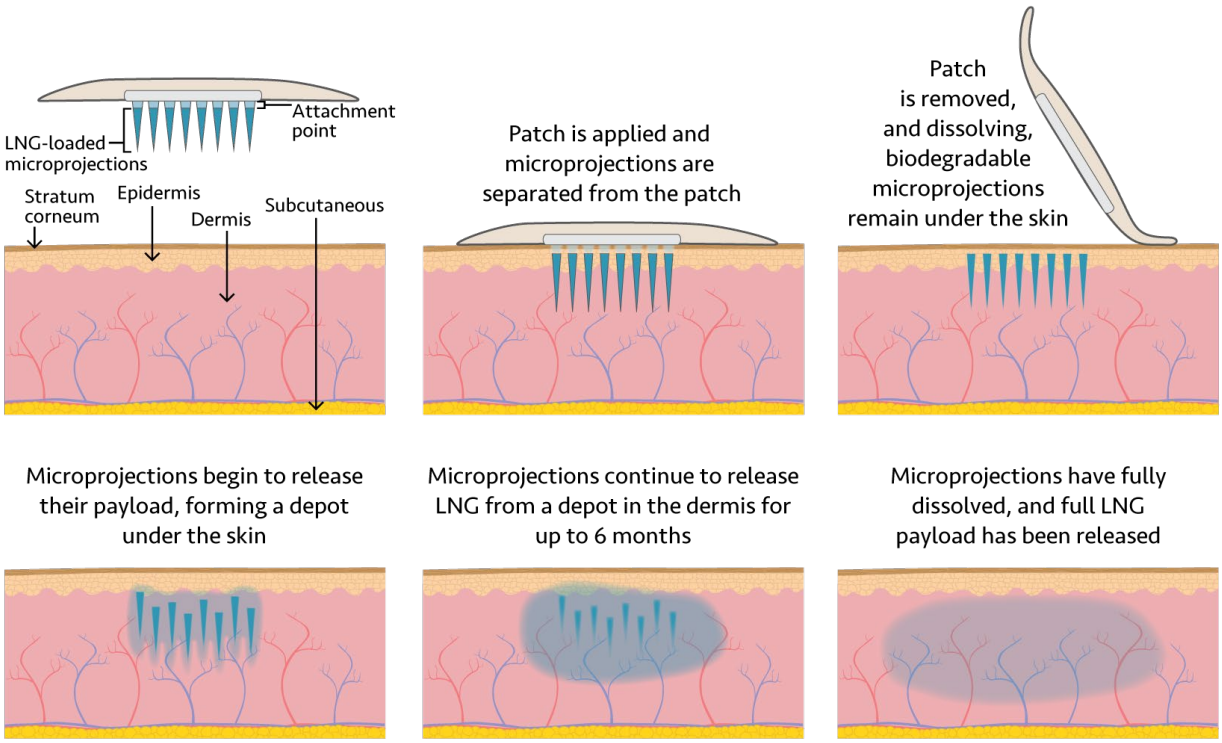
Figure 1. Drug and device components of a single-entity MAP combination product.



Dissolvable MAP-based integrated/single-entity drug-device combination products include (A) an array of microprojections (microneedles) with the active pharmaceutical ingredient (API) incorporated into the microprojections and (B) an application mechanism to apply the microprojections to the skin (e.g., patch backing, indicator, applicator). The patch backing is integrated with the drug component (i.e., single entity).

The LNG MAPs within the scope of this consultation were dissolving/biodegradable microprojections approximately 600 to 1,500 µm in length that encapsulate LNG. An illustration of the expected mechanism of action for long-acting dissolvable LNG MAPs was shared with the regulatory experts for reference (Figure 2).

Figure 2. Overview of levonorgestrel microneedle array patch administration.



Note: The figure represents a generic LNG MAP with a patch backing (i.e., no applicator or indicator), focusing on the release of LNG from the dissolving/biodegradable microprojections.

The target product profile (TPP)[4] also informed the development of the regulator briefing packages. It emphasizes a long-acting, user-centered contraceptive option designed to address key access and adherence barriers. Core attributes include sustained contraceptive efficacy for six months, a pharmacokinetic (PK) profile that maintains LNG concentrations above the threshold for pregnancy prevention, and a safety profile consistent with established LNG products. The product is intended to be simple, discreet, and suitable for self-administration, with strong usability across diverse populations. From a programmatic perspective, priorities include room-temperature stability, extended shelf life, and cost-effective manufacturing to support scalability in low- and middle-income settings. Other factors outlined in the TPP that will be critical to LNG MAP development and future adoption include that the product be (1) easy to use following minimal training and (2) provide reliable and consistent delivery of LNG. A summary of key LNG MAP product attributes is shown in Table 1.

Table 1. Key LNG MAP product attributes outlined by the Gates Foundation target product profile.

Attribute	Description
Target population	Individuals assigned female at birth seeking longer-term protection against unintended pregnancy, including nulliparous individuals.
Intended use	Prevention of pregnancy.
Duration of protection	6 months.
MAP type	Dissolving, fully biodegradable microprojections that encapsulate LNG.
Application	Applied manually (patch backing only) or using an applicator. The patch backing is integrated with the drug component (i.e., a single entity).
Disposal	Non-sharps waste disposal.
Preparation	No preparation required; ready for administration as soon as the packaging is opened.
Thermostability	No cold chain required; stable for 36 months at 30°C/75% RH; stable for at least 24 hours at 60°C/75% RH.
User groups	Suitable for administration by a health worker or for self-administration following minimal training.
Wear time	The MAP remains on the skin until the microprojections have separated from the patch backing (e.g., a few seconds to less than one hour). Afterward, the patch is removed, and the dissolving/biodegradable microprojections remain in the epidermis and/or dermis.
Efficacy	Similar (non-inferior) to available long-acting progestin-only contraceptive methods (including contraceptive implants). The 99% efficacy stated is based on hormonal contraceptive products conventionally used in the target populations (e.g., contraceptive implants including Jadelle ®, DMPA-IM, DMPA-SC) under perfect use, and can be implied by a number of biomarkers, with the following possible hormonal contraceptive PK targets as reference: • LNG from Jadelle: 280–440 pg/mL. • 30 µg/day dose based on steady state of LNG implant. • 4:1 peak: trough max peak 120µg/day (optimistic). • Min trough 25 µg/day (based on LNG implants).
Safety	Similar (non-inferior) safety profile to the Jadelle LNG subdermal implant.
Removability	Not removable or reversible during the labeled duration of action.

Abbreviations: DMPA-IM, depot-medroxyprogesterone acetate intramuscular; DMPA-SC, depot-medroxyprogesterone acetate subcutaneous; LNG, levonorgestrel; PK, pharmacokinetic; RH, relative humidity.

Note: This table reflects key attributes outlined in the Gates Foundation iTPP (V1.1, 02 Jan 2025), which are expected to be refined as LNG MAP development progresses. The attribute descriptions were not modified based on the regulatory feedback summarized in this white paper. While the delivery mechanism differs from that of the LNG MAP, the Jadelle subdermal implant is a long-acting progestin-only contraceptive product containing LNG that may serve as a relevant benchmark for target systemic LNG exposure, PK targets, duration of contraceptive efficacy, and overall product performance.

Outcomes from the scientific advice consultations are summarized below. Results are organized by topic area (product quality development, nonclinical program, clinical program) and include the positions presented to regulators, a comparison of feedback received from the three agencies, and PATH's recommendations to developers. The scientific advice received is nonbinding, and the opinions are those of the experts and do not reflect the official positions of the agencies. The opinions shared are based on the product-agnostic information presented and may evolve as regulators are approached with specific product details and/or as new data emerge from similar products in development. As such, this guidance does not replace the need for product-specific regulatory consultations for individual LNG MAP development programs.

3. Product quality development

3.1. Microbial specifications

The position presented to regulators is summarized below.

