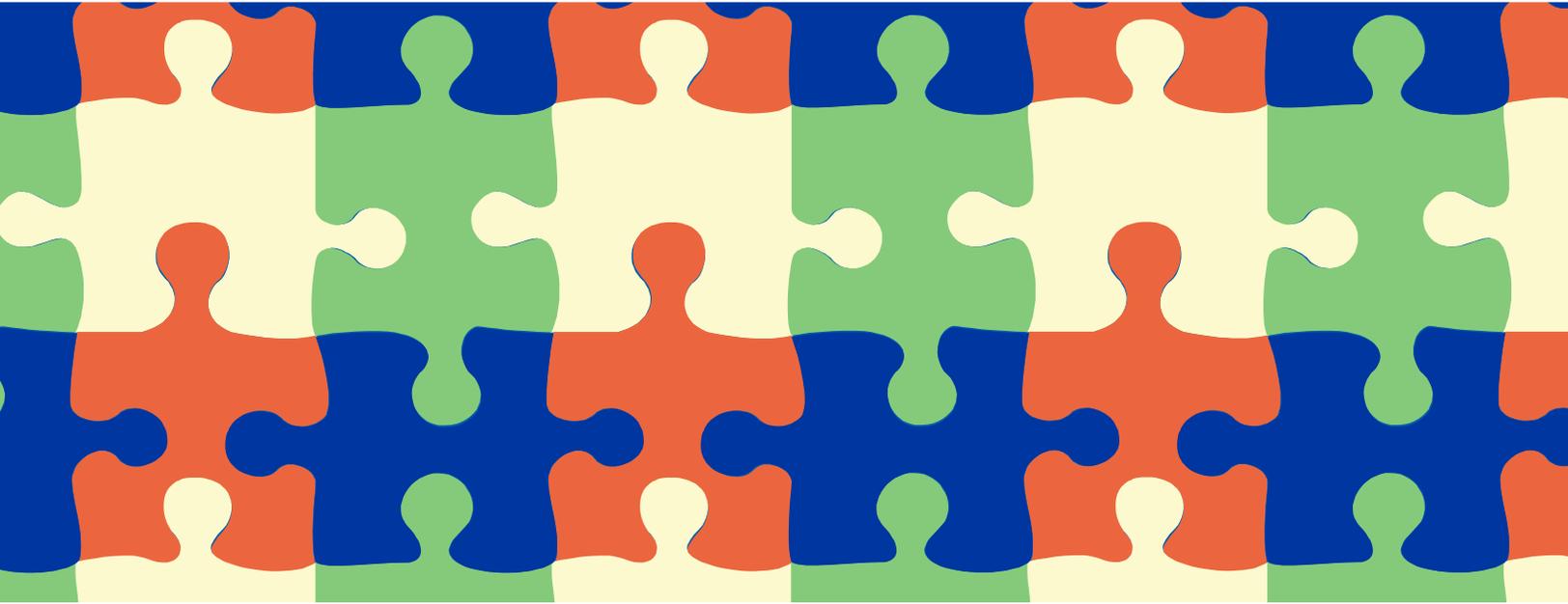# FACILITATING REGULATORY APPROVAL OF MULTIPURPOSE PREVENTION TECHNOLOGIES FOR REPRODUCTIVE HEALTH

END-OF-PROJECT REPORT AND RESOURCES

Aide-Mémoire

Facilitating Regulatory Approval of Multipurpose Prevention Technologies for Reproductive Health

End-of-Project Report and Resources

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Background

This aide-mémoire provides an overview of the Population Council's three-year "Facilitating Regulatory Approval of Multipurpose Prevention Technologies (MPTs) for Reproductive Health" (RA for MPTs) project, funded through a cooperative agreement from the Office of Population & Reproductive Health at the US Agency for International Development (USAID). The information is purposely provided in the context of the Initiative for MPTs (the IMPT; see www.mpts101.org), and highlights the Council's contributions to the MPT field through this project.

