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

*Target Product Profile (TPP) for MAP Delivery of an Antiretroviral Drug and Hormonal Contraceptive*
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Acknowledgment

This project is made possible by the generous support of the American people through the United States Agency for International Development (USAID) through the United States President’s Emergency Plan for AIDS Relief (PEPFAR), under the terms of Cooperative Agreement #AID-OAA-A-17-00015. The contents are the responsibility of PATH and do not necessarily reflect the views of USAID, PEPFAR, or the United States government.

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Suggested citation:

PATH. Target Product Profile (TPP) for MAP Delivery of an Antiretroviral Drug and Hormonal Contraceptive. Seattle: PATH; 2021 (revised).

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Abbreviations

AEs  adverse events
API  active pharmaceutical ingredient
ARV  antiretroviral
CAB  cabotegravir
CAB LA  long-acting nanosuspension of cabotegravir
CAB Na  micronized cabotegravir sodium salt
CDC  United States Centers for Disease Control and Prevention
COGS  cost of goods sold
FTC  emtricitabine
IM  intramuscular
INSTI  integrase strand transfer inhibitor
IUD  intrauterine device
LA  long-acting
MAP  microarray patch
MHRA  Medicines and Healthcare products Regulatory Agency
MPT  multipurpose prevention technology
PD  pharmacodynamics
PK  pharmacokinetics
PrEP  pre-exposure prophylaxis
QUB  Queen’s University Belfast
RH  relative humidity
RPV LA  long-acting nanosuspension formulation of rilpivirine
TDF  tenofovir disoproxil fumarate
TPP  target product profile
USAID  United States Agency for International Development
FDA  United States Food and Drug Administration
WHO  World Health Organization
Introduction

The purpose of this target product profile (TPP) is to define minimal and optimal targets for microarray patch (MAP) delivery of (1) cabotegravir (CAB) antiretroviral (ARV) drug for HIV pre-exposure prophylaxis (PrEP) and (2) CAB co-delivered with a long-acting hormonal contraceptive as a multipurpose prevention technology (MPT) for simultaneous HIV PrEP and pregnancy prevention. The TPP also includes a ‘rationale/annotations’ column for notes to provide evidence and further discussion on the targets. This TPP is a living document that will evolve over time as new data are generated.1

1. Public health need for alternative delivery technologies for HIV PrEP and MPT products

The global health community needs highly effective methods of HIV PrEP that do not depend on daily patient adherence, are suitable for use in low- and middle-income country (LMIC) settings, and fit within the context of a patient’s life.2,3,4 Long-acting, injectable formulations that could be administered every two months, such as long-acting CAB (CAB LA) offer promise in this regard; however, these formulations may also be limited by their route of administration (intramuscular [IM] injection), which can be painful and requires access to trained health care providers. A low-cost, easy-to-use, discreet delivery system that provides long-acting formulations and could be self-administered would benefit those without routine access to health care providers and may increase adherence to HIV PrEP.5

In addition to needing improved HIV prevention options, women globally have an unmet need for family planning. The unmet need is highest among adolescent girls and young women who want to delay a first birth or space births. An easy-to-use, discreet, woman-initiated MPT may offer an opportunity for increased uptake, particularly where women face significant personal, social, or religious barriers.5 MPTs are designed to protect women against unintended pregnancy and sexually transmitted infections, including HIV. Male and female condoms are currently the only market-available MPT products. Condoms, however, require partner negotiation, which is not always feasible, and there is a need for woman-initiated MPT products that do not rely on partner cooperation and integrate seamlessly into service delivery and cultural contexts.7,8,9,10,11,12

2. Dissolving MAPs—a potential technology solution

MAPs, also known as microneedle patches, are an innovative pharmaceutical delivery technology currently in development. MAPs may offer an alternative option for delivery of HIV PrEP and as an MPT. MAPs consist of an array of micron-scale (<1 mm long) projections that are applied to the skin like a bandage with manual pressure or with the aid of an applicator.13 MAPs may have particular benefit in LMIC settings due to their anticipated ease of use, safety, and thermostability.14 Studies show MAPs are pain-free, acceptable to patients—including pediatric patients and their parents—and could enable self-administration.15,16

Queen’s University Belfast (QUB) developed a unique dissolving MAP formulation with higher drug-loading capacity compared to standard MAP technology platforms.17 Polymer excipients provide structural rigidity to insert the projections into the skin and the MAP projections dissolve rapidly upon contact with the skin’s interstitial fluid to release the drug. The drug formulations delivered by dissolving MAPs could provide sustained release of the drug over time.18 The delivery system is self-disabling and eliminates the potential for reuse, since the MAP projections dissolve following application and only the patch backing is removed (Figure 1). Polymer deposited into the skin biodegrades or is absorbed systemically and excreted by glomerular filtration.13,19 Thus, repeat application over time is possible without inducing
polymer accumulation in the skin. QUB has also shown in an in vivo animal model that repeat application of dissolving MAPs does not alter skin architecture, barrier function, or biochemistry and that the risk of introducing microbial contamination is very low.\textsuperscript{20,21} Dissolving MAPs for delivery of an ARV for HIV PrEP or co-delivery (not co-formulated, but in a separate, segmented configuration—see Figure 2) of an ARV and hormonal contraceptive as an MPT would be regulated and approved as a novel device/drug combination. Regulatory approval by the United States Food and Drug Administration (FDA) of the novel ARV MAP combination product will require an Investigational New Drug application and successful clinical trials. The project team will incorporate feedback from meetings with the FDA into a regulatory strategy document that outlines preclinical and clinical study design to enable a first-in-human trial of the ARV MAP.\textsuperscript{22,23} PATH has collaborated with partners to conduct user studies in South Africa & Uganda in 2020, and results have been incorporated into this document. An additional study on next-generation product design is anticipated to be completed in Kenya in 2022; when results are available, they will also be incorporated into the TPP.

Figure 1. Dissolving MAP application.