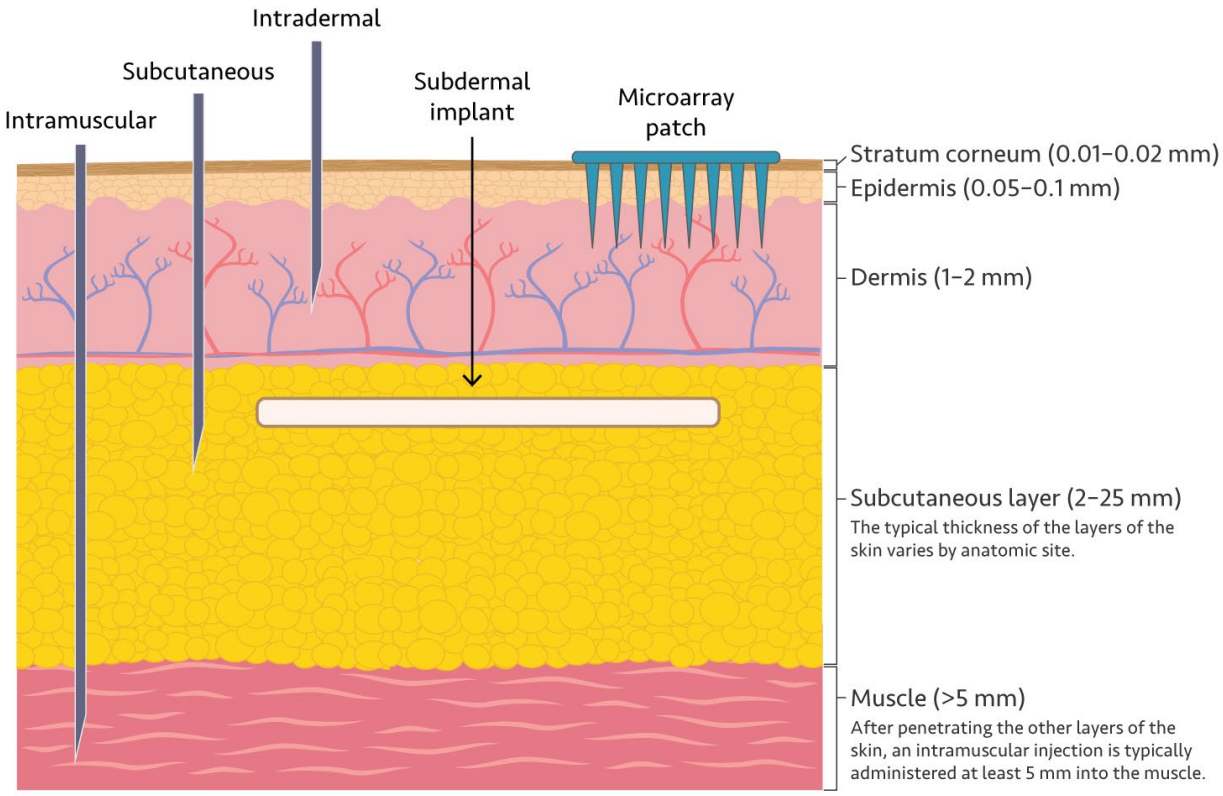
Microbial specifications (i.e., whether the product should be sterile or non-sterile) are broadly applicable across MAP products and are primarily relevant to commercial product specifications rather than those required for FIH studies. For early-stage clinical trials, regulators have generally accepted non-sterile products when supported by appropriate risk-based controls. Clinical studies of MAPs delivering vaccines and therapeutics have included both sterile and non-sterile products, with non-sterile microbial limits ranging from 10 to 1,000 colony-forming units per MAP for total aerobic microbial count and total yeast and mold count, with the absence of specified organisms.[5,6]

While current clinical trial experience with MAPs for drugs and vaccines suggests that non-sterile products may be acceptable in early development,[5] regulatory agencies have not formally endorsed non-sterile approaches for commercial manufacturing. Existing regulatory guidance[7,8,9] relevant to MAP manufacturing supports a risk-based decision-making framework and allows for consideration of non-sterile production. However, requiring sterility without a clear risk-based justification may introduce unnecessary manufacturing complexity and could limit the availability of MAP-based products for critical medicines, such as contraception.

A key feature of the MAP dosage form is its “ability to mechanically disrupt the outermost nonliving skin barrier, the stratum corneum, to facilitate passage of an API to the viable epidermis and/or dermis.”[10,11] The depth of penetration for MAPs is designed to be shallow enough to avoid the nerves and blood vessels present within the dermis. The epidermis and top layers of the dermis have not previously been deliberately targeted for therapeutic use, and thus, there are no clear clinical data beyond those generated in MAP clinical trials. The US FDA defines a transdermal delivery system as intended “to deliver an active ingredient (drug substance) across the skin and into systemic circulation.”[12] Percutaneous delivery is defined by the US FDA as “administration through the skin.”[13] Although LNG MAPs use microprojections to penetrate the skin rather than relying purely on diffusion, the API is delivered along the microprojection shaft and subsequently diffuses within the living layers of the skin. As a result, the microbiological risk profile may be more similar to that of a transdermal patch than an intradermal injection or a subdermal implant (i.e., the Jadelle subdermal implant, which breaches into the subcutaneous space).

The target tissue depth of MAPs is distinct from that of parenteral products, which deliver drugs into deeper sterile tissue sites such as the dermis, subcutaneous tissue, or muscle (Figure 3). The targeted area of MAPs contains resident microbes within segregated structures (e.g., follicles, sweat glands) that exist in homeostasis in this part of the skin in healthy individuals.[14] Thus, MAPs sit in a gray area with no defined standards or guidelines based on the route of administration, depth of skin penetration, and delivery mechanism.

Figure 3. Depth of penetration for common routes of administration compared with MAPs.



Note: This graphic illustrates how the depth of penetration differs among common routes of administration. However, the graphic is not to scale.

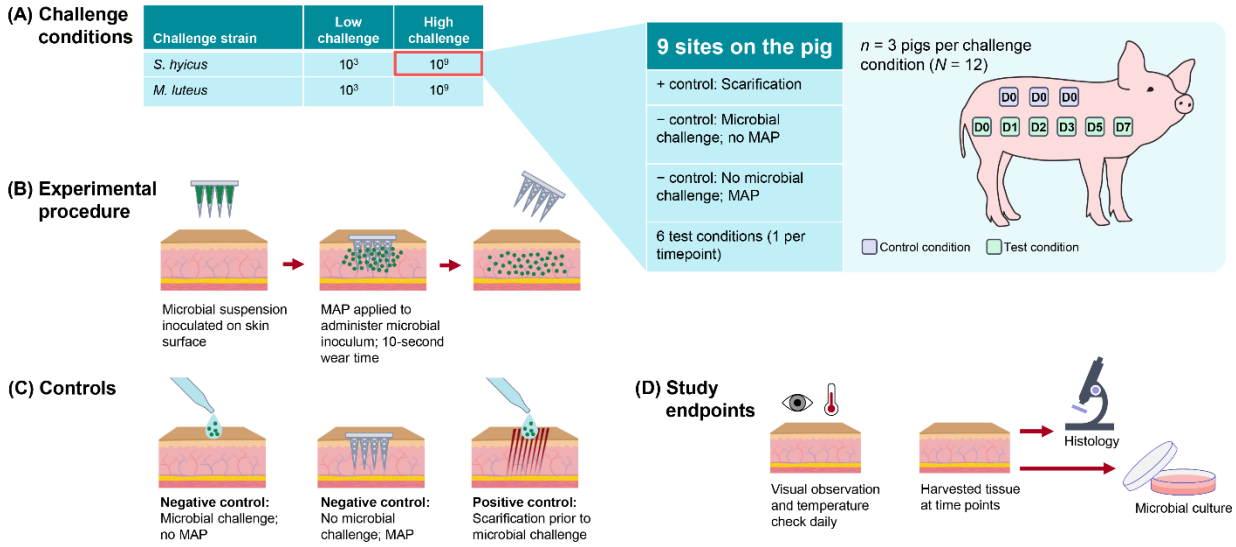
The current body of scientific knowledge lacks systematic, well-controlled studies that assess the risk of infection at specific locations within the skin. Additional research is needed to better understand the potential risk of infection and to inform the development of appropriate microbiological specifications for MAPs. In this context, a nonclinical approach was proposed to regulators to assess whether the proposed model and experimental designs could generate data sufficient to support the feasibility of non-sterile MAP manufacturing.