The Population Council confronts critical health and development issues—from stopping the spread of HIV to improving reproductive health and ensuring that young people lead full and productive lives. Through biomedical, social science, and public health research in 50 countries, we work with our partners to deliver solutions that lead to more effective policies, programs, and technologies that improve lives around the world. Established in 1952 and headquartered in New York, the Council is a nongovernmental, nonprofit organisation governed by an international board of trustees.

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Executive Summary

As the RA for MPTs project drew to an end in September 2013, the Population Council held an end-of-project meeting to share project achievements and lessons, and to discuss next steps for advancing the MPT agenda. The meeting was held at the Population Council's office in Washington, DC, on September 19, 2013. A select group of experts representing supporting agencies, product developers, regulators, and policy, advocacy, and program leaders were invited to participate. The consultation began with an introduction by Judy Manning (USAID project manager), who provided the context for the project within USAID's family planning and reproductive health (FP/RH) priorities. Martha Brady, Population Council, presented an overview of project activities and outputs, shared a new conceptual framework and MPT typology created under this initiative, and highlighted key lessons and areas for future work. A round-table discussion among meeting participants drew out important insights from their experiences with various regulatory and commercialization processes for their respective FP/RH products, three of which are MPTs. The end-of-project meeting served to consolidate learning across agencies as a foundation for moving the MPT agenda forward.

Why this Project?
Rationale and Background

The inherent challenges of developing and approving MPTs are quite complex, necessitating creativity and strategic thinking by multiple stakeholders. USAID, as a key stakeholder, has played a leadership role in spurring investment in product development and introduction of new products for sexual and reproductive health (SRH). Building on decades of support for developing countries, as well as for reproductive health product development, USAID is providing focused support to facilitate research and development, regulatory approval, and ultimately introduction of MPTs. A key component of USAID's strategy was to attempt to clarify and inform regulatory pathways for MPTs by competing a small project in 2010 to focus on that effort. The RA for MPTs project was awarded to the Population Council, given its unique combination of expertise in reproductive health technology development and introduction, obtaining regulatory approval, advancing products into production, and implementing strategies to ensure successful introduction into national programs. Expertise from the Council's HIV and AIDS Program, Reproductive Health Program, and the regulatory and quality assurance team contributed to this effort.

Stimulating Thought Leadership and Distilling Key Lessons

The Population Council has played a key role in the overall effort to define, shape, and influence the MPT global research and action agenda. Ms. Martha Brady, Council Senior Associate, led the RA for MPTs project, collaborating with major stakeholders in the field to clarify possible regulatory pathways, lay the groundwork for future product access, and advance the MPT agenda overall. Although MPTs are still under development, we have been successful in advancing the idea that it is not only possible, but critical, to be proactive in elaborating an understanding of and planning for regulatory processes in advance. It is noteworthy that now, upon the completion of this three-year project, there is active strategic engagement between key US government agencies [including the Food & Drug Administration (FDA) and the National Institutes of Health (NIH)], international organizations, product developers, and supporting agencies. MPTs have increasingly been included on the global FP, SRH, and HIV agendas of such fora as the International Family Planning Conference, the International AIDS Conference, the Wellcome Trust Global Forum, CONRAD's Product Development Workshop, and the Women Deliver International Conference, among others.