3. Selection of CAB for the ARV MAP

The primary aim of this project is to develop a dissolving MAP for delivery of long-acting HIV PrEP. Currently, the only FDA-approved medications for HIV PrEP are daily oral pills marketed by Gilead as Truvada (a fixed-dose combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC)) and Descovy (emtricitabine and tenofovir alafenamide)®. There are, however, a number of long-acting (LA) forms of HIV PrEP in development, including CAB.\textsuperscript{24} CAB LA, a long-acting ARV nanosuspension
developed by ViiV Healthcare, is intended as a monotherapy for HIV PrEP\textsuperscript{25,26} and has been approved in combination with long-acting rilpivirine (RPV LA) for HIV treatment (Cabenuva). CAB is under review by the FDA to be approved for PrEP use through a Supplemental New Drug Application submitted by ViiV Healthcare.\textsuperscript{27} An analog of dolutegravir, CAB is a potent integrase strand transfer inhibitor (INSTI) with a high barrier to HIV resistant mutants and a relatively long half-life (21 days to 50 days).\textsuperscript{26,29} CAB LA has been studied as PrEP in a phase 2b/3 clinical trial in HIV-uninfected cisgender men and transgender women who have sex with men and a phase 3 clinical trial in HIV-uninfected women. It was shown in the studies that CAB LA is potentially more effective in preventing HIV when compared to daily oral FTC/TDF tablets.\textsuperscript{25,26} In both trials, participants received daily oral CAB (sodium salt formulation) during the lead-in phase for five weeks to assess drug safety and tolerability followed by IM injections of CAB LA administered as one 3-mL (600-mg) dose given at two time points four weeks apart and every eight weeks thereafter.

CAB was selected for MAPs for PrEP development due to its advanced development status, and because it has a long half-life compared to other ARVs, due to its low solubility, which may enable less frequent dosing and/or smaller MAP size.\textsuperscript{30} Finally, CAB has a favorable resistance profile compared to other INSTIs.\textsuperscript{29} Minimal and optimal targets for the CAB MAP defined in this TPP are based on current clinical guidelines for HIV PrEP (daily oral Truvada) and currently available clinical data generated from injectable CAB LA and oral micronized CAB sodium salt (CAB Na).\textsuperscript{31,32} Successful development of a CAB MAP that is suitable for use in LMIC settings could provide a discreet, alternative option for both men and women to increase access and potentially adherence to long-acting HIV PrEP.

CAB MAP formulation work to date by QUB has shown that using CAB Na will result in MAPs that exhibit comparable properties to that of CAB LA in terms of drug content, mechanical strength, insertion capability, dissolution in PBS and the skin, and drug disposition in the skin, while maintaining drug plasma concentrations significantly above the human therapeutic levels for up to 28 days in rats. As CAB Na is much lower cost to produce than the CAB LA nanosuspension and more straightforward to formulate as a MAP, it has been prioritized for CAB MAP development.

4. Selection of hormonal contraceptive for an MPT MAP

Dissolving MAP technology may also provide unique benefits for delivery of long-acting hormonal contraception. The secondary aim of this project is to develop a dissolving MAP for delivery of long-acting contraception to enable future development of a segmented MPT MAP (a MAP that delivers two distinct drugs from separate microarrays located on the same patch, but is not co-formulated, Figure 2). The decision to load the two APIs on separate patches, and not co-formulate the two on one patch, stemmed from manufacturing and development concerns, making separate patches a more feasible option. In contrast to currently available transdermal contraceptive patches, which rely on passive diffusion of hormone through intact skin and require continuous wearing of the patch, a dissolving contraceptive MAP would be designed to provide long-acting protection (up to several months) following removal of the patch after a single, short application. This could provide a novel family planning option for women.

The study team selected an off-patent contraceptive progestin to formulate into a slow-release dissolving MAP. Potential off-patent contraceptive progestin candidates included levonorgestrel, etonogestrel, and norelgestromin, which are used in intrauterine devices (IUDs), implants, and contraceptive patches. PATH decided to move forward with norelgestromin, as its current delivery method of transdermal patches made it a good candidate for MAP delivery, and its low cost aligned with the project objectives.

Minimal and optimal targets for the MPT MAP defined in this TPP are based on currently available long-acting forms of hormonal contraception, such as injections, IUDs, and implants, as well as MPT drug delivery products in development, such as the dapivirine/levonorgestrel vaginal ring.\textsuperscript{10,33} Targets for attributes of the contraceptive MAP, such as dosing frequency, will be designed to align with those of the
ARV MAP to enable a future dual-indication MPT product. Development of an MPT MAP that is suitable for use in LMIC settings could provide a discreet, alternative option for women to increase access to long-acting HIV PrEP and contraception.

Figure 2. Single ARV MAP and segmented MPT MAP concepts for long-acting HIV PrEP and contraception.
## Target product profile

### 1. Indication

<table>
<thead>
<tr>
<th>MAP product</th>
<th>Minimally acceptable target</th>
<th>Optimal target</th>
<th>Rationale/annotations</th>
</tr>
</thead>
</table>
| **ARV MAP** | The primary indication of a CAB MAP for HIV PrEP is to reduce the risk of acquiring HIV-1 in adults (≥18 years old) of both genders with substantial risk for HIV infection. CAB MAP should be suitable for use in LMIC settings, particularly sub-Saharan Africa, where the need for HIV PrEP is greatest and access may be limited. | Broader indications for a CAB MAP would include indication for special populations, including pregnant women and adolescents (<18 years old) and could include prevention of HIV-2. | • A CAB MAP for HIV PrEP would be prescribed according to current US Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) guidelines as part of a prevention strategy in combination with counseling and access to other HIV prevention services for adults, and ideally adolescents, with substantial risk for HIV acquisition.\(^{32,34}\)  
• Target populations within LMIC settings include PEPFAR priority populations for HIV prevention, which may include adolescent girls, young women, sex workers and their clients, and mobile populations, depending on the country and as defined by populations with documented HIV prevalence or incidence greater than the HIV prevalence or incidence of the general population in the country.  
• Additional clinical trials will be required to assess safety and efficacy in other populations beyond healthy adults and for whom HIV PrEP may be appropriate, such as pregnant women and adolescents.  
• A CAB MAP could potentially be used in combination with another antiretroviral agent, such as rilpivirine, for treatment of HIV in all age groups, but is beyond the scope of this TPP.\(^{30}\)  
• The primary indication for a CAB MAP is to prevent HIV-1, same as Truvada, but could be expanded to prevention of HIV-2 as well, depending on where clinical trials are conducted and if sufficient data are gathered on HIV-2. |
| **MPT MAP** | The primary indication of an MPT MAP is to reduce the risk of acquiring HIV-1 in adult (≥18 years old) women with substantial risk for HIV infection, while simultaneously preventing unintended pregnancy.\(^{32,36}\) An MPT MAP should be suitable for use in LMIC settings, particularly sub-Saharan Africa, where the need for HIV PrEP and family planning is greatest and access may be limited. | Same as minimally acceptable, with broader indication to include adolescent girls (<18 years old) and HIV-2. | • Same as above, except an MPT MAP would exclude men.  
• Development pathway for an MPT MAP would be approval in adult women first, followed by approval in adolescent girls based on requisite clinical trials. |
### 1.2 Contraindications