3.1.1. In vivo study to understand the microbiological risk of MAPs

The goal of the proposed study (Figure 4) is to validate that the animal model can detect microbiological risks associated with MAP use. As the microbiological risk of infection is predicted to be independent of most active agents, the intention is to study 3D-printed MAPs devoid of any active ingredients that can deliver a liquid bacterial suspension to allow adequate assessment of a penetration depth of 750 µm. A porcine system will be utilized, as evidence supports that pig skin most closely models human skin characteristics and immunological state.[15] The study will use a non-sterile MAP containing a predefined bioburden to apply a bacterial suspension at a depth of 750 µm to the back of pigs to represent the risk of topical contamination during MAP application. These studies will initially be conducted under worst-case conditions to demonstrate that the proposed animal model can detect infection if present. Subsequent studies would then be designed to evaluate MAP characteristics that might be associated with the risk of infection.

Based on the initial results, secondary studies are expected to investigate how other parameters (e.g., projection density, projection length, wear time) impact the associated microbial risk. The goal of the secondary studies will be to identify the boundaries for MAP characteristics that are associated with microbial risk. For example, using the model established in the first study, investigations into the impact of projection length could be conducted to elucidate the impact of length and specify the maximum length that would be appropriate for a non-sterile specification. The design of the secondary studies will be informed by the results of the proposed study and the characteristics of a specific drug- or vaccine-containing MAP combination product.

Figure 4. Experimental design of the proposed study to generate supporting data to determine whether MAPs could be manufactured as non-sterile.



Note: The pilot study experimental procedures are shown here. (A) There will be four unique challenge conditions based on challenge strain and challenge level. Each challenge condition, as shown in each cell of the table in panel (A), will be evaluated in three pigs, and each pig will be assessed over seven days. Each pig will have six test areas (one per time point) and three control areas, as shown in panel (C). (B) The test conditions will be administered by applying a solid MAP that delivers a liquid bacterial suspension to the skin. The experimental conditions will be replicated in three pigs (N = 12 pigs total). (C) Three control conditions will be included for each pig: microbial suspension without a MAP (negative control), MAP without microbial suspension (negative control), and scarification with microbial suspension (positive control). (D) Animals will be monitored daily for signs of infection, and biopsies will be collected on days 0 to 3, 5, and 7. Tissue biopsies will be homogenized and enumerated on microbial growth media to determine the number of organisms present in the skin. Additional tissue biopsies will be fixed and stained to visualize the tissue and bacteria. Note: Slightly different versions of the study design were shown to each regulatory agency; however, we do not perceive that these differences affected the feedback received from regulators.

3.1.2. Regulator feedback

EMA and UK MHRA expressed a preference for MAPs to be considered sterile products. EMA was open to a risk-based justification for a non-sterile approach on a case-by-case basis.

Regulators agreed that data from nonclinical animal studies could be included in risk-based justifications to support product specifications. However, concerns were raised regarding the limitations of worst-case nonclinical study designs, given that empirical data cannot encompass all potential scenarios involving a non-sterile MAP. Key study design elements, such as strain selection and inoculum levels, were not discussed. UK MHRA also noted the absence of standardized nonclinical assays capable of reliably determining the safety of non-sterile MAPs and expressed that skin breach is typically associated with

sterile product requirements. As such, the outcomes of the proposed study would not necessarily be predictive of outcomes in humans.

US FDA agreed that the proposed study would be informative in determining whether MAPs could be manufactured as non-sterile products, while emphasizing that sterility decisions would be product-specific. Justification should include data from the nonclinical, clinical, and chemistry, manufacturing, and controls (CMC) development programs. For an FIH study, a non-sterile product could be appropriately justified if it is consistent with USP <1111>, *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*.

3.1.3. Recommendations to developers

For early clinical development of LNG MAPs, low-bioburden manufacturing will generally be accepted.[6] The final microbial specification for large-scale commercial production warrants further discussions with regulators, which could be informed by the results of the proposed nonclinical study. Some regulators suggested that they view the MAP breaching the skin as more similar to a parenteral product than a transdermal product. Developers should have a strong scientific package by the start of pivotal Phase 3 studies to support the late-stage clinical microbial control strategy that will be carried over to the commercial specifications.

As previously highlighted by the MAP Regulatory Working Group—a collaborative group co-chaired by PATH and Cardiff University that serves as a critical mechanism for communication among MAP developers, manufacturers, regulators, and global health institutions to inform, guide, and define the regulatory science of the MAP dosage form—"the innovative nature of a microneedle-based dosage form may necessitate new understandings of an existing term, or development of new terms (e.g., 'trans-/intra-epidermal' or 'epicutaneous') to effectively describe the route of delivery."[11] Therefore, MAP developers should discuss the proposed route of administration with regulators early in the development process to confirm alignment.

As MAP developers modify their array designs to increase drug loading and support the target duration, they should be cognizant of the sterile requirements for tattoo ink. Tattooing punctures the skin hundreds of times per second and deposits ink 1.5–2 mm into the dermis. Due to reports of skin infections associated with contaminated ink,[16,17] US FDA guidelines for tattoo inks recommend validated sterilization methods. To mitigate risk, if LNG MAPs breach tissue to a depth similar to that of tattooing, long-acting contraceptive MAP developers should assess whether terminal sterilization is technically feasible (e.g., polymer and API degradation, microneedle integrity) and whether it would meet key product targets (e.g., cost of goods sold [COGS]). Aseptic processing of MAPs that reach penetration depths of 1.5–2 mm could be considered but would require robust manufacturing science development and possibly novel manufacturing equipment design and validation.

Although the feedback provided by the experts was given in the context of the nonclinical study not yet being completed, a robust scientific rationale will be required to support non-sterile MAPs. If a non-sterile MAP is proposed for the FIH study, the acceptability of a non-sterile release specification should ideally

be discussed with regulatory authorities before submission of a clinical trial application (CTA) or investigational new drug application (IND) through a product-specific scientific advice meeting.

Key takeaways

- A sterile product would reduce regulatory risk during late-stage development of LNG MAPs.
- Developers seeking to manufacture LNG MAPs as non-sterile will need a robust, data-driven rationale to justify non-sterile specifications.

3.2. Critical quality attributes and test methods

A risk-based approach should be applied to define critical quality attributes (CQAs) that are necessary to ensure patient safety and product quality, guided by quality-by-design principles.[18] The proposed CQAs aim to assess the performance of long-acting LNG MAPs and the attributes critical to their safety, efficacy, and quality.

For formulation and process development, the proposed CQAs would support (1) identification of attributes that are potentially critical to safety, efficacy, and stability; (2) understanding of the relationship between material attributes, process parameters, and final product quality; and (3) establishment of a robust formulation and manufacturing process that ensures consistent product performance over the proposed shelf life.

For batch release of the product that will be used in the Good Laboratory Practice (GLP) toxicology study and the Phase 1 clinical trial, a targeted list of CQAs was identified based on patient safety considerations and regulatory expectations. These CQAs are intended to ensure manufacturing consistency and safety for administration to human subjects.

This list of CQAs (Table 2) was proposed to regulators for their assessment of the appropriateness of the proposed testing for long-acting LNG MAPs to be evaluated in an FIH study.

The focus of the CQAs was exclusively on the drug product components of the MAP and did not include those related to the device component(s) or the microbiological specification. Separate CQAs and associated test methods may be necessary for the patch application mechanism.

Given the product-agnostic nature of the consultation, no specific data related to a particular array or test method were provided to regulators. It was noted that LNG is a well-known API and that the MAP would generally consist of biodegradable polymer excipients that have been clinically evaluated in other routes of administration.

3.2.1. Regulator feedback

All three agencies agreed that the proposed CQAs were appropriate for an FIH study. They noted that CQAs will need to be tailored to the specific MAP design and manufacturing process and will evolve as the product development advances. Specific feedback from each agency is provided below.

EMA emphasized that the CQAs should convey the overarching development strategy and demonstrate a thorough understanding of the product and process. For complex manufacturing processes, additional CQAs may be warranted. Wider specification limits may be acceptable in early clinical development, provided that the product remains adequately controlled for the FIH study. EMA also highlighted the importance of evaluating polymers and potential polymer-derived impurities using a risk-based approach informed by the formulation and manufacturing process. If the spatial distribution of the drug and polymer

within the microneedle affects the release rate, particularly the initial burst, MAP developers should provide data demonstrating control of this attribute.

