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Review

Prioritizing multipurpose prevention technology development and investments using a target product profile

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ABSTRACT

Multipurpose prevention technologies (MPTs) represent a powerful opportunity to address the unmet sexual and reproductive health needs of women in at-risk populations around the world in an efficient and cost-effective manner. The development of MPT products for the combination prevention of pregnancy and sexually transmitted infections (including HIV) is a high-risk/high-gain, expensive process. The associated challenges are compounded by limitations in available resources for the development, evaluation, and delivery of such products. Consequently, an objective process for identifying MPT products with the highest public health impact potential is necessary to serve as the basis of coordinated investment of supporting agencies in the development of such products. Moreover, this process would serve as a framework for product development organizations, guiding their product development strategies. The Scientific Agenda Working Group of the Initiative for Multipurpose Prevention Technologies conducted an MPT pipeline evaluation exercise for the purpose of defining specific MPT product priorities, and to identify MPT technology gaps which need to be addressed in order to achieve development of optimal products. Through a formal and objective process, a set of MPT priority product recommendations emerged, along with several priority MPT gaps. Further, specific MPT development process priorities were identified. The detailed process and summary findings of this exercise are presented here. This article is based on a presentation at the "Product Development Workshop 2013: HIV and Multipurpose Prevention Technologies," held in Arlington, Virginia on February 21–22, 2013. It forms part of a special supplement to *Antiviral Research*.

Contents

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1. Introduction

Multipurpose prevention technologies (MPTs) are single entity formulations, technologies or strategies designed to address at least two sexual and reproductive health (SRH) medical indications (Harrison et al., 2013). Although such products could encompass a wide range of combination indications, MPT have come to specifically refer to single entity products that combine protection against unintended pregnancy and sexually transmitted infections (STIs), including HIV. MPT products represent a powerful means of achieving high public health impact in at-risk populations around the world. MPT products could achieve meaningful reductions in terms of cost of goods (COG), and lead to significant efficiencies in product delivery, and access when compared to efforts necessary for delivery of multiple products targeting separate indications. However, development of MPT products can be technologically complex, expensive, and risky. To accelerate efficient development of MPT products, a target product profile (Tebbey and Rink, 2009) defining appropriate product attributes necessary for achieving high public health impact is needed. Together, a general MPT TPP, a prioritized pipeline, and identified gaps in MPT development can serve as the basis for objective, and coordinated global investment by supporting agencies in the development of MPT products with highest impact potential.

To support the scientific, technical, and investment needs of the MPT field, the Initiative for Multipurpose Prevention Technologies (IMPT) convened a Scientific Agenda Working Group (SAWG) in 2011 to develop a TPP for MPTs, and to evaluate and prioritize the current MPT product development pipeline. The IMPT is an international partnership of relevant stakeholders who support the multi-disciplinary needs of MPTs. The IMPT is managed by the Coalition Advancing Multipurpose Innovations (CAMI; Folsom, CA), which serves as the formal Secretariat for the Initiative. As such, CAMI facilitated a series of formal IMPT efforts conducted by the SAWG to address the need for a general MPT-related TPP, as well as the need to conduct an objective evaluation and prioritization of the MPT development pipeline. Details regarding the activities and efforts of the IMPT and SAWG under CAMI management have been summarized elsewhere (Harrison et al., 2013). This report will summarize specific efforts by the IMPT/SAWG to define and evaluate the current MPT development pipeline and candidate MPT component technologies, to prioritize candidate technologies within the pipeline, and to identify relevant gaps in the MPT pipeline or product development process.

2. The MPT pipeline prioritization process

MPT products can exist as a range of product types, including multi-target vaccines; co-formulation of multiple drugs–each for different indications-into a single dosage form; or drug(s) + device combinations targeting multiple indications. Although MPT-type vaccines have been developed, and are commercially available for other indications (Lievano et al., 2012), MPT-type vaccine products to address multiple SRH needs are lacking. In particular, the continuing absence of an effective vaccine against HIV infection has precluded any possibility of developing an MPT-type vaccine that targets HIV and an additional STI. Although an efficacious HPV vaccine is available and is being introduced (Hopkins and Wood, 2013), there has not been similar success with the long range effort to develop an anti-HSV vaccine, or vaccines against other STIs (e.g., *Chlamydia trachomatis*, *Treponema pallidum*, *Neisseria gonorrhoeae*, etc.). Given the early stage of development of vaccines for HIV or other STIs, MPT type vaccines for these indications are generally thought to be on a relatively long development timeline that will require a combination of basic science research and vaccine development type investments. However, it is arguably possible that drug + drug or drug + device combination MPT products for the prevention of HIV, other STIs, and unintended pregnancy could be developed, and available in less than 10 years. Therefore, the current focus of the product prioritization and pipeline gap analysis efforts was on these types of MPT combination products instead of MPT vaccine development.