<table>
<thead>
<tr>
<th>MAP product</th>
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</table>
| **ARV MAP** | CAB MAP is contraindicated for adults with acute or chronic HIV infection. | Same as minimum. | - To avoid potential for drug resistance, the CAB MAP would only be prescribed if acute and chronic HIV infection were excluded by symptom history and HIV testing prior to PrEP initiation and every three months during use, according to current PrEP guidelines.\(^{32}\)
- Contraindications for the CAB MAP to be updated pending FDA or other stringent regulatory authority approval of CAB and during clinical development of CAB MAP. |
| **MPT MAP** | MPT MAP is contraindicated for women with acute or chronic HIV infection, post-menopausal women, and pregnant women. | Same as minimum. | - Same as above, except post-menopausal women and pregnant women (with either suspected or confirmed pregnancy) would also be contraindicated for the MPT MAP due to the progestin.
- Additional contraindications for the MPT MAP will depend on the selected progestin, but may also include:\(^{36,37}\)
  - Known or suspected breast cancer.
  - Past or current thrombosis or thromboembolic disorders.
  - Liver disease, including cirrhosis and liver tumors.
  - Abnormal vaginal bleeding of unknown etiology.
  - Cardiovascular disease.
  - Lactating women.
  - Women who smoke.
  - Women with a history of depression.
- Contraindications for the MPT MAP to be confirmed during clinical development. |

### 1.3 Intended use case and required monitoring

<table>
<thead>
<tr>
<th>MAP product</th>
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<th>Rationale/annotations</th>
</tr>
</thead>
</table>
| **ARV MAP** | MAP enables the potential for self-administration by the minimally acceptable and optimal target populations defined in 1.1. | Same as minimum | - Prescription and use of a CAB MAP should integrate into the service delivery structure established for HIV PrEP, which may vary by country.
- Current clinical guidelines for HIV PrEP require that patients return to the clinic every three months for pregnancy and HIV testing, every three to six months for sexually transmitted infection screening, and renal screening at three months, then every three to six months.\(^{32}\) These guidelines may or may not be the same for a CAB MAP and will depend on clinical trial results for safety, duration of protection, and potential for generating resistance to CAB upon incident HIV infection.

Use case for an ARV MAP will depend on dose frequency of the MAP (see 2.5):
- Assuming a one-month or shorter dose frequency for the CAB MAP, it would be prescribed in a clinic and the first dose (MAP or CAB LA injection) potentially administered by a health care provider qualified to prescribe HIV PrEP. The patient would receive the remainder of the three-month supply of CAB MAPs for self-administration in a home setting to maintain protective levels of CAB until the next scheduled clinic visit three months later (similar how Truvada is currently provided).
- If a three-month or greater dose frequency is feasible for other ARV MAPs, these could either be administered at the clinic or sent home with the patient for self-administration.
- Ultimately, the decision when to start and stop HIV PrEP will depend on a patient’s risk for HIV acquisition, side effects, and health care provider recommendation. |
2. Dosage and administration

<table>
<thead>
<tr>
<th>MAP product</th>
<th>Minimally acceptable target</th>
<th>Optimal target</th>
<th>Rationale/annotations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPT MAP</td>
<td>Same as above.</td>
<td>Same as above.</td>
<td><strong>Although a contraceptive MAP alone would potentially be distributed through family planning/reproductive health clinics and services, an MPT MAP that co-delivers HIV PrEP will likely need to adhere to the service delivery structure established for HIV PrEP.</strong>&lt;br&gt;<strong>Ultimately, a women’s decision about when to start and stop use of the MPT MAP will depend on her risk for HIV acquisition, side effects, health care provider recommendation, and desire for contraception.</strong></td>
</tr>
</tbody>
</table>

### 2.1 Recommended dose

<table>
<thead>
<tr>
<th>MAP product</th>
<th>Minimally acceptable target</th>
<th>Optimal target</th>
<th>Rationale/annotations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARV MAP</td>
<td>CAB MAP delivers a sustained, uniform, clinically effective dose comparable to the dose delivered by injectable CAB LA to achieve systemic plasma concentration levels required for HIV PrEP.</td>
<td>CAB MAP delivers a sustained, uniform, clinically effective dose that is less than the dose delivered by injectable CAB LA to achieve systemic plasma concentration levels required for HIV PrEP.</td>
<td><strong>Clinical trial participants for safety and efficacy of CAB LA for HIV PrEP received daily oral CAB during the lead-in phase for five weeks, followed by 600 mg of injectable CAB LA delivered by IM injection at two time points four weeks apart (weeks 5 and 9) and every eight weeks thereafter.</strong>&lt;br&gt;<strong>A lead-in phase of daily oral CAB may also be required to assess safety and tolerability to CAB prior to administration of the LA form of CAB or the CAB MAP.</strong></td>
</tr>
<tr>
<td>MPT MAP</td>
<td>Same as above for the ARV component. The dose delivered by MPT MAP containing norelgestromin should match clinically effective plasma concentration levels by other routes of its administration such as transdermal patches (taking into account the different route of administration, and therefore potential bioavailability).</td>
<td>Same as minimally acceptable target.</td>
<td><strong>The CAB and hormonal contraceptive will be in separate microarrays on the MPT MAP and the dose for each should match clinical guidelines for each drug.</strong>&lt;br&gt;<strong>Dose range-finding experiments, first in animals and then in humans, will help determine optimal dosing strategy and must account for the transdermal mode of delivery.</strong></td>
</tr>
</tbody>
</table>