EMA further noted that *in vitro* drug release is an important CQA, with results highly dependent on the test method. As such, test conditions should be designed to predict *in vivo* performance, and *in vitro–in vivo* correlations should be established in the overall MAP development program as more data become available. Additional CQAs, such as microneedle appearance, mechanical strength, and microneedle detachment, should be assessed and tightly controlled to ensure consistent dose delivery. Pharmacopoeial compendial methods and other harmonized methods should be used where possible. For novel MAP-specific test methods, developers should demonstrate their suitability and applicability.

UK MHRA highlighted the need for additional batch release tests, including identity, drug purity, and API and excipient degradation products, as applicable. If a sterile product is required, sterility testing should replace bioburden testing. Similar to EMA, the UK MHRA noted that release specifications should include justified acceptance criteria, and stability studies should support the proposed shelf life and storage conditions for clinical use.

Like EMA, the US FDA emphasized characterization of the spatial distribution of LNG and excipients in the microprojections and backing layer. It was further recommended that this attribute be assessed in both fresh and aged (accelerated and real-time) arrays to evaluate potential LNG migration that could affect dose delivery and PK. Regulators emphasized that whole-patch content uniformity is not sufficient to address this and that alternative methods, such as imaging (Raman spectroscopy mapping, micro-CT, or confocal microscopy), component-specific extraction and analysis, and solubility studies in each polymer matrix, would be useful in conjunction with stability studies incorporating *in vitro* release testing.

Finally, the US FDA recommended evaluating the degradation rates of the specific polymer and polymer blends under physiological conditions, with identification and quantification of degradation products over time to ensure safe and appropriate clearance. During accelerated and real-time stability studies, polymer excipients and their degradants should be evaluated throughout the proposed shelf life.

3.2.2. Recommendations to developers

The consensus among the regulators is that the proposed CQAs are adequate but should be supplemented by additional CQAs related to safety (e.g., assessment of potential impurities from the API and excipients). The original CQA list proposed to regulators has been updated to incorporate their feedback, as shown in Table 2. As part of development ahead of a Phase 1 study, MAP developers should generate adequate data to justify their test methods and specification limits for their Phase 1 good manufacturing practice material.

Table 2. Proposed critical quality attributes and associated example test methods with input from regulators.

Green highlighting denotes changes made based on regulator input.

Attribute	Example method(s)	Notes	Updates based on regulator feedback
Formulation and process development			
Drug content (assay)	HPLC		
Drug identity	HPLC		CQA added based on UK MHRA input
Content uniformity (whole patch)	HPLC	USP <905> Ph. Eur. 2.9.40	
Drug purity	HPLC		The UK MHRA requested the inclusion of substances and degradation products
Microneedle appearance	Visual inspection	Examination of MN length and quality	
Mechanical strength	Axial compression testing or insertion testing		
LNG particle size distribution in MAP	Light diffraction Micro-CT imaging		
Crystallinity of LNG in MAP	X-ray powder diffraction		
Drug-release kinetic profile	*In vitro* release under sink* or non-sink conditions	e.g., Apparatus 7	
Microneedle detachment from the application mechanism	Insertion into *ex vivo* skin; confirmation by optical coherence tomography		
Microbial content	USP/Ph. Eur. Commission method	USP <61> USP <62> Ph. Eur. 2.6.12 Ph. Eur. 2.6.13	
Endotoxin content	USP/Ph. Eur. Commission method		
Residual solvents	Gas chromatography		
Thermal characterization	Differential scanning calorimetry		
Excipient characterization (e.g., polymer MW and PDI)	Gel permeation chromatography		EMA requested further characterization (MW, MN, MZ, and PDI).

Attribute	Example method(s)	Notes	Updates based on regulator feedback
			EMA and US FDA requested spatial distribution of the excipient and API in the microprojections. The US FDA requested the inclusion of excipient degradation products
Moisture content or water activity	USP/Ph. Eur. Commission method; Karl Fischer titration		
Packaging seal integrity	USP/Ph. Eur. Commission method	Packaging integrity, moisture ingress, and impact on MN integrity	
Batch release			
Drug content (assay)	HPLC		
Drug identity	HPLC		CQA added based on UK MHRA input.
Content uniformity (whole patch)	HPLC	USP <905> Ph. Eur. 2.9.40.	
Drug purity	HPLC		The UK MHRA requested the inclusion of substances and degradation products.
Accelerated *in vitro* drug release	*In vitro* release under sink* or non-sink conditions	E.g., Apparatus 7	EMA noted that developers should ensure the method is appropriate to mimic or predict *in vivo* performance.
Microneedle appearance	Visual inspection, including magnification	Examination of shape, length, uniformity, absence of missing needles, and quality of microneedles	EMA noted that shape and length should be tightly controlled.
Mechanical strength	Axial compression testing or insertion testing		CQA added for batch release based on EMA input.

Attribute	Example method(s)	Notes	Updates based on regulator feedback
Microbial content	USP/Ph. Eur. Commission method	e.g., USP <1111>	UK MHRA requested that this be replaced with sterility, if deemed necessary.
Endotoxin content	USP/Ph. Eur. Commission method		
Residual solvents	Gas chromatography		
Packaging seal integrity	USP/Ph. Eur. Commission method	Moisture ingress	

Abbreviations: API, active pharmaceutical ingredient; CQA, critical quality attribute; EMA, European Medicines Agency; HPLC, high-performance liquid chromatography; micro-CT, micro–computed tomography; MN, microneedle; MW, molecular weight; PDI, polydispersity index; Ph. Eur., European Pharmacopeia; US FDA, United States Food and Drug Administration; USP, US Pharmacopeia.

Note: These CQAs are specific only to the API-containing microneedle array for a generic LNG MAP. Separate CQAs and associated test methods may apply to the patch application mechanism (e.g., applicator or indicator), which are not covered in this table. Specific MAP designs may require additional CQAs and/or test methods not captured in this table.

* Sink conditions refer to a total testing volume that would be capable of dissolving at least ten times the dose.

Key takeaways

- There is general agreement among experts that CQAs should encompass extensive physicochemical characterization of LNG MAPs, with a focus on safety and stability attributes.
- CQAs should demonstrate the development story, indicating how the process and final product are appropriately controlled.
- For an FIH product, acceptance criteria for release specifications may be broad; however, adequate justification will be expected.

4. Reference product

The safety and efficacy of LNG-releasing contraceptives have been well characterized in clinical studies in many countries and through decades of consumer use. The Jadelle subdermal implant manufactured by Bayer HealthCare[19] is often considered an appropriate reference product for novel systemic, LNG-containing, long-acting contraceptive products because it has a long-established clinical and regulatory track record of safety, efficacy, and controlled LNG release over extended durations of use. As such, the proposed nonclinical and clinical programs presented for regulator feedback (described below) leveraged Jadelle reference data.

Jadelle has been registered in more than 47 countries.[20] Its PK profile, contraceptive effectiveness, and tolerability have been documented across diverse populations, making it a useful benchmark for evaluating whether a novel LNG-containing product achieves comparable systemic exposure and clinical performance. Although Jadelle received US FDA approval in 1996, it was never marketed in the United States. However, Jadelle remains a valid Reference Listed Drug (RLD) because it was approved by the US FDA and not withdrawn for reasons of safety or effectiveness.[21,22]

Although a specific question was not posed to regulators for feedback on appropriate reference products and/or bridging studies as part of this product-agnostic consultation, the US FDA commented that it anticipates significant challenges in establishing an acceptable bridge to Jadelle because it generally does not accept bridging studies that compare a proposed product solely with a non-US-approved product. EMA and UK MHRA did not provide any comment on the use of Jadelle as a reference product. In addition, the US FDA emphasized that clinical trials will be necessary to establish substantial evidence of effectiveness and an appropriate safety profile in the intended US population. Based on this feedback, although existing LNG-containing products can provide useful safety, efficacy, and PK benchmarks for MAP development, their suitability as reference products is context-dependent, and regulatory acceptance may be limited by their approval status and/or availability in the target jurisdiction. Therefore, developers may want to consider seeking licensure outside the United States in countries where Jadelle is approved and available. Developers seeking US licensure should seek US FDA feedback on which, if any, US-approved products may be acceptable for clinical bridging. Regardless of where developers plan to initiate clinical studies and seek licensure, PATH recommends seeking further feedback on clinical bridging through a product-specific scientific advice meeting.