The overall goal of the MPT pipeline prioritization exercise was to provide an objective basis for coordinated investments by supporting agencies and developer partnerships for those MPT products with the highest potential for public health impact. Therefore, it was important for the IMPT/SAWG to include experts who could represent those funding organizations interested in supporting MPT development. Further, the SAWG members needed to have sufficient technical expertise related to MPT product concepts and the associated indications, while remaining independent from any organizations directly involved in specific MPT product development. Consequently, the members of the IMPT/SAWG represented major government and private funding organizations with strong interest in developing prevention products appropriate for at-risk populations in low resource settings around the globe. Further, the SAWG also included independent SRH researchers from South Africa, India, and China, to assist in ensuring attention to different regional needs for specific combinations of indications.

Alongside the formation of an appropriately comprised SAWG, it was also necessary to establish relevant evaluation criteria for assessment of the MPT development pipeline. This milestone was achieved by the IMPT in 2011 with the completion of a comprehensive process resulting in a general MPT TPP (IMPT, 2011). A partial listing of key elements of this TPP are provided in Table 1a, and include the priority combination indications for MPT products. Importantly, the TPP development effort revealed that the specific prioritization of these combination indications varied by geographic region, suggesting that highest impact MPT products would need to accommodate specific regional needs. Other relevant variables outside of the TPP that were deemed critical for MPT development were also defined (see Table 1b). These additional evaluation criteria focused on variables associated with time, and cost of development, user acceptability, and factors affecting feasibility, and cost for delivery, and access.

The final element required for the MPT pipeline prioritization and gap analysis was the exhaustive compilation of MPT products and relevant MPT component technologies currently in development. The process of identifying these entities involved an extensive literature review, as well as a review of published information on the funding of MPT or MPT component entities. A summary of the types of products identified by this effort is provided in Table 2, and includes more than 100 total drugs and products.

Table 1a
TPP parameters for priority MPT development.

Parameter	Preferred criteria	Comments
Indications*	• Prevention of HIV/Contraception • Prevention of HIV/STI • Prevention of STI/Contraception	• Priority STI: HSV, HPV • Prevention of BV
Target efficacy	• HIV: 80% • Contraception: > Current levels per contraceptive form • STI: 80%	• HIV minimally 40% • Current levels with recommended use • STI minimally 40%
Side effects	• Grade 1 adverse events	
Dosage forms	• Sustained release and long acting • On-demand	• >1 month to years • Gels, films, oral pills, etc.
Contraindications	• No pregnancy or major systems warnings • Compatible with other vaginal products and regional treatment needs	• E.g., TB treatment, yeast infections, other
Reversibility	• 0–24 h for topical/oral options • <14 days for injectables, implants	• Oral pills, gels, IVR • Up to 90 days upper limit
Shelf life	• >36 months	• 24 months minimal
Storage conditions	• 40 °C/75% relative humidity (RH)	• 15–30 °C/65% RH minimally acceptable

* Note: Indication priorities varied by geographic region. For example, the priority combination indications in sub-Saharan Africa are HIV prevention/contraception; in India, they are STI prevention/contraception.

Table 1b
Non-TPP parameters relevant to MPT prioritization.

Cost of goods	Potential for discreet use/concealability
Cost of development to licensure	Required level of provider support
Time to regulatory licensure	Acceptability and adherence potential
Manufacturing and scalability	Effects on lifestyle
Intellectual property status	Effects on sexual experience
Product development organization	Feasibility for delivery and access
Product presentation/packaging	Disposal requirements/waste material

Table 2
MPT products, component technologies, and drug types identified for prioritization.

10 MPT IVR	10 Single indication IVR	31 HIV entry inhibitors
3 On-demand MPT	12 On-demand HIV only	11 HIV enzyme inhibitors
2 barrier MPT	2 Injectable HIV only	7 Other HIV inhibitors
23 HC products	2 Lacto-based products	29 Non-HC products

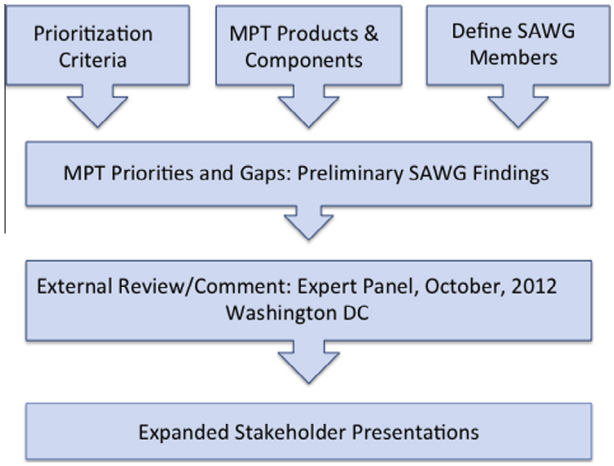

Fig. 1. MPT pipeline prioritization and gap analysis. This figure depicts the progression of activities used in the MPT pipeline prioritization and gap analysis process by the SAWG.