### 2.2 Dose delivered

<table>
<thead>
<tr>
<th>MAP product</th>
<th>Minimally acceptable target</th>
<th>Optimal target</th>
<th>Rationale/annotations</th>
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</thead>
<tbody>
<tr>
<td>ARV MAP</td>
<td>MAP projections are successfully inserted into the skin during each application to ensure that drug delivery is sufficient and consistent.</td>
<td>Same as minimally acceptable target.</td>
<td><strong>Dose of active pharmaceutical ingredient (API) delivered will depend on the percentage of MAP projections inserted in the skin and dissolved by interstitial fluid.</strong>&lt;br&gt;<strong>MAP projections should be sufficiently robust to pierce the skin’s stratum corneum without breaking or bending.</strong>&lt;br&gt;<strong>Consistency of dose delivered must be validated in both in vitro and in vivo studies that quantify API remaining in the MAPs following application.</strong>&lt;br&gt;<strong>MAP projection geometry and length may be altered to optimize dose delivery efficiency.</strong></td>
</tr>
<tr>
<td>MPT MAP</td>
<td>Same as above.</td>
<td>Same as above.</td>
<td>Same as above.</td>
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<tr>
<td>MAP product</td>
<td>Minimally acceptable target</td>
<td>Optimal target</td>
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<tr>
<td><strong>2.3 Drug loading efficiency</strong></td>
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<tr>
<td>ARV MAP</td>
<td>API should be concentrated in the tips of the MAP projections to maximize drug delivery.</td>
<td>Same as minimally acceptable target.</td>
<td>The MAP manufacturing process should concentrate API in the tips of the MAP projections that penetrate the skin, rather than the base, to maximize delivery efficiency and reproducibility and minimize waste and environmental hazards of excess API.</td>
</tr>
<tr>
<td>MPT MAP</td>
<td>Same as above.</td>
<td>Same as above.</td>
<td>Same as above.</td>
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<tr>
<td><strong>2.4 Single patch size</strong></td>
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</tbody>
</table>
| ARV MAP | Smaller than the largest commercially available transdermal patches (<140 cm²—about 12 cm x 12 cm). | Similar to the smallest commercially available transdermal patches (<20 cm²—about 5 cm x 4 cm) and can be successfully applied with one or two fingers. | • Commercially available transdermal patch size range:  
  - 140 cm² lidocaine patches.38  
  - 30 cm² nicotine patches.39  
  - 25 cm² fentanyl patches.40  
  - 20 cm² contraceptive patches.41  
  - CAB MAP size should be as small as is feasible for loading the needed dose of drug, enabling successful application, and maintaining long-term adhesion to skin.  
  - In vitro and in vivo testing will help determine the size of the patch required to deliver a complete dose.  
  - Prototype patches shown to users had dimensions ranging from 46 cm² to 193 cm², including both array area and adhesive borders. User studies in Uganda and South Africa indicated a preference for smaller patches, however a subset of participants showed interest in larger patches with longer duration of protection.  
  • User feedback should also include recommendations and input on maximum acceptable patch size. |
| MPT MAP | Same as above. | MPT MAP will be larger than the CAB MAP, since it will contain two drugs in separate microarrays, but is no more than double the size of the CAB MAP (≤40 cm²: about 6.3 cm x 6.3 cm). | • The MPT MAP is expected to be larger than the CAB MAP, since it will contain two drugs (CAB Na and progestin) in separate microarrays.  
  • Ultimately, the size of the MPT MAP will depend on the intersection of technical feasibility (from both drug-loading and application perspectives) and user acceptability. |
| **2.5 Route of delivery and site of administration** | | | |
| ARV MAP | Transdermal. CAB MAP can be applied to locations on the body (such as the upper arm, back, stomach, or thigh) that provides a relatively flat, firm surface without too much hair to help ensure successful application. Location shall be visible to the patient to facilitate a visual feedback indicator during self-application. | Same as minimally acceptable target. | • MAPs deliver drugs through the skin to target systemic circulation and may facilitate targeting delivery to the lymphatic system, which could be particularly useful for accessing HIV reservoirs for both HIV PrEP and treatment.42  
  • The loaded API should be deposited as a depot and dissolve in interstitial fluid over time to slowly release drugs into the systemic circulation.18  
  • Site of administration will depend on technical feasibility and should be clearly described in labeling and/or package insert/instructions for use.  
  • Feedback from end users during stakeholder interviews and usability studies influence the optimal/target administration site to ensure future product uptake and success. |
<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>MPT MAP</td>
<td>Same as above.</td>
<td>Same as above.</td>
<td>Same as above.</td>
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</table>

### 2.6 Wear time

| ARV MAP | CAB MAP wear time is one hour, which is sufficient for the MAP projections to dissolve completely and deposit the drug formulation. | CAB MAP wear time is less than 20 minutes, which is sufficient for the MAP projections to dissolve completely and deposit the drug formulation. | • Wear time will depend on technical feasibility (i.e., how quickly MAP projections can dissolve in interstitial fluid to deliver the complete drug payload) and must be evaluated in preclinical and clinical studies.  
• Previous market research with MAP delivery for HIV PrEP suggests that end users prefer as short a wear time as possible.  
• User studies in Uganda indicated a strong preference for the wear-time being under 30 minutes, and 20 minutes being the ideal wear-time.  
• In the user studies in South Africa, data indicated that most participants would be willing to wear the patch for up to one hour, though 30 minutes was the limit for a large proportion, with a smaller proportion willing to wear for longer than one hour. |
| MPT MAP | Same as above. | Same as above. | Same as above. |

### 2.7 Frequency of administration

| ARV MAP | CAB MAP is administered once a week to achieve therapeutic efficacy. | CAB MAP is administered monthly. | • Goal of the CAB MAP is to achieve a duration of protection of at least a month; however, a simple MAP product administered weekly may still be beneficial compared to IM injections and is therefore included as a minimal target.  
• Clinical trial participants for safety and efficacy of CAB LA for HIV PrEP have received daily oral CAB during the lead-in phase for five weeks, followed by 600 mg of injectable CAB delivered by IM injection at two time points four weeks apart (weeks 5 and 9) and every eight weeks thereafter.  
• Frequency of administration will ultimately depend on technical feasibility (dosing, clinical efficacy, and duration of protection provided by a single CAB MAP) and will be evaluated in preclinical and clinical trials.  
• The CAB MAP may require an oral lead-in phase, if an oral lead-in phase were still required for the CAB LA injectable at the time of introduction (section 2.1). A loading dose of CAB LA may also be required prior to MAP administration.  
• Frequency of administration should also consider programmatic fit and end user preferences; feedback from end users during stakeholder interviews and usability studies will influence the optimal frequency of administration to help ensure future product uptake and success. Suitability of a higher frequency of administration (e.g., weekly) will likely be dependent on the product being eligible for self-administration.  
• Administration frequency should also align with required frequency of HIV testing for those on PrEP (currently every three months). |
### MAP product