Over the course of the RA for MPTs project, the Council developed a body of work delineating key components of the MPT regulatory agenda, providing information for understanding and planning for regulatory processes, and preparing for introduction by bringing users' perspectives into the agenda. This work includes publications, presentations, and convening of thought leaders. (See attached annotated bibliography for selected materials.)
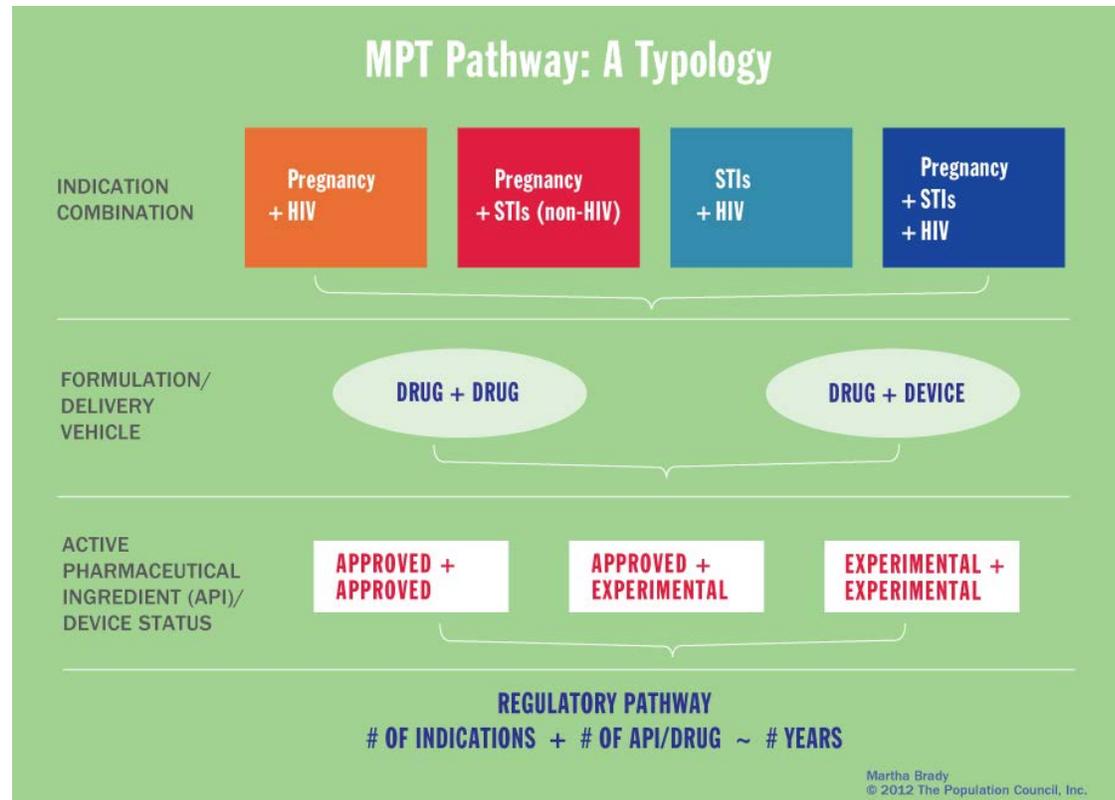
Because of the novelty and complexity of developing MPTs for SRH and HIV prevention, product developers face unique challenges in navigating regulatory channels and bringing MPTs to market. MPTs require sharper focus and strategic coordination across the development process, new types of study designs to test combination products, and innovative approaches to the regulatory approval process. This project underscored how critical it is that all three of these domains be addressed in order to effectively move MPT development—and ultimate delivery—forward.

Nomenclature, MPT Typology, and Critical Path Framework

At the start of the RA for MPTs project, it was clear that an understanding of the regulatory requirements for such MPT combination products was needed. But before that could be advanced, it was evident that there was confusion around definitions and terminology, with different terms and definitions being used by various constituents. Early on in the RA for MPTs project, the Council convened a "Day of Dialogue on MPT Nomenclature" in an effort to clarify language and terminology moving forward.

MPTs that are currently being developed combine several active pharmaceutical ingredients (APIs) and delivery platforms. As such, they do not fit neatly into the discrete categories of drug, device, or biologic typically used by regulatory agencies—though they may involve any or all of these. Given that MPTs are designed to address different indications, regulatory review may involve more than one section of a regulatory agency, such as antivirals and/or contraception. Given both the diversity and complexity associated with MPTs, understanding the regulatory pathway is critical to success.

A key conceptual piece developed under the project was an MPT Typology, which visually depicts the various permutations of potential indications and the possible combinations of delivery platforms/systems (see below). This Typology has been widely cited as a useful tool for the MPT field.