The prioritization and gap analysis process was built upon the MPT TPP and involved a series of steps managed by the SAWG, as outlined in Fig. 1. In the context of the established TPP and other prioritization criteria, the members of the SAWG analyzed the compiled summary of MPT and MPT component technologies, resulting in a preliminary prioritization summary of MPT products. Importantly, the SAWG did not conduct this evaluation for purposes of specifically endorsing individual products for investment by supporting agencies. First, there was insufficient research data available to the SAWG to allow for such a detailed review of individual product candidates in the pipeline. Further, the SAWG effort was designed to maintain neutrality by the IMPT in terms of specific product endorsement. The priority mission of the IMPT is to serve the broad interests of the MPT field, which is best achieved by remaining neutral with regard to specific product development decisions. The prioritization process also served to identify specific gaps in the MPT pipeline through the determination of product or technology deficiencies relative to the priorities defined in the TPP.

The final element of the prioritization and gap identification exercise was a comprehensive review of the preliminary SAWG findings by external experts and stakeholders. This was achieved by a two-step process. First, in October 2012 the preliminary findings were presented to a panel of experts external to the SAWG, who had relevant expertise in terms of the unmet medical needs targeted by MPTs, and the critical development, and delivery/access issues confronting MPT products. This panel was comprised of experts who were not aligned with the development of any specific MPT product in order to maintain a neutral review. The panel was comprised of representatives from academia, industry, the public health arena and governments, and was organized into four key review areas: technical development and manufacturing, regulatory, acceptability, and end user prospective, and delivery/access. Once this neutral expert review was completed, the revised findings were presented in a standardized presentation format to groups of stakeholders in multiple public venues for additional comment and critique. Specifically, in February 2013 the prioritization and gap analysis findings were presented at the *2013 Annual Meeting of the Microbicides Trial Network* (Bethesda, MD) and the CONRAD sponsored *Product Development Workshop 2013: HIV Prevention and MPTs* (Arlington, VA). The findings were also presented to a subgroup of the *Reproductive Health Supplies Coalition* (Washington, DC) in March, 2013. Based upon meeting participant feedback and comments to a standardized series of questions incorporated into each presentation, the summary findings, and associated comments have been organized into this final reporting of the MPT pipeline prioritization and gap analysis.

3. Summary prioritization of the MPT pipeline

A summary of the prioritization and pipeline gap findings is provided in Table 3.

3.1. Active pharmaceutical ingredients (APIs)

MPT products require active pharmaceutical ingredients (APIs), or drug substances, that are active for the specific priority indications identified in the TPP, namely the prevention of HIV infection, the prevention of other STIs, and the prevention of unintended pregnancy. A wide range of physically and chemically distinct molecular entities is available for potentially addressing the HIV prevention and unintended pregnancy indications (less so for other STI prevention, as described below). Some of these available APIs are licensed drugs and already commercially available, while others are in the very earliest stages of post-discovery evaluation. These compounds differ in terms of mechanism of action (MoA), potency, safety, complexity for synthesis, and manufacturing scale up, dosage form compatibility, storage requirements, and shelf life, cost, and other relevant development parameters. Based on the requirements of the MPT TPP, and other criteria that are generally relevant to drug product development, specific API types for each of the target MPT indications were prioritized.

3.1.1. Prevention of HIV

The SAWG determined that small organic molecule anti-retroviral (ARV) agents are the priority API for MPTs targeting HIV prevention. This conclusion was based on a number of factors including: 1) the established potency and safety of such drugs; 2) the efficacy of such compounds in the treatment of HIV infection (Maltêz et al., 2011); 3) the successful use of such drugs for HIV prevention (Grant et al., 2010; Baeten et al., 2012; Karim et al., 2010); 4) the fact that many such drugs have been licensed by regulatory agencies around the world; 5) the pre-existing safety and quality data for such drugs; and 6) the fact that API manufacturing and supply issues for many ARVs have already been resolved. The advanced state of many ARVs either as treatment or prevention products has less risk than that associated with the development of new, early stage drugs. Other types of HIV prevention API were considered, including protein and peptide options (e.g., Lederman et al., 2004; Emau et al., 2007), broad spectrum type products (Karim et al., 2011), and natural products (Talwar et al., 2000). Although these types of compounds have several positive attributes as HIV prevention APIs, issues regarding stage of development, costs, time to approval, compatibility with appropriate dosage forms, and other factors prevented their being characterized as higher priority options.

Despite the many advantages of ARV-based APIs for HIV prevention in MPT products, several concerns regarding these drugs were identified by the SAWG and the reviewing groups. First, current ARV-based HIV prevention is heavily focused on the development of reverse transcriptase inhibitors (RTIs), including both nucleoside (NRTIs), and non-nucleoside RTIs (Karim et al., 2010; Baeten et al., 2012). Other antiviral MoAs have not had the benefit of such comprehensive evaluation for HIV prevention. Recently however, drugs with other MoAs have received increasing consideration for HIV prevention, including the CCR5 entry blocker *Microbicides* (Neff et al., 2011), and the integrase inhibitor GSK ′744 (Andrews et al., 2013). Given this high level of focus on RTIs for HIV prevention, the SAWG called for an expansion in the evaluation of ARVs for MPT development to include additional antiviral MoAs. Other issues regarding ARV-based MPT products included concerns over the long term use of such products by otherwise healthy HIV-negative people, the potential risk for resistance selection in seroconverters using ARV-based MPTs who are unaware of their HIV status, the effects of intermittent use of ARVs in MPT products designed for on-demand use only, and the likely need for periodic HIV testing in the medical management of people using ARV-based MPTs.