The selection of appropriate reference products and potential bridging approaches has important implications for the LNG MAP clinical development pathway and regulatory strategy. Although PK bridging to a relevant approved LNG product is expected to allow reference to supportive efficacy and safety information, a pivotal Phase 3 study will likely still be required to demonstrate the safety and efficacy due to the novel MAP delivery system and long-acting formulation. However, using prior LNG data should support a smaller Phase 3 program. For example, in the United States, Phase 3 study(ies) encompassing 10,000 rather than 20,000 cycles could be proposed because LNG is not a new molecular entity.[23]

Key takeaway

- In the United States, Jadelle may not be a suitable reference product for clinical bridging. MAP developers should seek further regulatory feedback on their proposed clinical bridging approach.

5. Nonclinical program

5.1. Proposed nonclinical program

5.1.1. Non-GLP and GLP studies

Regulator feedback was requested on the proposed nonclinical program to support an FIH study with an LNG-containing MAP. This program, conducted in Göttingen minipigs, consists of a non-GLP PK study and a GLP toxicology study (Table 3).

The objective of the PK study is to evaluate (1) the steady-state LNG release rate (target: 30 µg/day at 6 months) and (2) the LNG burst release rate immediately after application (target of less than 120 µg/day). The objective of the pivotal toxicology study is to evaluate the local and systemic tolerability of the MAP as well as obtain the toxicokinetics of the LNG MAP formulation. Minipigs were identified as the most relevant animal model because of the similarity of their skin to human skin in terms of anatomical, physiological, and immunological features.[15,24,25]

Table 3. Summary of the proposed nonclinical program.

Parameter	Pharmacokinetic study	Pivotal toxicology study
GLP status	Non-GLP	GLP
Overall objectives	Demonstrate (1) the steady-state LNG release rate (target: 30 µg/day at 6 months) and (2) the LNG burst release rate after application (target: <120 µg/day)	Evaluate the local and systemic tolerability of the MAP, as well as obtain the toxicokinetics of the LNG MAP formulation
Species	Göttingen minipig	Göttingen minipig
Dose	Proposed human dose	Proposed human dose
Primary endpoints	PK parameters, including: • Maximum observed serum concentration (C_{max}) • Time to C_{max} (t_{max}) • Area under the concentration-time curve (AUC) • Apparent absorption half-life ($t_{1/2}$) • Minimum observed serum concentration (C_{min}) • Number of days serum concentration > C_{min} • Calculated LNG release rate over time	• Gross pathology and organ weights: brain, heart, kidney, adrenal gland, spleen, thymus, ovaries, and uterus • Histopathology of the full list of tissues, including reproductive tissues and the skin administration site
Secondary endpoints	• Draize dermal scoring • Body weight • Food consumption • Clinical signs	• LNG serum concentration • Draize dermal scoring • Body weight • Food consumption • Clinical signs

Parameter	Pharmacokinetic study	Pivotal toxicology study
Study duration	Minimum of 6 months; follow-up will continue until the PK tail is fully characterized (e.g., 6–9 months)	13 weeks
Sample size	3 females per group (n = 6, assuming two application sites)	6 females per group (n = 12, assuming LNG MAP and excipient-only MAP groups)

Abbreviations: C_{max}, maximum observed serum concentration; GLP, Good Laboratory Practice; PK, pharmacokinetic.

The non-GLP and GLP studies will evaluate an LNG MAP at the proposed human dose. The starting human dose used in both the proposed nonclinical and clinical programs could be informed by minipig MAP feasibility PK data, reference minipig LNG PK data following intravenous (IV) dosing,[26] and reference human PK data from LNG implants.[27] The selected dose should result in LNG concentrations and/or release rates over six months that are predicted to be consistent with the steady-state LNG PK and/or release rate at year 3 for the Jadelle LNG implant.[28,29]

A key assumption of this approach was that the proposed nonclinical package would leverage LNG nonclinical and clinical reference data to support a reduced GLP toxicology package. Given that the nonclinical risk assessment and clinical safety profile of LNG and the MAP components are well established for chronic dosing, a 13-week duration for the local tolerability study was proposed to adequately evaluate the safety of a single dose for the Phase 1 clinical study. In addition, this assumes that all LNG MAP excipients and polymers are not novel and have been evaluated clinically in other products with well-established safety profiles and risk assessments.

5.1.2. Biocompatibility testing

Per ISO 10993,[30] LNG MAPs—classified as a drug-device combination product—will require comprehensive biocompatibility testing to support licensure. Although information may be accrued throughout development, specific guidance on the scope of testing required prior to the FIH study relative to later development stages is limited. Accordingly, regulators were asked for concurrence on the proposed strategy whereby select aspects of biocompatibility testing, consistent with ISO 10993, would be conducted prior to the FIH study, with the remaining aspects deferred to the final product stage.

To identify the biocompatibility endpoints that should be evaluated prior to the initiation of the FIH study, it was proposed to regulators that a biological evaluation plan and biological evaluation report should first be prepared, describing the MAP body-contacting materials and summarizing publicly available information on their biocompatibility to reduce unnecessary testing. This includes the contact type and duration planned for the FIH study as compared to the intended MAP product. Assuming that materials that contact or are delivered into the body are known to be safe through use in other products, limited biocompatibility testing will be conducted. This assumption is based on the MAP application process, where the LNG MAP microprojections mechanically disrupt the skin barrier, the MAP remains on the skin for a few seconds to less than one hour to deliver the full payload, and the dissolving/biodegradable microprojections remain in the dermis for up to six months. As part of the initial minipig MAP feasibility studies, the MAP developers will confirm that the microprojections have fully dissolved after six months via physical evaluation of microprojection remnants and/or LNG plasma levels.

Based on the risk assessment, the biocompatibility endpoints that may be evaluated as part of the nonclinical GLP study include:

- Cytotoxicity.
- Sensitization.
- Irritation or intracutaneous reactivity.
- Acute and chronic systemic toxicity (including evaluation of reproductive tissues).

These endpoints would be evaluated at the following time points:

- Initial MAP administration, when the MAP remains on the skin for less than one hour (i.e., detailed clinical observations on day 1).
- Throughout the study (Draize scoring).
- At termination (macroscopic observations/necropsy and clinical pathology/histopathology).

To support future marketing authorization, additional biocompatibility evaluations should be conducted on the final LNG MAP design in parallel with clinical data collection and in compliance with ISO 10993.

5.2. Regulator feedback

All three agencies agreed that the proposed nonclinical program, including the deferral of certain biocompatibility studies to later stages of development, was adequate to support initiation of the FIH study. Product-specific scientific advice (e.g., via a Scientific Advice procedure or pre-CTA or pre-IND meetings) is recommended, including confirmation of whether any additional nonclinical studies would be needed to support licensure of the product.

The agencies provided additional recommendations:

For the PK study, in addition to measuring LNG plasma levels, the US FDA advised measuring excipient (e.g., polymer/copolymer) levels. To evaluate local toxicity and tolerance, clinical and histopathological assessments of local tissue irritation should also include evaluation of both the application site and adjacent control sites.

For the GLP toxicology study, the agencies emphasized the importance of assessing both local and systemic side effects using the proposed human dose. UK MHRA commented that the 13-week duration of the GLP toxicology study was shorter than the intended duration of human exposure. As such, the UK MHRA recommended further justification for the 13-week duration, including the available clinical and nonclinical data for each component of the MAP to support extrapolation to the full duration of exposure planned for the FIH study. In addition, the US FDA commented that MAP developers consider the potential to combine the local tolerance/toxicology, toxicokinetic, and biocompatibility evaluations with the PK assessment into one minipig study to evaluate chronic use of the product (i.e., six months); however, this may not be feasible in early-stage development, in which the PK assessment is needed to optimize the formulation and determine the dose.