MPT Pathway: A Typology

INDICATION COMBINATION

| Pregnancy + HIV | Pregnancy + STIs (non-HIV) | STIs + HIV | Pregnancy + STIs + HIV |

FORMULATION/ DELIVERY VEHICLE

DRUG + DRUG   DRUG + DEVICE

ACTIVE PHARMACEUTICAL INGREDIENT (API)/ DEVICE STATUS

| APPROVED + APPROVED | APPROVED + EXPERIMENTAL | EXPERIMENTAL + EXPERIMENTAL |

REGULATORY PATHWAY
 # OF INDICATIONS + # OF API/DRUG ~ # YEARS
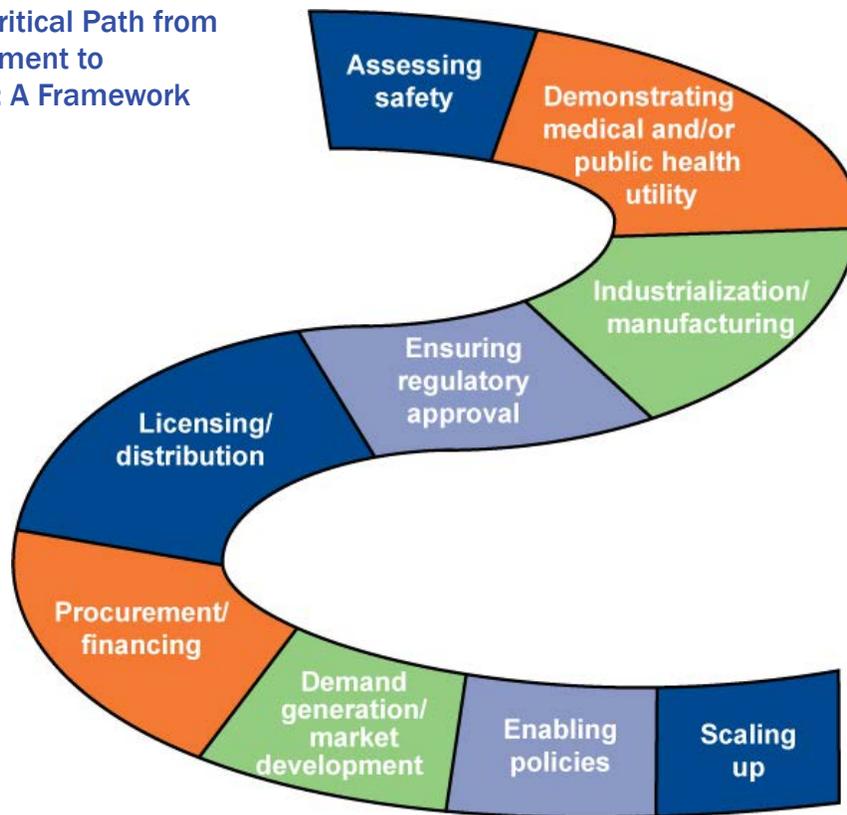
Martha Brady
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If we consider the product configuration in tandem with the various potential combination of indications, it's clear that MPT development becomes quite complex from a regulatory perspective—especially given that such combination pharmaceutical products have additional regulatory complexity beyond that of single-agent, single-indication products. The presence of more than one API in a combination product increases both the nonclinical and clinical development requirements. This is further compounded when a combination product targets more than one medical indication, such as MPTs designed as either a *drug+drug* or *drug+device* combination to protect against HIV, other STIs, and unintended pregnancy. Further, MPTs can be developed from various combinations of approved and/or experimental drugs and/or devices for different single indications. While specific development requirements will vary with each MPT product, the same relevant factors provide the basis for development of guidelines that would inform the broad spectrum of possible MPTs: 1) **experimental versus approved API, 2) drug versus device, 3) systemic versus topical**.

Another conceptual piece developed under this project was the Critical Path Framework (see below), which identifies key activities and data required along the pathway from product development through commercialization and access, including regulatory approval. The first steps of any product development effort will be to assess safety and demonstrate medical and/or public health utility of a given product. Next will be to begin the process of industrial-

ization. These three areas are the focus of the FDA's critical path initiative, and involve both pre-clinical and clinical activities. Equally important elements in delivering a product to the end user include, but are not limited to:

▶ Ensuring regulatory approval

▶ Establishing licensing and distributions channels

▶ Seeding and developing markets

▶ Negotiating financing and procurement mechanisms

▶ Generating demand among potential users, providers, and policy makers

▶ Creating an enabling policy environment and developing product champions

▶ Developing service delivery guidelines and training plans

▶ Planning for scale-up of both manufacturing process as well as country programming

Constructing a Critical Path from Product Development to Access for MPTs: A Framework

Martha Brady
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Each of these elements has a number of activities associate with it; all require human and financial resources, and especially political commitment. Illustrative activities of each element are described further in the Critical Path Brief (see page 9).