3.1.2. Prevention of unintended pregnancy

For the contraception indication, the SAWG recommended prioritizing hormonal APIs in MPT development. This recommendation was based on the long established safety and effectiveness of hormonal contraceptives (HCs), the successful development of different configurations of HC dosage forms (oral, injectable, implantable, etc.), as well as the fact that such products are already in widespread use in the populations that would benefit from MPTs. The synthetic progestin levonorgestrel (LNG) was seen as a potential priority HC option for MPTs based on its safety and effectiveness (Mansour, 2012), but other HC options for MPT should also be explored.

Further, the SAWG and the expert review panel noted that drug alternatives to HCs, although desirable, were in very early stages of development, and would likely not be viable options for MPT products in the next 7–10 years. Although non-hormonal drug options for contraception are a clear priority, given their potential for fewer side effects and use in "on-demand" products, these candidates are still at an early stage of post-discovery evaluation, and are, therefore, of limited availability for development. The SAWG and the expert review panel noted that, while barrier devices (e.g., female condoms, diaphragms, and cervical caps) are available forms of non-hormonal contraception, concerns about user adherence and efficacy led to their being ranked a lower priority for the unintended pregnancy indication, except possibly in an on-demand formulation (see Section 3.2.3.).

Like ARVs for the HIV prevention indication, it was also acknowledged that there are a number of unresolved issues associated with the use of HCs for prevention of unintended pregnancy. A concern identified by the SAWG and the expert reviewers was the fact that episodic use of HCs in on-demand type MPT products could be problematic due to potential effects on menses and ovulation. Inconsistent use patterns with MPTs containing low dose HCs could lead to unacceptable effects for users, such as frequent intermittent bleeding. It was also recognized that even with a sustained use HC-based MPT, effects on menses (e.g., amenorrhea, intermittent bleeding) and the product use requirement during menses (e.g., continuous use of vaginal rings) could present use issues for different populations. Lastly, it was recognized that there are outstanding questions regarding the use of certain HC products and the risk of HIV infection (Heffron et al., 2012). Although this is an important issue relevant to MPT development strategies, it was recognized that the debated increased HIV infection risk potentially associated with the use of certain HCs was being independently studied within HIV prevention and family planning fields, and any outcomes would be used to inform, and refine MPT development strategies.

3.1.3. Prevention of STIs

STIs are a complicated mix of specific infections caused by very different bacteria, viruses, and protozoa. The situation regarding STI prevention prioritization is further complicated by the limited availability of surveillance data from key regions of the world. The MPT TPP exercise indicated that prevention of HPV and HSV-2 were priority indications among the many STIs (IMPT, 2011); however, it is clear that other STIs also represent major public health risks, and thus need to be part of the broader MPT development strategy. Independent of the diversity and complexity of the STI prevention indications of MPTs, the SAWG determined that a lack of pathogen–specific drugs for the prevention of either viral or cellular STIs is a significant gap in the MPT development pipeline. It was recognized that specific anti-HSV agents for infection prevention have been evaluated (Keller et al., 2012; Fernández-Romero et al., 2012), as has at least one compound for the prevention of HPV (Marais et al., 2011). However, there has been very little success in the identification of compounds appropriate for the

prevention of other STIs. Early attempts to use broad spectrum type compounds for STI prevention were not successful (Karim et al., 2011). Although the need for more potent pathogen–specific drugs was recognized, none have been forthcoming for development into MPTs or other prevention products. Thus, the lack of STI-specific APIs was identified as a major gap in the MPT field.

3.2. MPT dosage forms

The SAWG recognized that different populations of MPT users will prefer alternative dosage forms for MPT products. Consequently, it was concluded that it would be necessary to develop a suite of product types so as to accommodate the diverse needs and preferences of women at risk. The following sections outline the highest priority dosage forms identified by the SAWG and confirmed by expert and stakeholder review.

3.2.1. Sustained release devices/vaginal rings

Intravaginal rings (IVRs) have been successfully developed and commercialized as contraceptive products (Wieder and Pattimakiel, 2010), and are also being developed as HIV prevention products (Malcolm et al., 2012). IVRs offer several advantages as an MPT dosage form. As sustained release devices, users do not need to adhere to a complex prescribed dosing regimen; an IVR can simply be inserted at monthly (or longer) intervals. This has the potential to improve adherence issues associated with other user-controlled dosage forms that require more involved practices. Also, various IVR technologies exist that allow for the formulation of more than one API, which is suitable for MPT formulations requiring more than one drug substance (Johnson et al., 2010), and has potential application for combination indications (Baum et al., 2012). Large scale manufacturing for commercialization of IVRs has been successfully implemented for multiple licensed products, and several of the licensed IVR products involve the delivery of hormones (e.g., Nuvaring®, Merck; Femring®, Warner-Chilcott; Estring®, Pfizer), establishing technical precedent for the delivery of HCs in an IVR MPT.