Regarding LNG dose levels, the US FDA recommended evaluating a minimum of two dose levels along with an adequate control to support local and systemic assessment at the proposed dose and daily release rate in toxicology and toxicokinetic studies, evaluating any potential toxicities associated with the drug-device delivery system. The dose levels should be supported by the literature and/or preclinical data. MAP developers should justify how preclinical data inform dose justification (i.e., how clearance is used to deconvolute the release rate from the MAP using IV PK reference data). Moreover, the US FDA commented that evaluating the loading dose and release rate of LNG and excipients (e.g.,

polymers/copolymers) throughout the administration period will inform the potential for dose dumping that could lead to supraphysiologic hormone levels and adverse effects. This would also facilitate comparison of loading and release amounts between the nonclinical and clinical studies. A recovery group that exceeds the drug and excipient exposure period of the LNG MAP was also recommended to facilitate assessment of the reversibility or persistence of any observed treatment-related adverse findings and/or any delayed effects following cessation of exposure.

Regarding excipient levels, the US FDA recommended evaluating excipient levels at amounts similar to or greater than those expected to be used in humans. For established excipients, additional nonclinical studies may be needed if the approved reference product is used in a different context from the MAP (e.g., dose, route, duration). For polymers/copolymers that need to be qualified, MAP developers should characterize the potential fate of the polymers/copolymers, including degradation products and their toxicological profiles, to complement bench testing of the polymer/copolymer degradation. Comprehensive assessments of potential immunological responses should be included to characterize the immunogenicity profile of the formulation, such as (1) complement activation assessments, (2) evaluations of antibody formation against the specific polymers/copolymers used in formulations (e.g., anti-polyethylene glycol [PEG], anti-polylactic acid [PLA], anti-poly[lactic-co-glycolic acid] [PLGA]), and (3) assessments of cross-reactive and/or neutralizing antibodies in the toxicology studies that could impact the PK or safety profile of the product.

Since the microprojections are intended to remain in the skin for six months—referred to by the US FDA as skin resonance time—they suggested measuring the depth of penetration and demonstrating that the depth of the microprojections (or fragments thereof) remains constant over the full intended six-month duration and that the skin rapidly recovers following MAP application. This could be incorporated into the non-GLP PK and/or GLP studies.

Regarding biocompatibility testing in alignment with ISO 10993, the agencies were supportive of preparing a biological evaluation plan and a biological evaluation report describing the MAP body-contacting materials and summarizing publicly available information on their biocompatibility, including the contact type and duration that will be used in the FIH study compared with the intended MAP product. The agencies commented that a risk-based approach could facilitate reduced testing if materials are well characterized and that new biological testing should be required only where previous data are insufficient. However, the relevance of reference products will depend on formulation, manufacturing, and contact conditions (duration and type). UK MHRA commented that MAP developers should refer to the recently released ISO 10993-1:2025.

The adequacy of the proposed nonclinical program using material representative of the FIH product will depend on multiple factors related to product characteristics and intended clinical use. The US FDA commented that formulation changes, unexpected or significant toxicity, novel excipients, impurities, or emerging clinical safety concerns could warrant additional nonclinical studies ahead of the FIH study.

5.3. Recommendations to developers

Given the consensus among the agencies on the proposed nonclinical program, PATH recommends that MAP developers consider the study design elements outlined for the non-GLP PK and GLP toxicology studies in Table 4 and Table 5, respectively, which have been updated to reflect key feedback from the regulators. If measuring excipient plasma levels is not feasible due to degradation, PATH recommends conducting a risk assessment that summarizes published preclinical and clinical data, noting the dose, route, and duration of excipient exposure. These risk assessments could be obtained from a CRO and do

not need to be newly developed by individual MAP developers. Developers should consider product-specific scientific advice for further evaluation of the toxicology study duration in relation to the planned duration of LNG MAP exposure in the FIH study.

Table 4. Summary of study parameters to be assessed in a non-Good Laboratory Practice pharmacokinetic study in minipigs.

Green highlighting denotes changes made based on regulator input.

Parameter	Parameter endpoint	Updates based on regulator feedback
Objective	Utilize LNG PK and appropriate modeling and simulation strategies to determine the FIH dose	Note: The objective was refined based on internal feedback *after* the nonclinical program was presented to regulators. The revised objective listed here more accurately captures dose selection strategies.
Species	Göttingen minipigs	
Age	4–5 months at the start of dosing	
Route	Dermal	
MAP application site	Two different application sites (e.g., ventral hind limb, posterior flank)	
Duration	Minimum of 6 months; follow-up will continue until the PK tail is fully characterized (e.g., 6–9 months)	
Dosing frequency	Single dose	
Number of animals per group	3 females per group (n = 6, assuming two application sites)	
Dose levels (concentrations; mg/kg/day) and dose volumes (g/kg)	Starting clinical dose (e.g., sufficient dose to maintain a release rate of 30 µg/day in humans, as identified through PK modeling)	
Dose formulation preparation	Supplied as a MAP containing LNG	
Control (optional)*	LNG subcutaneous implant (e.g., Jadelle, Levoplant®); LNG IV bolus	
Body weight	Day 1, weekly thereafter	
Food consumption	Day 1, weekly thereafter	
Clinical signs	Daily	
Detailed clinical observations	Day 1, weekly thereafter	
Draize dermal scoring	Days 0, 1, 2, 3, and 7; weekly for the first month; and every other week until the end of the study	

Parameter	Parameter endpoint	Updates based on regulator feedback
Serum sample collection	Samples collected on days 0, 0.5, 1, 3, and 7; weekly for the first month; and every other week until the end of the study	
Bioanalytical sample analysis	Plasma LNG using HPLC-MS (LLOQ 10 pg/mL)[31]	US FDA: Measure both LNG and excipient levels
	Plasma excipient levels	
Depth of penetration and micropore closure assessment	Depth of penetration *in vivo*; confirmation with optical coherence tomography	US FDA: Measure depth of penetration at the time of application and over clinical use; demonstrate that the skin rapidly recovers following MAP application
Euthanasia	End of study	
Reporting	Standard	

Abbreviations: GLP, Good Laboratory Practice; HPLC-MS, high-performance liquid chromatography-mass spectrometry; IV, intravenous; LLOQ, lower limit of quantification; PK, pharmacokinetic; US FDA, United States Food and Drug Administration.

Note: Some non-GLP studies may include a commercial subcutaneous implant and/or an IV bolus arm as a control group. If a control group is not used, reference data from a subcutaneous implant and IV bolus administration in minipigs will be used to assist in the interpretation of the MAP PK profile.

Table 5. Summary of study parameters to be assessed in a Good Laboratory Practice toxicology study in minipigs.

Green highlighting denotes changes made based on regulator input.

Parameter	Parameter endpoint	Updates based on regulator feedback
Objective	Evaluate the local and systemic tolerability of the MAP, as well as obtain the toxicokinetics of the LNG MAP formulation	
Species	Göttingen minipigs	
Age	4–5 months at the start of dosing	
Route	Dermal	
MAP application site	Single application site (e.g., ventral hind limb, posterior flank)	
Duration	13 weeks	US FDA: Include a recovery group in which a subset of animals undergoes a drug-dosing phase followed by a drug-free period to evaluate the persistence of adverse effects, if observed
	Extended follow-up for the recovery group (e.g., 6−9 months)	
Dosing frequency	Single dose	

Parameter	Parameter endpoint	Updates based on regulator feedback
Number of animals per group	6 females per group	
Dose levels (concentrations; mg/kg/day) and dose volumes (g/kg)	Dose levels will be chosen to provide release rates of 30 µg/day or higher in humans for 6 months (as identified through PK modeling)	US FDA: Minimum of two dose levels; dose levels of the excipients in the treated and control cohorts should be similar to or greater than the amounts expected to be used in humans
Dose formulation preparation	Supplied as a MAP with or without LNG; if an excipient-only MAP is not technically feasible (i.e., mechanically suitable), then an injectable formulation containing the excipients will be used	Regulators recommended prioritizing the inclusion of an excipient-only MAP
Body weight	Day 1, weekly thereafter	
Food consumption	Day 1, weekly thereafter	
Clinical signs	Daily	
Detailed clinical observations	Day 1, weekly thereafter	
Draize dermal scoring:	Daily for the first week, weekly from days 7 to 28, and every other week until the end of the study	
Hematology	Standard; at termination	
Clinical chemistry	Standard; at termination	
Bioanalytical sample analysis:	Plasma LNG measured on days 0, 0.5, 1, 3, and 7; weekly for the first month; and every other week until the end of the study	
Toxicokinetic sample collection	Samples collected on days 0, 0.5, 1, 3, and 7; weekly for the first month; and every other week until the end of the study	
Necropsy and tissue collection	End of study; organ weights and histopathology, including reproductive tissues and skin administration sites	
Euthanasia	End of study	
Gross pathology/organ weights	Brain, heart, kidney, adrenal gland, spleen, thymus, ovaries, and uterus	
Histopathology	Tissues: full list, including reproductive tissues and skin administration sites	US FDA: Evaluate skin sites adjacent to the MAP administration site
	Adjacent skin sites	
Reporting	Standard	
SEND dataset	Yes	

Abbreviations: PK, pharmacokinetic; SEND, Standard for Exchange of Nonclinical Data; US FDA, United States Food and Drug Administration.