Regulatory Agencies, Processes, and Guidance

Another key project activity was to delineate the role of regulatory bodies and to review existing guidance to ascertain their relevance to MPTs. What follows is a brief synopsis.

The regulatory strategies in use by different product developers may vary, but for the most part depend on the use of Stringent Regulatory Authorities (SRAs) such as the US Food and Drug Administration (USFDA), the European Medicines Authority (EMA), and a significant number of other drug regulatory agencies primarily, although not exclusively, in developed countries. Many developing country stakeholders look to the EMA procedure known as Article 58 and/or the World Health Organization (WHO) prequalification process and recommendations for global use of products. Article 58 is used to review marketing applications for medicinal products for human use that are intended exclusively for markets outside of the European Union (EU). WHO prequalification is a service provided by WHO to assess the quality, safety, and efficacy of medicinal products. Since its inception in 2001, more than 240 medicines have been prequalified. The list of prequalified products has become a vital tool for international agencies and organizations involved in bulk purchasing at the country or international level, including Ministries of Health, PEPFAR, UNAIDS, UNFPA, and USAID.

The USFDA, EMA, and International Conference on Harmonization (ICH) have each produced guidance documents that provide summary information on the nonclinical and quality requirements for pharmaceutical product development. Although no specific guidance documents exist at this time for the specific development of MPT products for SRH indications, a number of relevant guidance documents exist and have been summarized elsewhere (see annotated bibliography). Every pharmaceutical product will have its own specific requirements for development and regulatory approval, and communication with regulatory agencies is a key element of MPT, and all, product development efforts.

Socio-behavioral Correlates of MPTs from Users' Perspectives

The Council has been actively engaged in the overall work of the Initiative for Multipurpose Prevention Technologies (IMPT; see www.mpts101.org), the Secretariat for which is the Coalition Advancing Multipurpose Innovations (CAMI). One specific area of work is thinking through the range of socio-behavioral issues that will influence demand and uptake of MPT products. Ms. Brady chairs the Access, Demand, and Uptake (ADU) Working Group for the Initiative. Focused work includes laying out the socio-behavioral dimensions of prioritized MPTs. To that end, a relevant paper co-authored by Council staff entitled "Aligning Product Development with User Perspectives: Social Behavioral Correlates of MPTs" is under review for publication in *BJOG: An International Journal of Obstetrics and Gynaecology*.

End-of-project Meeting Roundtable Discussion

Representatives from organizations developing FP/RH or MPT products—including PATH, FHI360, CONRAD, and IPM—discussed the status, steps, and challenges encountered as they brought their respective products (at varying stages in the development pipeline) through the regulatory process. Examples of products discussed include: ARV-based vaginal rings, a new type of female condom, a new type of diaphragm, a microbicide vaginal gel, and a generic contraceptive implant. The roundtable discussion topics included the WHO pre-qualification process, regulatory strategies related to specific products, and commercialization efforts. Lessons learned from these products and agencies will serve as a useful foundation as we advance current and future MPT products.

Key Insights Arising from the Roundtable Discussion

▶ National Regulatory Authorities (NRAs) in many developing countries have comparatively little experience with regulatory review of new drugs. NRAs often look to product reviews already conducted by Stringent Regulatory Authorities such as the USFDA or the EMA.

▶ (As mentioned above) EMA has a specialized process, known as Article 58, which can be used for products that are intended for developing country markets and where there is likely no local approval process in place.

▶ The WHO prequalification process for new drugs is based on similar product types already on the WHO Essential Medicines List (EML). The EML application process can take 12-18 months. Whether and how a product secures a place on the EML is an area for further exploration. Understanding and engaging with that process may be beneficial for MPTs in the future.