A number of limitations with IVRs were recognized. While IVRs have the potential to address poor adherence associated with other dosage forms, there is little acceptability or market demand data on IRVs available from regions of the world most likely to benefit from MPT products. Although some acceptability data are starting to emerge for IVR use in these settings (Smith et al., 2008; van der Straten et al., 2012; Montgomery et al., 2012), the gaps in acceptability and market data need to be addressed in parallel with technical development of IVR-based MPTs. Further, the polymer options for IVR fabrication are limited, which may limit the API options that can be formulated with these polymers due to chemical compatibility. This is particularly important in terms of achieving adequate API release from an IVR for the desired indications. Suppliers for medical grade raw materials for IVRs, as well as contract manufacturing organizations capable of producing IVRs, are both limited. Lastly, socio-behavioral issues regarding involuntary IVR expulsion or voluntary removal by users due to personal preferences both need to be understood so as to better inform a specific TPP for an MPT IVR.

3.2.2. Long acting injectable products

Multiple long-acting (LA) HC products have been successfully developed (Affandi, 2002), and are being used in many regions of the world most likely to benefit from MPT products. In light of well-established low adherence associated with several user-controlled HIV prevention products that are in development (van Damme et al., 2012; Marrazzo et al., 2013), the ability to address such adherence challenges with a LA injectable MPT product would represent a major advancement in combination prevention product delivery. Although there are several advantages to the development of a single LA injectable product that would deliver both contraceptive and HIV prevention drugs, the SAWG recognized that a co-administration strategy of two injectables (one for each indication), would be an acceptable option during the interim period required to develop and approve a co-formulated single product. Importantly, even with a co-administration strategy, the duration of effect for each indication must be the same, as asynchronous delivery of injections for different indications on alternative dosing regimens could lead to insurmountable service delivery and adherence challenges.

At present, there are a limited number of LA injectable HIV prevention products in development (Andrews et al., 2013; Jackson et al., 2012), and none currently exist for the prevention of STIs. Thus, there is a gap in the level of development for this priority MPT dosage form. Other challenges are potentially associated with LA MPT formulations. For example, safety studies will likely have to establish preliminary tolerance of an injected ARV (or other drugs), since once a LA formulation has been administered, it cannot be removed. Therefore, a LA injectable MPT may likely require a preliminary oral run-in phase to establish tolerability. This requirement may create challenges for adherence and acceptability. Similarly, the prolonged half-life of LA nano-suspension formulations could result in persistent levels of drug in users well after the final injection of product. As drug concentrations decrease over time after a final injection, levels will eventually fall below effective concentrations, allowing for the possibility of HIV infection in the presence of sub-prevention levels of drug. This potentially creates an increased risk of selection for resistance. Other key elements of a LA injectable MPT TPP that would need to be addressed during product development include the limited acceptable volume for subcutaneous and intramuscular injection, storage requirements, education of user populations on product advantages, and risks, and the likely requirement for periodic HIV testing.

3.2.3. On-demand formulations

On-demand formulations refer to those dosage forms that are used around the time of sexual intercourse, and are appropriate for use on an intermittent basis. The need for such products is based on the changes in risk and frequency of intercourse that can occur over a woman's reproductive life cycle, and the need for more woman-initiated prevention products to increase options for protection. Such products will also be needed to serve those populations in need of MPTs that will not be interested in using IVRs or LA injectable products. Some of the dosage forms that could be used as on-demand products include topical formulations (e.g., vaginal gels, films, and tablets; used with or without a contraceptive barrier device), and systemic formulations (e.g., oral pills). Different MPT end-user populations have different levels of experience with these dosage forms. Although several on-demand types of formulations and barrier devices are available for contraceptive purposes (Batar, 2010; von Mollendorf et al., 2010), these products are currently not in high demand in those regions of the world most likely to benefit from MPTs. Moreover, multiple vaginal gels for the prevention of HIV infection have been evaluated in large clinical trials, but have often been plagued by poor product adherence (Marrazzo et al., 2013). Although it is likely that certain populations would be highly adherent to on-demand MPT products, demonstrating efficacy of such products in pivotal phase 3 trials represents a major challenge.

The alternative topical dosage form options for on-demand MPT products would each require a specific TPP to guide development, due to the physical, chemical, and technical differences associated with each formulation type. This is also true for an oral on-demand MPT product. However, there are also several common issues that would need to be addressed for any on-demand MPT products.

First, there are few drug options for contraception that could be intermittently delivered. As noted earlier, the SAWG as well as the expert review panels did not recommend HC use in an on-demand fashion, due to possible multiple effects on the menstrual cycle. Until drug alternatives to HC for prevention of pregnancy are developed, on-demand MPT products with a contraceptive indication would need to combine a contraceptive barrier device with an MPT vaginal formulation. Intermittent use of ARVs for the prevention of HIV infection also has both efficacy and safety risks. Thus, limited drug substance options for on-demand MPT products and the potential need to use barrier methods represent challenges for current on-demand MPT development.