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>ARV MAP</td>
<td>Same as above.</td>
<td>Same as above.</td>
<td>• An ARV MAP with a dose frequency of &gt;=3 months is preferred by users and donors. Based on current PK data for the CAB MAP, this would require changing to a different, more potent API to achieve.</td>
</tr>
</tbody>
</table>
| MPT MAP     | Same as above.               | Same as above. | • Frequency of administration for the contraceptive portion of the MPT MAP should match the frequency of administration for the CAB portion of the MPT MAP.  
  • Similar to the CAB MAP, the first MPT MAP would be administered after the oral lead-in phase for CAB, if an oral lead-in phase were required (section 2.1), as well as a potential CAB LA injection loading dose.  
  • Other long-acting forms of contraception for comparison include:  
    ▪ IM injections of Depo-Provera administered every three months.  
    ▪ Contraceptive patches worn continuously and replaced every seven days. |

### 3. Safety and efficacy

#### 3.1 Safety, adverse events (AEs), and reactions

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<thead>
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</table>
| ARV MAP     | AEs following administration of the CAB MAP are either mild or moderate in severity and percentages of drug-related events are comparable to drug-related events observed during IM injection:45  
  Grade 1—34%  
  Grade 2—44%  
  Grade 3—20%  
  Grade 4—0%  
  Reactions at the site of application, such as redness, tenderness, or swelling, are mild, resolve quickly, and are tolerable to patients and health care providers. | AEs following administration of the CAB MAP are either mild or moderate in severity, with fewer Grade 3 (<20%) drug-related events than the percentage of Grade 3 drug-related events observed during IM injection.45  
  Fewer and less severe reactions observed at the site of application. | • Nausea, headache, and fatigue are common ‘start up syndrome’ side effects associated with currently available oral PrEP. Longer-term changes in renal function and bone density may also occur with Truvada.46  
  • Most common AEs associated with injectable CAB LA include:45,47,48  
    ▪ Injection site reactions (pain, erythema, warmth, nodules, induration, pruritus, swelling, and discoloration); however, participants found these reactions tolerable and preferable compared to daily oral pills.  
    ▪ Upper respiratory tract infection, back pain, headache, chills, nausea, diarrhea, myalgia, and insomnia.  
  • Preclinical and clinical trials are needed to assess the safety of a CAB MAP, including longer-term consequences of exposure to CAB and potential drug-drug interactions.  
  • CAB MAP may require an oral lead-in phase to assess safety and tolerability to the drug in individual patients, the same as injectable CAB LA.  
  • Specific counseling messages may be required to inform patients of potential side effects and how to manage them. |
| MPT MAP     | Same as above for the CAB MAP. Safety profile of the hormonal contraceptive portion of the MAP is comparable to the safety profile of the norelgestromin delivered by current modes of delivery (e.g., injection, transdermal patch, IUDs, implants). | Same as above for the CAB MAP. Safety profile of the hormonal contraceptive portion of the MAP is improved when compared to the safety profile of the progestin delivered by current modes of delivery | • In addition to the potential side effects listed above, an MPT MAP may also include side effects specific to the selected progestin.  
  • Typical side effects of some progestins include:  
    ▪ Weight gain.  
    ▪ Menstrual changes.  
    ▪ Headache.  
    ▪ Nausea and vomiting.  
    ▪ Cramps.  
    ▪ Bloating. |
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<tr>
<th>MAP product</th>
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<th>Optimal target</th>
<th>Rationale/annotations</th>
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</table>
|             | (e.g., injection, transdermal patch, IUDs, implants). |وسط | • Breast tenderness.  
• Upset stomach.  
• Skin irritation.  
• Preclinical and clinical trials are needed to assess the safety of an MPT MAP, including potential drug-drug interactions.  
• Specific counseling messages may be required to inform women of potential side effects and how to manage them. |

### 3.2 Efficacy

| ARV MAP | Efficacy of CAB MAP should be equivalent to efficacy of injectable CAB LA. | Efficacy of CAB MAP should be equivalent to or better than efficacy of injectable CAB LA. | • Efficacy of currently available daily oral PrEP depends largely on adherence.⁴⁹,⁵⁰,⁵¹,⁵²  
• Efficacy of CAB LA injection has been found to be superior to oral PrEP in phase 3 clinical trials.²⁵,²⁶,²⁷ |
| MPT MAP | ARV portion of MAP—same as ARV alone. Contraceptive portion of MAP—efficacy comparable to other forms of long-acting reversible contraception when used correctly (94% effective). | ARV portion of MAP—same as minimally acceptable target. Contraceptive portion of MAP—efficacy comparable to other forms of long-acting reversible contraception when used correctly (better than 94% effective). | • Efficacy of contraceptives depends largely on adherence and correct and consistent use.⁵³,⁵⁴  
• When used correctly, efficacy of currently available long-acting reversible contraception ranges from approximately 94% for injectable contraception to better than 99% for implants, contraceptive patches, and IUDs.⁵⁵,⁵⁶  
• Studies should be conducted to confirm that the hormonal contraceptive does not influence or reduce efficacy of CAB.⁵⁷,⁵⁸  
• Efficacy may also depend on body mass index, which should be taken into account.⁵⁹,⁶⁰ |

### 3.3 Effectiveness

| ARV MAP | Effectiveness of CAB MAP should be equivalent to effectiveness of injectable CAB LA. | Effectiveness of CAB MAP should be better than effectiveness of injectable CAB LA. | • In a meta-analysis of 18 studies, the use of TDF or TDF/FTC reduced the risk of HIV acquisition by 70% in patients highly adherent to PrEP.⁶¹  
• Effectiveness of CAB MAP will be determined once a product is available, but end user feedback on design and programmatic fit may help increase effectiveness of a CAB MAP compared to other delivery options for HIV PrEP. |
| MPT MAP | ARV portion of MAP – same as ARV alone. Effectiveness of MPT MAP should be equivalent to effectiveness of currently available methods of long-acting reversible contraceptives. | Effectiveness of MPT MAP should be equivalent to or better than effectiveness of currently available methods of long-acting reversible contraceptives. | • Same as above.  
• Long-acting reversible contraceptive methods, such as IUDs and implants, may have higher effectiveness compared to methods that rely on the user for consistent use, such as contraceptive pills, injectables, patches, and rings, though use of long-acting reversible contraceptives in some countries may be quite low.⁶²,⁶³ |
### 4. Clinical pharmacology