To estimate the starting human dose[26] for the proposed non-GLP PK and GLP toxicology studies, MAP developers should use modeling and simulation. One method is to use the release rate from the initial MAP feasibility studies in minipigs (determined from the LNG MAP product's PK data), reference minipig IV LNG PK data, and reference human PK data and/or release rates from LNG implants. The minipig IV PK data can be used to estimate clearance and deconvolute the release rate from the MAP. Due to the duration of the proposed nonclinical PK study, the clearance value will be adjusted based on body weight. Key inputs from Ko et al. (2022) include Göttingen minipig IV clearance of 21.5 L/hr and a mean body weight of 11.5 kg.

$$Predicted\ Clearance,\ \frac{L}{hr} = \text{Estimated Clearance},\ \frac{L}{hr} \times \left(\frac{Body\ Weight, kg}{Average\ Body\ Weight, kg}\right)^{3/4}$$

$$Release\ Rate,\ \frac{\mu g}{day} = \text{LNG Concentration},\ \frac{pg}{mL}\ \times \text{Predicted Clearance},\ \frac{L}{hr} \times \frac{1000\ mL}{L} \times \frac{24\ hr}{day} \times \frac{1\ \mu g}{10^6 pg}$$

Assuming that the LNG release rate is dose-dependent, the estimated MAP release rate could then be used to select the amount of LNG that will be loaded into the MAP to achieve a minimum release rate of 30 µg/day for six months.

Regarding biocompatibility testing, MAP developers should develop a biological evaluation plan and a biological evaluation report, including the biocompatibility endpoints to be evaluated in the GLP study. The biological evaluation report should describe how all biocompatibility endpoints included in ISO 10993-1 were addressed (e.g., testing, literature, or justified omission). The relevant endpoints should be identified based on the type and duration of body contact. ISO 10993-1 encourages a risk-based approach, emphasizing the use of existing data whenever possible to reduce unnecessary animal testing. MAP developers should refer to the recently released ISO 10993-1:2025, which shifts biological evaluation from a test-driven approach to a risk management process integrated with ISO 14971, emphasizing chemical characterization over animal testing. Furthermore, biological evaluation is now expected to be a continuous process, with risk estimation and evaluation implemented at every stage from early design to post-market surveillance. For guidance on using ISO 10993-1, MAP developers should refer to the US FDA's guidance document, *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management process."*[32]

Regarding the potential for immunological responses to the LNG MAP formulation, PLA and PLGA are non-antigenic, biodegradable excipients that degrade into endogenous metabolites and have an established safety record in clinical use.[33,34,35] As synthetic polyesters that lack protein epitopes, they are not expected to directly elicit anti-drug antibody responses. Any immunogenicity observed with PLA/PLGA-based formulations is generally attributable to the therapeutic payload or formulation characteristics rather than the polymer itself. As such, PATH recommends using reference data that evaluated the potential immunological responses of the excipients (e.g., polymers/copolymers) included in the specific formulation. If these data are not available, MAP developers could consider adding immunological response endpoints to their nonclinical program.

To characterize impurities and degradation products, all impurities and degradants that exceed the ICH Q3 reporting limits should be adequately qualified or reduced in accordance with ICH Q3 (including under physiological conditions). It is recommended to include a risk assessment for the potential presence of nitrosamine impurities.

Key takeaways

- Overall, the regulatory experts considered the proposed abbreviated nonclinical program adequate to support the FIH study, with additional recommendations on endpoints to consider.
- For the duration of the GLP toxicology study, if developers wish to proceed with the 13-week study, scientific advice and consensus from the agencies should be obtained, supported by a sound scientific justification. Otherwise, the study should be extended to a minimum of 6 months to capture the intended clinical use.
- Developers should prioritize evaluating the proposed biocompatibility endpoints ahead of the FIH study. As part of the biological evaluation plan and biological evaluation report, MAP developers should describe how all biocompatibility endpoints included in ISO 10993-1 were addressed (e.g., testing, literature, or justified omission) based on contact type and duration.

6. Clinical program

Regulators were asked to comment on the overall design, objectives, and outcome measurements for a Phase 1 FIH clinical study of a long-acting LNG MAP product.

The proposed outcomes for the Phase 1 study included safety, tolerability, and PK (Table 6). Pharmacodynamic measures were not included as formal study outcomes, but they may be assessed for exploratory purposes. The FIH study proposed to evaluate a single dose of a long-acting LNG MAP intended to sustain plasma concentrations of LNG over six months (e.g., a sufficient dose to maintain a C_{min} of >200 pg/mL in an individual, as identified through PK modeling). The study follow-up period would be informed by the nonclinical data to ensure collection of the LNG PK tail (e.g., until plasma samples indicate that LNG is below the lower limit of quantification). To evaluate reactogenicity associated with the MAP delivery platform alone compared with administering LNG to the skin via a MAP, it was proposed that a placebo MAP containing microprojections formulated without LNG (i.e., excipients only) may also be included; however, if a placebo MAP is not technically feasible (i.e., mechanically suitable), this group would be excluded.

Table 6. First-in-human Phase 1 study outcomes and outcome measures.

Outcome	Example outcome measures
Safety and tolerability	• Local tolerability at the MAP application site assessed at regular intervals throughout the study. • The incidence and severity of local and systemic adverse events from the day of study product administration until the end of the study. • The incidence and severity of biochemical and/or hematological abnormalities. • Changes in vaginal bleeding patterns.
Pharmacokinetics	• Maximum observed serum concentration (C_{max}). • Time to C_{max} (t_{max}). • Area under the concentration-time curve from time zero to the last measurable concentration (AUC_{last}), to 6 months ($AUC_{6\ months}$), and extrapolated to infinity (AUC_{inf}). • Terminal half-life ($t_{1/2}$). • Serum concentration at 6 months ($C_{6\ months}$). • Minimum observed serum concentration (C_{min}). • Number of days with a serum concentration >200 pg/mL.

Note: This table includes example outcomes and outcome measures for an FIH Phase 1 study. Not all FIH studies may include all outcome measures as proposed. Some FIH studies may not evaluate pharmacodynamics and may assess only safety, tolerability, and pharmacokinetics.

The FIH study population was proposed to be limited to individuals at low risk of pregnancy (e.g., sterilized, in an exclusively same-sex partnership, in a monogamous relationship with a vasectomized partner, abstinent) or individuals who are willing to use nonhormonal methods of contraception (e.g., a nonhormonal intrauterine device, spermicidal gel and a condom, or spermicidal gel and a diaphragm) for the duration of the study. Example inclusion and exclusion criteria are summarized in Table 7 and were shared only with the US FDA for consideration.