4. Other MPT development priorities and gaps

4.1. Process and strategy priorities and gaps

In addition to the drug substance and product configuration priorities identified by the SAWG and the expert review panel, a number of process and strategy priorities and gaps related to MPT development were also identified. For example, coordinated MPT development according to TPPs that are specific to product types was identified as a critical need, as was early engagement of regulatory agencies in the development of specific MPTs. In terms of clinical evaluation, it was noted that studying MPT products in younger women was very relevant to the potential for public health impact of such products. Given the vulnerability of this age group in many of the high at-risk regions of the world, this type of study may be required. Further, regional differences in behaviors and product preferences would need to be evaluated and addressed during clinical assessment.

4.2. Delivery, access and use of MPTs

A major development priority identified during this process was the consideration of challenges relevant to delivery, access to, and use of MPT products in at-risk populations in different settings. Even a safe and effective MPT product is of no benefit to public health or to individual women and men unless it can be delivered to, and used by those in need of such products. Therefore, it is crucial for the development of MPT products to go beyond technical feasibility and regulatory approval by addressing *early on* key elements of successful delivery, access, and use. Assessing user perspectives, and preferences, and working to ensure that product characteristics match these preferences as closely as possible is a renewed focus in the field. Estimating demand for specific MPT products and developing systems for accurate product forecasting are crucial, and both may be challenging for MPTs. It will also be necessary to ensure that products can be produced at scale, and that sufficient raw material supply options exist. Production contracts and intellectual property arrangements must be established to assure that the product can be produced at the required scale and cost. Confirmation that candidate products are consistent with procurement policies of organizations that will purchase MPT is also critical. Lastly, determination that existing supply chains can accommodate new MPT delivery is also necessary.

Critically, global public health funding and partner agencies need to commit to undertaking and financing the considerable commitments needed for delivery and diffusion of new products: policy development, training, health system strengthening, community engagement, marketing, and market development, user education, and ongoing support to women in their communities as they gain experience and confidence in using a new product. Policies, health care delivery systems, and providers will need to implement and champion these products, which may be particularly challenging given that they will cross what are often real divisions among systems and budgets that address HIV, other STIs, and family planning.

Table 3
MPT pipeline prioritization and gap analysis summary.

Priority API	• HIV: Small molecule anti-retrovirals (ARV) • Contraception: hormone based • STI: pathogen specific drug substances
Priority dosage forms	• Sustained release: intravaginal rings • Long acting: injectables • On-demand: Gels, films, tablets, etc.
Key gaps	• Pathogen specific API for STI prevention • Non-hormonal contraception options • Non-RTI small molecule options for HIV prevention • Adequate acceptability/adherence data for product dosage form options

4.3. Coordinated investments

Another crucial priority for the wider field of MPT product development is the efficient use of supporting agency investments. MPT development is a high risk and expensive undertaking, and in a resource-limited environment, it will be necessary for supporting agencies to coordinate their investments based on objective evaluation of product options. No single funding organization will have the resources to support all aspects of development and delivery/access of an MPT product. Therefore, coordinated investment in MPT products that are consistent with aligned priorities of multiple supporting agencies is a critical priority for the field. Consistent with this investment strategy priority, it will also be necessary to use objective development criteria to de-select certain product options and identify single lead candidate products to advance into pivotal phase 3 efficacy trials. The size and cost of such trials will limit their number, which will in turn limit the number of MPT products that can progress to regulatory licensure. This limitation in resources will dictate the need to assure that only the most appropriate MPT products are progressed through phase 3 trial evaluations. Thus, there will be a need to pool capacity, capability, expertise, and other resources across MPT product development partners in order to ensure success of the first generation of MPTs.

5. Summary

This report summarizes the MPT pipeline priority and gap analysis conducted by the SAWG of the IMPT. Through the application of a formal, objective process that utilized technical and strategic expertise within the SAWG, as well as an external expert review process, a set of priority recommendations for the MPT development pipeline was defined. By prioritizing specific API and dosage form options for MPT product development, the goal of achieving coordinated investment by supporting agencies in MPT products with the highest public health impact potential can be more readily achieved. Further, the identification of priority gaps in the MPT pipeline serves to encourage coordinated resolution of these issues, thus enhancing the potential for optimal MPT product development. Importantly, it will be necessary to review the MPT pipeline priorities and gaps on a regular basis. This process will be informed by new data emerging from ongoing MPT development efforts, as well as from the HIV and STI prevention and contraception fields. Clinical data from ongoing HIV prevention trials such as FACTS 001 (Facts Consortium, 2013) and ASPIRE (Microbicides Trials Network, 2013) will be of crucial consequence for MPT product development strategies, and will likely effect priorities and strategies of agencies supporting MPT development. Thus, MPT pipeline

prioritization will need to be an ongoing process that is informed by innovation and rooted in data-based evaluations, with the sole objective of identifying those MPT product options with the greatest potential of improving the sexual and reproductive health of women around the world.

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References

Affandi, B., 2002. Long-acting progestogens. Best Pract. Res. Clin. Obstet. Gynaecol. 16, 169–179.

Andrews, C., Gettie, A., Russell-Lodrique, K., et al., 2013. Long acting parenteral formulation of GSK 1265744 protects macaques against repeated inter-rectal challenges with SHIV. 20th CROI, Abstract 24LB, March 3-6, 2013, Atlanta, GA. http://www.retroconference.org/2013b/Abstracts/48044.htm. Accessed May 21, 2013.