#### 4.1 Pharmacokinetics (PK) and pharmacodynamics (PD)

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<th>MAP product</th>
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| **ARV MAP** | Minimum plasma concentration levels ($C_{\text{min}}$) for CAB LA IM injections (to maintain 4 x IC₉₀ at $C_{\text{min}}$).<sup>45</sup> | Similar exposures compared to CAB LA IM injections on minimum ($C_{\text{min}}$), maximum ($C_{\text{max}}$), and overall exposure (AUC) of drug concentration in plasma. | • PK/PD profile, plasma exposures, and distribution in tissue for CAB MAP may be different than CAB LA delivered by IM injection and must be determined in clinical trials.  
• Summary of PK parameters of 800 mg of CAB LA after four quarterly IM injections:<sup>47,64</sup>  
  ▪ $C_{\text{max}} = 3.3$ ug/mL  
  ▪ $C_{\text{min}} = 1.1$ ug/mL  
  ▪ $T_{\text{max}} = 15$ days  
  ▪ $\text{AUC} = 4467$ ug x h/mL  
  ▪ $T_{1/2} = 21–52$ days (LA injectable);<sup>64</sup> 40 hours (oral CAB)<sup>65</sup>  
• CAB is metabolized primarily by uridine diphosphate glucuronosyltransferase (UGT) 1A1 and does not induce the cytochrome P450 metabolic pathway.<sup>66</sup> |
| **MPT MAP** | Same as above for ARV alone. For contraceptive portion, clinical effectiveness should be comparable to standard route of delivery of norelgestromin (e.g., transdermal patches commercially available). | Same as above for ARV alone. For contraceptive portion, higher clinical effectiveness compared to standard route of delivery. | • Same as above for ARV alone.  
• The PK/PD profile and clinical effectiveness targets for the contraceptive portion of the MPT map should be comparable to approved norelgestromin products such as the transdermal patch.  
• Clinical effectiveness targets for the contraceptive portion of the MPT MAP will depend on the selected progestin.  
• Selected progestin should not interact with CAB. |

#### 4.2 HIV resistance profile

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| **ARV MAP** | Similar resistance profile to injectable CAB LA. | Reduced risk of resistance compared to injectable CAB LA. | • Based on current preclinical data, potential for generating resistant strains of HIV to CAB LA may be relatively rare in INSTI-naïve patients.<sup>29</sup>  
• An extended tail of sub-therapeutic drug level at the end of CAB LA therapy may increase the risk of developing resistance in patients lost to follow up.<sup>67</sup>  
• Similar to current guidelines for oral PrEP, patients may need to be tested for HIV once every three months to reduce the chance of developing HIV resistance should he/she become infected. |
| **MPT MAP** | Same as above for ARV alone. Not applicable for contraceptive portion. | Same as above for ARV alone. Not applicable for contraceptive portion. | • Same as above for ARV alone portion of the MPT MAP.  
• HIV resistance not applicable to progestin. |

#### 4.3 Formulation

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| **ARV MAP** | Formulation containing CAB as an active ingredient with necessary excipients (e.g., stabilizers, polymer, other inactive ingredients) that are currently used clinically and generally regarded as safe (GRAS) by the FDA. | Same as minimal. | • CAB MAP will be governed by United States Pharmacopeia and regulatory requirements that specify that the MAP product must be uniform in dose, content, identity, purity, sterility/endotoxins, etc.<sup>68</sup>  
• As dissolving MAP technology deposits polymer in the skin, it will be important to confirm through safety studies in humans that the polymer deposited in the skin biodegrades on site or is systemically absorbed and excreted by glomerular filtration.<sup>13</sup>  
• Future work in development of regulatory standards and quality assurance testing for MAPs will be required to move the delivery platform toward commercialization.<sup>50</sup> |
| **MPT MAP** | Same as above. | Same as above. | Same as above. |
## 5. MAP application and delivery