▶ WHO prequalification is particularly important for developing country authorities, especially regulatory agencies, Ministries of Health, and procurement agencies.

▶ Procurement agencies and non-governmental organizations (NGOs) will want/need WHO prequalification for products they wish to purchase and/or support programmatically.

▶ Preparing the dossier for WHO prequalification submission is time consuming. Applicants should be aware that the timeframe for the prequalification process can range from 18 to 24 months. However, pre-qualification may help to accelerate regulatory action by countries.

▶ Good Manufacturing Practice (GMP) inspections conducted as part of the WHO prequalification process can be numerous and costly, and oftentimes at cross-purposes regarding findings and recommendations. The product manufacturer must be prepared financially, and able to respond.

▶ As part of the WHO prequalification and/or country registration processes for new products, countries have often expressed interest in making site visits and/or GMP audits in the country of manufacture. The product manufacturer should be prepared and able to respond.

▶ It is critical that any new product has regulatory approval in the country of manufacture.

▶ Certain products that are suited for specific markets (e.g., the new diaphragm for European markets) may pursue EU CE marking rather than USFDA approval.

▶ Knowing your intended market and commercial strategy is key to choosing the appropriate regulatory strategy. For example, a product intended primarily for public sector markets in developing countries will need WHO prequalification.

Moving Forward and Next Steps

As MPT products move through the development pipeline, there will be increased need for regulatory agency engagement, both in developed regions (e.g., USFDA and/or the EMA) and, in particular, in developing countries. In addition, regional and/or country-specific consultations with regulatory authorities will be needed, and such consultations should be strategically timed as products move closer to Phase III efficacy trials. Product-specific discussions between MPT product sponsors and regulatory agencies should be held early on and at regular intervals in the product development timeline.

In an effort to accelerate regulatory approval and registration for new SRH products, several concrete suggestions for action were discussed, including:

► Developing a database of regulatory agencies by region/country

► Establishing a consultant database of regulatory experts who could be deployed to work with country regulatory agencies

► Convening regional/country workshops for regulators

► Encouraging and supporting regulatory harmonization efforts currently underway in Africa

At the same time, understanding the potential market and commercialization possibilities for any new MPT was deemed critical for future investment. Several areas for additional research and action were discussed, including:

► Indentifying commercialization partner(s) early on for specific products

► Collecting data/information around market potential

► Conducting market and users' perspectives research to inform future product R&D

► Identifying opportunities for greater collaboration between MPT development and contraceptive development

The future of MPTs will be influenced heavily by developments at global and country levels. The actions taken now to spur investment in research and development, and in creating innovative approaches to regulatory processes for MPTs, will make significant contributions to the reproductive health and HIV fields. The results of this work will benefit product developers, drug regulatory agencies, and developing country Ministries of Health, and, ultimately, the end users of future MPT products—women (and men) most in need.

Although this project concludes, the Population Council remains active in the MPT arena–both in terms of R&D, as well as on issues related to access, demand, and uptake. The array of materials prepared throughout the project will be disseminated and knowledge shared to advance the MPT agenda. This work has helped to bolster interest and advance discussion on MPTs among the scientific and advocacy communities, clarify language and regulatory processes, and draw out key components of behavioral and health systems research that will be critical as the MPT field moves forward.

Selcted Project Resources

Selected Publications

Facilitating Regulatory Approval of Multipurpose Prevention Technologies for Sexual and Reproductive Health (Project Brief). Martha Brady; January 2011

Overview of goals and activities of the Population Council's USAID-funded project to clarify and inform regulatory pathways for MPTs. Describes underlying philosophy and approach.
http://www.popcouncil.org/pdfs/2011HIV_MPTBrief.pdf

Day of Dialogue: Multipurpose Prevention Technologies: Toward Clarity in Nomenclature (Meeting Report). Martha Brady and Elizabeth McGrory; March 2011

Summary of a stakeholder meeting. Discussion included how different types of products are reviewed within the USFDA and existing processes that could be applied to MPTs, what guidance exists, possible additional information that may be needed for regulatory review of MPTs, and how the various stakeholders will take this work forward.
http://www.popcouncil.org/pdfs/events/2011DayOfDialogueNomenclature_Report.pdf

What Regulatory Guidance Exists for Multipurpose Prevention Technologies? A Review of Key Guidance Documents and their Applicability to MPTs (Brief). Martha Brady and Heeyoung Park; July 2011.