Baeten, J.M., Donnell, D., Ndase, P., et al., 2012. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N. Engl. J. Med. 367, 399–410.

Batar, I., 2010. State-of-the-art of non-hormonal methods of contraception: II. chemical barrier contraceptives. Eur. J. Contracept. Reprod. Health Care 15, 89–95.

Baum, M.M., Butkyavichene, I., Gilman, J., Kennedy, S., Kopin, E., Malone, A.M., Nguyen, C., Smith, T.J., Friend, D.R., Clark, M.R., Moss, J.A., 2012. An intravaginal ring for the simultaneous delivery of multiple drugs. J. Pharm. Sci. 101, 2833–2843.

Emau, P., Tian, B., O'keefe, B.R., Mori, T., McMahon, J.B., Palmer, K.E., Jiang, Y., Bekele, G., Tsai, C.C., 2007. Griffithsin, a potent HIV entry inhibitor, is an excellent candidate for anti-HIV microbicide. J. Med. Primatol. 36, 244–253.

Facts Consortium, 2013. FACTS 001 http://www.facts-consortium.co.za/?page_id=83/.

Fernández-Romero, J.A., Abraham, C.J., Rodriguez, A., Kizima, L., Jean-Pierre, N., Menon, R., Begay, O., Seidor, S., Ford, B.E., Gil, P.I., Peters, J., Katz, D., Robbiani, M., Zydowsky, T.M., 2012. Zinc acetate/carrageenan gels exhibit potent activity in vivo against high-dose herpes simplex virus 2 vaginal and rectal challenge. Antimicrob. Agents Chemother. 56, 358–368.

Grant, R.M., Lama, J.R., Anderson, P.L., et al., 2010. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N. Engl. J. Med. 363, 2587–2599.

Harrison, P.F., Hemmerling, A., Romano, J., Whaley, K.J., Young Holt, B., 2013. Developing multipurpose reproductive health technologies: an integrated strategy. AIDS Res. Treat. 2013. http://dx.doi.org/10.1155/2013/790154, Epub 2013 Feb 28.

Heffron, R., Donnell, D., Rees, H., Celum, C., Mugo, N., Were, E., de Bruyn, G., Nakku-Joloba, E., Ngure, K., Kiarie, J., Coombs, R.W., Baeten, J.M., Partners in Prevention HSV/HIV Transmission Study Team, 2012. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. Lancet Infect. Dis. 12, 19–26.

Hopkins, T.G., Wood, N., 2013. Female human papillomavirus (HPV) vaccination: global uptake and the impact of attitudes. Vaccine 31, 1673–1679.

IMPT, 2011. Multipurpose Prevention Technologies for Reproductive Health, 2011 Symposium, Washington DC, Nov 3-4, 2011, Final Report, http://www.cami-health.org/documents/MPT2011-Symposium-Report.pdf.

Jackson, A., Else, L., Tja, J., Seymour, N., Stafford, M., Back, D., Gazzard, B., Boffito, M., 2012. Rilpivirine-LA formulation: Pharmacokinetics in plasma, genital tract in HIV- females, and rectum in males. 19th CROI, Abstract 35, March 5-8, 2012, Seattle, WA. http://www.retroconference.org/2012b/Abstracts/44600.htm.

Johnson, T.J., Gupta, K.M., Fabian, J., Albright, T.H., Kiser, P.F., 2010. Segmented polyurethane intravaginal rings for sustained combined delivery of antiretroviral agents dapivirine and tenofovir. Eur. J. Pharm. 39, 203–212.

Karim, Q.A., Karim, S.S.A., Frohlich, J.A., et al., 2010. Effectiveness and safety of tenofovir gel, and anti retroviral microbicide for the prevention of HIV infection in women. Science 329, 1168–1174.

Karim, S.S.A., Richardson, B.A., Ramjee, G., Hoffman, I.F., Chirenje, Z.M., Taha, T., Kapina, M., Maslankowski, L., Coletti, A., Profy, A., Moench, T.R., Piwowar-Manning, E., Mâsse, B., Hillier, S.L., Soto-Torres, L., 2011. HIV Prevention Trials Network (HPTN) 035 Study Team, Safety and effectiveness of BufferGel and 0.5% PRO2000 gel for the prevention of HIV infection in women. AIDS 25, 957–966.

Keller, M.J., Malone, A.M., Carpenter, C.A., Lo, Y., Huang, M., Corey, L., Willis, R., Nguyen, C., Kennedy, S., Gunawardana, M., Guerrero, D., Moss, J.A., Baum, M.M., Smith, T.J., Herold, B.C., 2012. Safety and pharmacokinetics of aciclovir in women following release from a silicone elastomer vaginal ring. J. Antimicrob. Chemother. 67, 2005–2012.

Lederman, M.M., Veazey, R.S., Offord, R., Mosier, D.E., Dufour, J., Mefford, M., Piatak Jr, M., Lifson, J.D., Salkowitz, J.R., Rodriguez, B., Blauvelt, A., Hartley, O., 2004. Prevention of vaginal SHIV transmission in rhesus macaques through inhibition of CCR5. Science 306, 485–487.