Table 7. First-in-human Phase 1 inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria

• Willing and able to provide signed informed consent
• Assigned female at birth between 18 and 45 years of age (inclusive)
• Must not be pregnant and must have a negative plasma or urine pregnancy test within 24 hours before dosing
• Healthy based on the results of a medical evaluation, including medical history, vital signs, and physical examination
• Clinical laboratory tests must be within prespecified normal limits
• Has a regular menstrual cycle (21 to 35 days)
• At low risk of pregnancy (e.g., sterilized, in an exclusively same-sex partnership, in a monogamous relationship with a vasectomized partner, abstinent) or must be willing to use 1−2 additional medically acceptable nonhormonal methods of contraception (e.g., a nonhormonal IUD, spermicidal gel and a condom, or spermicidal gel and a diaphragm) for the duration of the study
• Has a BMI of 18 to 30 kg/m^2
• Provides normal mammogram results within the last year before enrollment for individuals 40 years of age or older
• Willing and able to comply with all study requirements and return to the investigational site for follow-up procedures and assessments as specified in this protocol
• Has a body site that is deemed suitable for MAP administration and skin assessment (e.g., lack of scars, tattoos, rashes, or other dermatological conditions)
	• Has multiple risk factors for cardiovascular disease (e.g., smoking, diabetes, obesity, hypertension, high LDL, or high triglyceride levels)
	• Has a current or past history of ischemic heart disease or cerebrovascular disease
	• Has current or previous thromboembolic disorders
	• Has systemic lupus erythematosus
	• Has rheumatoid arthritis requiring immunosuppressive therapy
	• Has migraine with aura
	• Has undiagnosed abnormal vaginal bleeding
	• Has known or suspected breast cancer, a history of breast cancer, or another progestin-sensitive cancer
	• Has a current or past history of dysplasia or invasive cervical cancer
	• Has cirrhosis, liver tumors (benign or malignant), or active liver disease
	• Has one or more baseline liver function test results above the local laboratory's normal range
	• Has a hemoglobin level <10.5 g/dL
	• Has used any injectable contraceptive in the past 6 months
	• Has used any of the following medications within 4 weeks before enrollment:
	  ○ Any investigational drug
	  ○ Prohibited drugs
	  ○ Oral contraceptives, contraceptive ring, or contraceptive patch
	  ○ LNG IUD or hormonal contraceptive implant
	• Has known or suspected pregnancy
	• Is currently breastfeeding
	• Desires to become pregnant within the next 12 months
	• Has been pregnant within the past 3 months
	• Is using or planning to use prohibited drugs during the intended study duration
	• Has abnormal cervical cytology requiring treatment
	• Has known hypersensitivity to LNG or any components used in MAPs (e.g., excipients, adhesives)
	• Plans to move to another location during the study
	• Is participating in any other clinical trial involving a biomedical intervention
	• Has any condition (social or medical) that, in the opinion of the site investigator, would make study participation unsafe, interfere with adherence to the clinical study requirements, or complicate data interpretation

Abbreviations: BMI, body mass index; IUD, intrauterine device; LDL, low-density lipoprotein.

Note: This table includes example inclusion and exclusion criteria for an FIH Phase 1 study. Developers should consider the specifics of their product when developing the inclusion and exclusion criteria.

6.1. Regulator feedback

Overall, regulators concurred that the proposed objectives for the Phase 1 study—safety, tolerability, and PK—were appropriate. Regulators also provided additional recommendations to support the design of the FIH study and future clinical development.

Several recommendations focused on safety monitoring and risk mitigation. Since LNG MAPs are nonremovable once administered, EMA and UK MHRA emphasized the importance of implementing risk-mitigation measures for studies involving participants of childbearing potential. They also recommended the use of a placebo MAP control to help distinguish adverse effects that may be attributable to the excipients or the device application mechanism rather than LNG. As part of the overall safety program, the US FDA further recommended evaluation of bone mineral density (BMD), as well as the use of a standard method for assessing the skin application site. When developing the FIH protocol, the US FDA advised that the planned assessment of return to fertility be described, recognizing that progestins have multiple mechanisms of action in the reproductive tract that result in contraception.

Regulators also provided recommendations related to PK assessment and characterization of product performance. The US FDA recommended testing plasma levels of both LNG and excipients as part of the PK evaluation. Because the microprojections will remain in the skin for an extended period (referred to by the US FDA as “skin resonance time”), the US FDA recommended evaluating the location and behavior of the detached microprojections over the intended six-month duration. A variety of approaches could be employed, including transepidermal water loss at serial timepoints to assess barrier function recovery, dye penetration studies to determine pore patency, optical coherence tomography, or confocal microscopy to visualize the microprojections within the skin.

Additional recommendations addressed the study population and broader clinical development considerations. EMA noted that the selection of Phase 1 trial sites and study populations should consider potential differences in drug metabolism across populations to support the relevance of the findings to the intended target population for LNG MAPs. The US FDA also noted that although the body mass index (BMI) range of 18−30 kg/m^2 in the inclusion criteria was considered adequate for the FIH study, the BMI range should be expanded in later-stage studies to be more representative of the intended target population.

The US FDA also encouraged the early development of instructions for use for providers and/or patients. For future studies involving at-home administration, developers were encouraged to prospectively define how scenarios such as inadvertent partial dosing, double dosing, and MAP loss would be managed. The US FDA further recommended that future study protocols include guidance for common skin conditions or external factors that could affect product use or performance, such as rashes, tattoos, concomitant use of transdermal products, showering, and hot tub use.

6.2. Recommendations to developers

Given the consensus among the agencies on the adequacy of the proposed safety, tolerability, and PK endpoints for the FIH study, developers should include each of these endpoints in their FIH study protocol. Additional considerations related to placebo control, study location, and risk mitigation for potential pregnancy may be incorporated into clinical study design planning. MAP developers should prioritize the manufacture of excipient-only placebo MAPs, if technically feasible, for inclusion in the FIH study.

To evaluate return to fertility following LNG MAP use, progesterone levels could be assessed as a surrogate marker for ovulation. However, there is concern that relying solely on progesterone measurements may overestimate fertility potential if residual circulating progestin from the MAP remains detectable. Therefore, regulatory authorities may also request additional assessments, such as ultrasound evaluation and measurement of estradiol, luteinizing hormone, and follicle-stimulating hormone levels, to more comprehensively assess return to fertility. Regarding the evaluation of BMD in the FIH study, PATH recommends delaying the measurement of BMD until late-stage clinical trials with sufficient sample sizes to detect clinically meaningful changes in BMD.

Finally, PATH recommends seeking product-specific scientific advice early regarding reference products and potential bridging approaches. Selecting appropriate reference products can have significant implications for the clinical development pathway. For example, leveraging existing LNG reference data may support a smaller Phase 3 program (e.g., 10,000 versus 20,000 cycles).

Key takeaways

- Regulators agreed with the proposed FIH study endpoints related to safety, tolerability, and PK; modifications to the study design may be necessary based on the MAP design and the scientific questions to be addressed in the FIH study.
- Developers are strongly encouraged to include a placebo MAP as a safety control.

7. Conclusion

Scientific and regulatory advice obtained from the EMA, the UK MHRA, and the US FDA provides a first look into preliminary regulatory perspectives on the development of LNG MAP products. A comparison of feedback across the three regulators demonstrates broad alignment on the proposed nonclinical and early clinical development approaches, as well as the importance of adopting a risk-based development strategy. Divergence in their feedback highlights areas where product-specific regulatory engagement will be important. The long-acting nature of LNG MAPs brings new challenges to the field of MAP development. As such, continued sharing of learnings across the field of MAP therapeutics will be critical to success.

The implications for MAP developers that emerged from the regulator feedback reinforce that:

- MAP developers should be prepared to integrate data across CMC, nonclinical, and clinical domains to demonstrate that the product is safe and efficacious. For example, excipient degradation products should be characterized at the benchtop and again through preclinical and clinical development.
- The development strategy should be grounded in strong characterization of PK, product performance, and safety.
- Early investment in the definition and validation of MAP-specific CQAs, as well as the development of appropriate test methods, will benefit the entire field of MAP developers.
- While PK bridging to a relevant approved LNG product is expected to allow reference to supportive efficacy and safety information, a pivotal Phase 3 study will likely still be required to demonstrate both the safety and efficacy of the novel MAP formulation or delivery system.
- For developers seeking to adopt a non-sterile specification, ongoing regulatory engagement will be critical as more data to support microbial specifications are generated and the MAP route of administration is clarified.

Although it was uncertain at the outset, regulatory agencies were receptive to a product-agnostic dialogue, suggesting that early engagement is both feasible and beneficial for novel platform technologies. This exercise in obtaining product-agnostic scientific advice provided valuable feedback on early-stage LNG MAP development that will benefit all developers; however, it does not supersede the need for product-specific regulatory consultations as development proceeds. For developers managing limited resources, cost-free approaches to obtaining scientific advice from high-maturity-level regulatory agencies may offer a viable means of obtaining preliminary feedback. Ultimately, in the absence of formal guidance, regulators encourage iterative engagement to ensure that early development remains aligned with the evolving field.

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