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<th>MAP product</th>
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<tr>
<td><strong>5.1 Human factors and ease of use</strong></td>
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<tr>
<td>ARV MAP</td>
<td>The device shall be useable by the widest practical range of users according to the general principles laid out in international standards. Minimal training required (e.g., 15 minutes) for MAP to be correctly administered by a health care provider or patient (self-administration).</td>
<td>No training required. Similar to currently available transdermal patches, MAP can be correctly administered by a health care provider or patient (self-administration) after reading simple product instructions or package insert.</td>
<td>• CAB MAP would be prescribed and delivered in a clinic by a health care provider qualified to prescribe HIV PrEP according to standard of care guidelines (see 1.1 Indication and target population), with the potential for self-administration depending on dosing frequency and PrEP guidelines. • Patches are designed to be easy to apply and have been shown to facilitate consistent, reproducible application by non–medically trained volunteers.69 • Injectable CAB LA may preclude self-administration, unless delivered in an easy-to-use, prefilled, autodisable syringe.70 • MAP application procedure must be evaluated according to human factors guidelines, such as IEC 62366,71 ANSI/AAMI HE75,72 and MHRA guidance.73</td>
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<tr>
<td>MPT MAP</td>
<td>Same as above.</td>
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<tr>
<td><strong>5.2 Applicator</strong></td>
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<tr>
<td>ARV MAP</td>
<td>Requires a simple, single-use, disposable applicator.</td>
<td>Use of an applicator is not required. Similar to standard transdermal patches, the MAP is a standalone patch that can be successfully administered manually.</td>
<td>• Ideally, the MAP could be successfully applied to the skin by manual pressure without the use of an applicator because an applicator would increase cost. • and package volume. • However, a simple, single-use disposable applicator may be required to ensure the MAP is applied consistently and correctly (to be determined). • The geometry and design of the MAP and its projections will inform the need for an applicator. • Regardless of the need for an applicator, usability studies will be required to ensure that the MAP can be successfully applied by intended users.</td>
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<tr>
<td>MPT MAP</td>
<td>Same as above.</td>
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<td>Same as above.</td>
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<tr>
<td><strong>5.3 Pretreatment of skin</strong></td>
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<tr>
<td>ARV MAP</td>
<td>Skin should be clean, dry, and disinfected prior to MAP application (same as requirements for IM injection).74</td>
<td>No pre-treatment should be necessary.</td>
<td>• MAP application should comply with requirements for pretreatment of skin prior to IM injection, though it is understood this may not always be applied in practice. • Studies to characterize MAPs have shown that microorganisms do not cross the epidermal skin layer following microarray puncture and that skin or systemic infection is highly unlikely.75 • Future studies should assess the effect of other skin parameters, such as sweat, moisture, oil, elasticity, and temperature on MAP delivery. • In case pre-treatment is determined to be needed for MAP application, the appliances needed (e.g., alcohol wipe) should be included in the MAP packaging.</td>
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<tr>
<td>MPT MAP</td>
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<td>Same as above.</td>
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<tr>
<td><strong>5.4 Indication of successful MAP application</strong></td>
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| ARV MAP | The design includes an auditory or visual cue as an integrated feature of the patch to indicate successful application. This indicator would provide the user feedback that the patch was properly applied to the skin. The indicator should be intuitive and easily understood by intended users. | Same as minimally acceptable with the addition of a time indicator, which would be added to indicate that the required amount of time for full dose delivery of the drug has been passed before patch removal. | • There is likely a need for an auditory or visual (color-based) indicator to confirm appropriate pressure has been applied over the entire surface area during patch application to ensure that all MAP projections are inserted into the skin correctly.  
• The user studies utilized mocked-up indicators in “crush” and “slide over” forms, which were a proxy to indicate successful application of the MAP. Study participants indicated a preference for the crush over the slide feedback indicator. However, the respondents explained that neither the crush or the slide feedback indicators/mechanisms gave them sufficient confidence that the MAP had been correctly applied or that all the drug has entered the body. They suggested feedback indicators/mechanisms that changed color or made noise in order to reassure the users that the MAP was correctly applied and the drug properly administered.  
• The success rate of delivery (penetration of the skin by a sufficient percentage of the microarray projections) by typical users in target countries should be validated under ideal and non-ideal conditions (e.g., with minimal or no prior training and instructions).  
• Future usability studies may be required to ensure that intended users can successfully understand and confirm indication of successful MAP application. |
| MPT MAP | Same as above. | Same as above. | Same as above. |
| **5.5 Adhesion** | | | |
| ARV MAP | Able to securely adhere to the skin for duration of treatment (see 2.3). | Same as minimally acceptable target. | • MAP should adhere to the skin for the duration of treatment (assuming 1-hour wear time or less) and be removed easily with two fingers at the end of treatment.  
• The patch should remain on the skin through typical movement and activities, excluding bathing, showering, and exercising, during the required patch wear time.  
• The ability of the adhesive backing on the MAP to remain adhered to the target site should be validated under different environmental conditions (e.g., temperature and humidity) that will be encountered in target countries of use and with a range of diverse skin types and locations on the body).  
• Clinical studies should evaluate the ability of the patch to stay in place for the duration of treatment.  
• For comparison, contraceptive patches are intended to remain in place for seven consecutive days. |
| MPT MAP | Same as above. | Same as above. | Same as above. |
| **5.6 Reproducibility** | | | |
| ARV MAP | User (health care provider) should successfully apply the patch after minimal training. User (health care provider and self-administration) should successfully apply the patch after reading instructions for use or the package insert. | Reproducibility of self-administration should be measured and assessed for the MAP product. | |
| MPT MAP | Same as above. | Same as above. | Same as above. |
### 5.7 Discreet use

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</table>
| **ARV MAP** | Similar to contraceptive patches, the MAP is not easily visible to casual observers during wear time (i.e., can be hidden under clothing). After removal, projections do not leave long-lasting marks (more than two to three days) on the skin and are acceptable to patients. | Same as minimally acceptable target, except duration of potential marks is less (e.g., potential marks after MAP application resolve within one hour). | • The MAP will be designed to be a discreet delivery device (as size will be minimized), it will not require long-term continuous wear, and it can be easily discarded after use.  
• MAP design and packaging should aim to be as inconspicuous as possible to enable self-administration in a home setting.44  
• MAP projections containing CAB will dissolve and should not leave a lasting mark on the skin or any indication that the individual received HIV PrEP to avoid any potential for stigma, partner violence, or dispute.  
• Potential marks could be assessed during acceptability studies and should be assessed during preclinical and clinical trials. |
| **MPT MAP** | Same as above. | Same as above. | Same as above for the CAB MAP.  
In addition, MAP projections containing the progestin will dissolve and should not leave a lasting mark on the skin or any indication that the individual received contraception to avoid any potential for stigma, partner violence, or dispute. |

### 5.8 Disposal

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| **ARV MAP** | MAP should be disposed of as non-sharps biohazard waste. MAP and packaging materials should be safe to dispose of in typical health care waste management practices (burning, burial). | MAP should be safe to dispose of at home. | • After removal of the patch, the MAP projections are dissolved and no longer able to penetrate skin, thereby precluding the potential for reuse or needlestick injury.  
• MAP technology holds particular promise for reducing the environmental impact of providing medical services by reducing the volume of biohazardous waste and eliminating the need for injections that generate sharps waste that can be an infectious disease hazard to communities if disposed of improperly.  
• MAP design features should mitigate risks to community, household members, and environment associated with exposure to residual drug on the MAP backing or surface of the skin after MAP use.  
• MAPs should be made of biodegradable materials that limit environmental impact; future assessments should review the MAP life cycle from manufacture to disposal to identify and address potential areas for reducing waste and minimizing environmental impact. |
| **MPT MAP** | Same as above. | Same as above. | Same as above. |

### 6. Storage, handling, and distribution

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| **ARV MAP** | Individual MAPs will be packaged in a protective primary container fabricated from a moisture-impermeable barrier material that prevents | Same as minimally acceptable target. | • Packaging components and design must follow regulatory guidance, such as FDA guidance and ISO standards.79,80  
Following are the recommendations for packaging based on PATH’s exploration of technical, usability, and general design considerations in PATH packaging report.81 |