Lievano, F., Galea, S.A., Thornton, M., et al., 2012. Measles, mumps, and rubella virus vaccine (M-M-R™II): a review of 32 years of clinical and postmarketing experience. Vaccine 30, 6918–6926.

Malcolm, R.K., Fetherston, S.M., McCoy, C.F., Boyd, P., Major, I., 2012. Vaginal rings for delivery of HIV microbicides. Intl. J. Women's Health 4, 595–605.

Maltêz, F., Doroana, M., Branco, T., et al., 2011. Recent advances in antiretroviral treatment and prevention in HIV-infected patients. Curr. Opin. HIV AIDS 6 (Suppl 1), S21–S30.

Mansour, D., 2012. The benefits and risks of using a levonorgestrel-releasing intrauterine system for contraception. Contraception 85, 224–234.

Marais, D., Gawarecki, D., Allan, B., Ahmed, K., Altini, L., Cassim, N., Gopolang, F., Hoffman, M., Ramjee, G., Williamson, A.L., 2011. The effectiveness of Carraguard, a vaginal microbicide, in protecting women against high-risk human papillomavirus infection. Antivir. Ther. 16, 1219–1226.

Marrazzo, J., Ramjee, G., Palanee, T., Mkhize, B., Nakabiito, C., Taljaard, M., Piper, J., Gomez Feliciano, K., Chirenje, M., and VOICE Study Team, 2013. Pre-exposure prophylaxis in women: daily oral tenofovir, oral tenofovir/emtricitabine, or vaginal tenofovir gel in the VOICE study (MTN 003), 20th CROI, abstract 26LB, March 3-6, 2013, Atlanta, GA. http://www.retroconference.org/2013b/Abstracts/47951.htm.

Microbicides Trials Network, 2013. ASPIRE - A Study to Prevent Infection with a Ring for Extended Use http://www.mtnstopshiv.org/news/studies/mtn020/backgrounder/.

Montgomery, E.T., van der Straten, A., Cheng, H., Wegner, L., Masenga, G., von Mollendorf, C., Bekker, L., Ganesh, S., Romano, J., Nel, A., Woodsong, C., 2012. Vaginal ring adherence in sub-Saharan Africa: Expulsion, removal, and perfect use. AIDS Behav. 16, 1787–1798.

Neff, C.P., Kurisu, T., Ndolo, T., Fox, K., Akkina, R., 2011. A topical microbicide gel formulation of CCR5 antagonist maraviroc prevents HIV-1 vaginal transmission in humanized RAG-hu mice. PLoS One 6 (6), e20209.

Smith, D.J., Wakasiaka, S., Hoang, T.D., Bwayo, J.J., Del Rio, C., Priddy, F.H., 2008. An evaluation of intravaginal rings as potential HIV prevention devices in urban Kenya: Behaviors and attitudes that might influence uptake within a high-risk population. J. Women's Health 17, 1025–1034.

Talwar, G.P., Raghuvanshi, P., Mishra, R., Banerjee, U., Rattan, A., Whaley, K.J., Zeitlin, L., Achilles, S.L., Barré-Sinoussi, F., David, A., Doncel, G.F., 2000. Polyherbal formulations with wide spectrum antimicrobial activity against reproductive tract infections and sexually transmitted pathogens. Am. J. Reprod. Immunol. 43, 144–151.

Tebbey, P.W., Rink, C., 2009. Target product profile: a renaissance for its definition and use. J. Med. Market. 9, 301–307.

Van Damme, L., Corneli, A., Ahmed, K., Agot, K., Lombaard, J., Kapiga, S., Malahleha, M., Owino, F., Manongi, R., Onyango, J., Temu, L., Monedi, M.C., Mak'Oketch, P., Makanda, M., Reblin, I., Makatu, S.E., Saylor, L., Kiernan, H., Kirkendale, S., Wong, C., Grant, R., Kashuba, A., Nanda, K., Mandala, J., Fransen, K., Deese, J., Crucitti, T., Mastro, T.D., Taylo, R.D., FEM-PrEP study group, 2012. Preexposure prophylaxis for HIV infection among African women. N. Engl. J. Med. 367, 411–422.

Van der Straten, A., Montgomery, E.T., Cheng, H., Wegner, L., Masenga, G., von Mollendorf, C., Bekker, L., Ganesh, S., Young, K., Romano, J., Nel, A., Woodsong, C., 2012. High acceptability of a vaginal ring as a microbicide delivery method for HIV prevention in African women. AIDS Behav. 16, 1775–1786.

Von Mollendorf, C.E., van Damme, L., Moyes, J.A., Rees, V.H., Callahan, M.M., Mauck, C.K., Puren, A.J., Tweedy, K., Taylor, D., 2010. Results of a safety and feasibility study of the diaphragm used with ACIDFORM gel and KY jelly. Contraception 81, 232–239.

Wieder, D.R., Pattimakiel, L., 2010. Examining the efficacy, safety, and patient acceptability of the combined contraceptive vaginal ring (NuvaRing®). Int. J. Womens Health 2, 401–409.