Reviews and summarizes key regulatory guidance documents (from USFDA, EMA, ICH) to determine whether and how they might apply to MPTs for SRH.
http://www.popcouncil.org/pdfs/2011HIV_RegGuidanceMPTs.pdf

Nonclinical Development Needs and Regulatory Requirements for Multipurpose Prevention Technologies: A Primer (Brief). Joe Romano, Martha Brady, Judy Manning; October 2012.

Outlines key nonclinical development needs and potential regulatory requirements for various configurations of MPTs for the simultaneous prevention of HIV, other STIs, and/or pregnancy.
http://www.popcouncil.org/pdfs/2012HIV_MPTDevPrimer.pdf

Lessons from Reproductive Health to Inform MPT Development: Don't Reinvent the Wheel (Paper). Martha Brady and Judy Manning; *Antiviral Research* 100 (supplement): S25–S31; 2013.

Presents the public health rationale for MPTs based on regional trends in demographic and SRH indicators, and distills important lessons from the introduction of contraceptive products over the past several decades to inform the development and future introduction of MPTs
http://www.sciencedirect.com/science/article/pii/S0166354213002672

Aligning Product Development and User Perspectives: Socio-behavioral Dimensions of Multipurpose Prevention Technologies (Paper). Martha Brady and Elizabeth Tolley; in review for *BJOG* special supplement on MPTs; forthcoming 2014.

Overview of key user-related social and behavioral dimensions of three broad categories of MPTs: 1) sustained release vaginal rings, 2) peri-coital vaginal products, and 3) co-formulated or co-administered injectables. The authors build upon the broad parameters of target product profiles for such products, aligning them with user perspective considerations.

Selected Presentations and Forums

Convened Regulatory Panel of African Regulators at Global Forum on MPTs, Wellcome Trust (London; January 2012); also presented Regulatory Pathways for MPTs: Distilling and Clarifying the Process.

Overview of MPTs and the roles of regulatory agencies, including SRAs and developing country regulatory bodies. Reviewed existing regulatory guidance documents.
http://www.popcouncil.org/pdfs/presentations/2012HIV_Brady_MPTForum.pdf

Convened Satellite Session "New Products, New Paradigms: Combination Products for Women"—AIDS2012 Conference (Washington, DC; July 2012)

Provided platform for discussion of regulatory challenges for MPTs by USFDA regulators. Discussed how MPTs might combine protection against HIV with contraception and/or protection against other STIs, what evidence would be needed, and what a regulatory pathway for MPTs might look like.
http://pag.aids2012.org/session.aspx?s=183

What Have We Learned From Other Health Technologies? How Do They Apply to MPTs?— presented at Indian Council of Medical Research (ICMR) MPT Symposium (New Delhi, India; 11-12 December 2012)

Examined acceptability issues and key barriers encountered when various reproductive health products were first introduced into the market, and their potential applicability to future MPTs.
http://www.popcouncil.org/pdfs/events/2012Brady_MPTIndiaWhatHaveWeLearned.pdf

Users' and Providers' Perspectives on MPTs: What Do We Know, and What Do We Need to Know?—presented at Indian Council of Medical Research (ICMR) MPT Symposium (India; 12 December 2012)

Described how, why, and when users' and providers' perspectives should be incorporated into product development and/or introduction of new technology.
http://www.popcouncil.org/pdfs/events/2012Brady_MPTIndiaUserProviderPerspectives.pdf

A Critical Look Down the Critical Path to MPT Development—presented at CONRAD-hosted Product Development Workshop (Washington, DC; February 2013)

Provided an overarching critical path framework for MPTs, laying out key steps and processes from product development up through introduction.
http://www.popcouncil.org/pdfs/presentations/2013HIV_Brady_MPT-PDWorkshop.pdf