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44: Reference or citation.
79,80: References or citations.
81: Reference or citation.
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|             | damage to the MAP projections. CAB MAP is stable in primary packaging in hot and very humid storage conditions of 30°C, 75% relative humidity (RH) (climatic zone IVb).<sup>78</sup> | • An integrated MAP delivery device can reduce packaging waste and lessen requirements for further packaging.  
• 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.  
• 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.  
• 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.  
• For MAP products anticipating high-volume production, packaging solutions that are easily scalable, such as web-based designs, should be prioritized.  
• The MAP will require a moisture-impermeable barrier, such as a foil pouch, and protection from the environment and mechanical impact during shipping.  
• CAB MAP may also need to be packaged with a desiccant.  
• CAB MAP should be effective in the intended use environment (i.e., sub-Saharan Africa); should not require cold chain storage (currently available oral PrEP can be stored at room temperature and must be protected from light and moisture; injectable CAB LA can be stored at room temperature, with excursions permitted 2°C–30°C).  
• Stability studies according to regulatory guidance of the CAB MAP will be required to ensure safety and efficacy of the product throughout the duration of labeled shelf life and required storage conditions.<sup>82,83,84</sup>  
• The environmental impact of primary packaging should be minimized. |
| MPT MAP     | Same as above.               | Same as above. | Same as above for the CAB MAP.  
In addition, long-acting reversible contraceptives, such as injectable Depo-Provera, should be protected from light and moisture and stored at room temperature.<sup>85,86</sup> |
| 6.2 Product shelf life | | | |
| ARV MAP     | At least three-year shelf life from date of manufacture when stored according to instructions. | More than three-year shelf life from date of manufacture when stored according to instructions. | Storage of CAB MAP should be comparable to storage of the CAB LA injectable formulation, which is stable for three years at room temperature from date of manufacture. |
| MPT MAP     | Same as above.               | Same as above. | Shelf life of long-acting contraceptives, such as injectable Depo-Provera, ranges from 18 months to two years depending on packaging presentation (e.g., vial or syringe). |
| 6.3 Secondary packaging and storage volume | | | |
| ARV MAP     | MAPs within their individual primary packages will be grouped into a secondary package, such as a cardboard box, to facilitate transport and storage. | Same as minimal. | • Secondary packaging should facilitate transport, storage, and handling within the public-sector health system and distribution channels.  
• Storage volume should be efficient and minimized as much as possible, though cold chain is not required.  
• Future packaging should be developed to optimize packaging configuration from a technical, programmatic, and usability standpoint. |
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<tr>
<td>MPT MAP</td>
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### 6.4 Labeling

| ARV MAP      | Labels should comply with regulatory guidance and include required sections and formatting. | Same as minimal. | • MAPs should be clearly labeled on both the primary and secondary packaging with simple language to explain pertinent information, such as product title, indication and usage, dosage forms and strength, and contraindications, which enables consistently successful use by the intended end user.  
• If more detail is required, a package insert with instructions for use may be added and a job aid developed. Simple pictorial instructions may be included. |
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<td>MPT MAP</td>
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### 6.5 Product shelf life

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<tr>
<th>ARV MAP</th>
<th>At least three-year shelf life from date of manufacture when stored according to instructions.</th>
<th>More than three-year shelf life from date of manufacture when stored according to instructions.</th>
<th>Storage of CAB MAP should be comparable to storage of the CAB LA injectable formulation, which is stable for three years at room temperature from date of manufacture.</th>
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<td>MPT MAP</td>
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<td>Same as above.</td>
<td>Shelf life of long-acting contraceptives, such as injectable Depo-Provera, ranges from 18 months to two years depending on packaging presentation (e.g., vial or syringe).</td>
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### 6.6 Stability outside of primary packaging and before skin application

| ARV MAP      | Patch is stable up to 10 minutes at 30°C, 75% RH, outside of primary packaging before skin application. | Patch is stable for up to 20 minutes at 30°C, 75% RH, outside of primary packaging before skin application. | • The MAP will be exposed to ambient humidity after the primary package is opened and therefore the projections will slowly start to dissolve (as they are designed to do in contact with moisture), eventually rendering them non-functional. Therefore, patch application is expected immediately after opening the primary packaging.  
• Stability of the MAP projections outside primary packaging will be validated in future studies.  
• Limitations of exposures (temperature, light, humidity) should be included in instructions and labeling on the final product. |
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<td>MPT MAP</td>
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### 6.7 Distribution/supply chain considerations

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<tr>
<th>ARV MAP</th>
<th>Storage volume of a CAB MAP (in secondary packaging) is feasible for distribution through the public health system in target countries.</th>
<th>Same as minimal.</th>
<th>Packaging volume should be suitable to allow for consumer supply and use within existing HIV PrEP or pharmacy distribution channels.</th>
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<tbody>
<tr>
<td>MPT MAP</td>
<td>Same as above.</td>
<td>Same as above.</td>
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<tr>
<td>MAP product</td>
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| **ARV MAP** | To be determined             | To be determined | • Currently available PrEP can be cost-effective, and LA PrEP may be even more cost-effective, since LA APIs are typically potent and effective at low doses.\(^2,8^8\)
• Developing and establishing an efficient Good Manufacturing Practices manufacturing process for scaled MAP production will take initial investment.\(^6^9\)
• The cost of a CAB MAP will contribute to overall acceptability and uptake, similar to other forms of PrEP.\(^9^0\) Different formulations of CAB may influence the cost and overall acceptability and uptake a CAB MAP.
• A preliminary cost of goods sold (COGS) analysis for a dissolving MAP for delivery of a vaccine suggests that the COGS of the MAP could be less than US$1 per dose at high production volumes, excluding the cost of the vaccine antigen.\(^9^1\) However, in case of a CAB MAP, API dose volume, and the percent of the API successfully delivered to the tissue via a MAP, determine the necessary the size of a MAP. Under current production methods, a MAP delivering a dose size required for CAB would be several times larger than an equivalent dissolving MAP delivering a vaccine, and thus will require multiple arrays and will increase cost significantly.
• Future economic analyses, including COGS and cost of delivery, will need to be conducted for more precise cost estimates.
• Ultimately, costs of MAP delivery for HIV PrEP will need to be evaluated within the broader societal context and landscape of the HIV epidemic.\(^9^2\) |
| **MPT MAP** | To be determined             | To be determined | • Same as above for the CAB MAP.
• Long-acting reversible contraception can be cost-effective but depends on uptake and use.\(^9^3\) |
References


91 PATH unpublished data. Results presented at International Microneedles Conference. 2016.
