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Contraceptive Special Issue

# Towards a roadmap to advance non-hormonal contraceptive multipurpose prevention technologies: strategic insights from key stakeholders†

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## Abstract

The development of non-hormonal contraceptives is critical to increase options for women. In combination with prevention against sexually transmitted infections, they can become an important component of multipurpose prevention technologies (MPTs) which address multiple reproductive health needs with a single product. Resulting from multiple rounds of expert consultations, this framework aims to guide the development of non-hormonal contraceptive MPTs. Key informant interviews with experts in family planning and HIV and STI prevention and MPT product developers and funders from around the globe were conducted, reviewed, and coded. Identified key themes were discussed by experts at the November 2019 *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Contraceptive Development Meeting in Houston, Texas. Seven action strategies were identified to address key research gaps and priorities for advancing the field. They highlight the importance of identifying target populations, a systematic approach to collaborative research, and leveraging knowledge from other fields, including regulatory and patenting, manufacturing, and commercialization expertise. Employing expanded target product profiles and setting go/no-go decisions for non-hormonal MPTs will help to prioritize the most promising candidates in the drug development pipeline. Further, they call for optimizing investments and engagement of stakeholders from public and private sectors. These action strategies aim to facilitate collaboration and innovation amongst multidisciplinary MPT stakeholders. Paramount to success will be enhancing strategic alliances and reconciling the

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essential social–behavioral context and market forces that drive product use with the complexities of research and development, regulatory approval, and commercialization.

## Summary Sentence

The objective of this paper is to present an actionable framework that guides development of non-hormonal contraceptive MPTs.

**Key words:** hormone, human reproduction, pregnancy, reproductive behavior.

## Introduction

In 1960, FDA approval of the first hormonal contraceptive revolutionized sexual and reproductive health, giving women unprecedented control over their fertility for the first time in history. An array of contraceptive methods for women subsequently emerged in the later part of the twentieth century in the form of gels, pills, intrauterine devices, implants, and rings, most of which have been hormonal (with hormonal contraceptives defined here as using hormones that work by manipulating the hypothalamic–pituitary–gonadal [HPG] axis). Yet, as highlighted by Deborah Anderson in her article published in the *New England Journal of Medicine*, "With approximately 40% of pregnancies being unplanned, the time seems ripe for another contraceptive revolution to provide options for the diverse populations that are not currently being served by modern contraception." [1]. Women who prefer to avoid the use of contraceptive steroids can use a copper IUD or condoms (both male and female). Condoms also provide safety from most sexually transmitted infections (STIs) if used correctly and consistently by the end-user. Hormonal contraceptives acting on the HPG axis are critical to enable women to control their fertility, but do not provide safety from other infections associated with sexual contact nor from the potential risks of using hormonal contraceptive steroids for extended periods of time [2–4]. New options for non-hormonal contraception and multipurpose prevention technologies (MPTs) are now emerging. MPTs are an innovative class of products that deliver varied combinations of HIV prevention, other STI prevention, and contraception [5]. The focus of this paper is on critical actions recommended to advance the development of non-hormonal contraceptives that prevent HIV/STI infections. The process used in this work draws from that used previously to identify strategic actions for hormonal contraceptive and anti-HIV MPTs [6].

### A brief history of recent advances in contraceptive development

Funding and enthusiasm for contraceptive development has ebbed and flowed throughout the past few decades. Through the 1990s and early 2000s, there was significant investment and momentum in both the public and private sectors that advanced hormonal as well as non-hormonal contraceptive research and development (R&D) [7]. Many large pharmaceutical companies have supported active contraceptive R&D programs in the past, including Wyeth, LLC, Pfizer Inc., Schering AG, Organon International, Merck & Co., Inc., and Bayer AG. There was also significant US government funding for large reproductive health programs to support reproductive health and contraceptive development. Many private–public partnerships were created that provided significant support to contraceptive R&D efforts, including the Consortium for Industrial Collaboration in Contraceptive Research (CICCR) at CONRAD (Arlington, VA), with global industrial partners and private sector engagement. Over the past decade and a half, interest in supporting contraceptive R&D has dropped within the private sector, and advancement has stalled. The progress on non-hormonal contraceptives was impacted when priorities shifted to female condoms and vaginal microbicides for HIV prevention, as well as increased access to hormonal contraception—with no significant advances in non-hormonal contraceptive method development in nearly 20 years.

### The need for new approaches

An immense unmet need for improved contraception and HIV and STI protection remains in the United States and globally. In the United States, nearly half of all pregnancies are unintended [8], and most US women will contract an STI in their lifetime [9–12]. Many women of reproductive age who wish to prevent a pregnancy are not using a modern contraceptive method consistently [13]. Globally, 85 million unintended pregnancies occur per year, and each day, 830 women die from preventable causes related to pregnancy and childbirth [14]. While there are myriad barriers to contraceptive uptake and continued use, dissatisfaction with available contraceptive approaches appears to be a common issue and likely a main contributor to nonuse of contraception. Research indicates that women who discontinue hormonal contraceptive methods often do so for method related concerns such as side effects and misinformation [15]. Many women have expressed a dislike for hormonal methods [16–19] citing in particular concerns over side effects such as irregular bleeding/amenorrhea [20], effects on lactation [21], weight gain [22, 23], pulmonary embolism [24], and misperceptions around the link between contraception and infertility [15]. Non-hormonal methods may be appealing for some women and would be a new and critically needed area of innovation in the contraceptive space.

Hormonal contraception does not protect women against STIs. According to the Centers for Disease Control and Prevention (CDC), after decades of decline, combined cases of syphilis, gonorrhea, and chlamydia have risen again in the United States since 2013 [25]. STIs can have severe health consequences for women and their children, including pelvic inflammatory disease, infertility, and even death, as illustrated by a 22% increase in newborn deaths in the United States between 2017 and 2018 related to congenital syphilis [25]. The World Health Organization (WHO) estimates that more than 1 million STIs are acquired every day globally [26]. In 2016, the WHO estimated 376 million new infections of curable STIs: chlamydiasis (127 million), gonorrhea (87 million), syphilis (6.3 million), and trichomoniasis (156 million). More than 500 million people worldwide are living with genital herpes (HSV) infection, and an estimated 300 million women are infected with human papillomavirus (HPV), the primary cause of cervical cancer [27]. HIV is a leading cause of death for women globally [28]. Yet for so many, the risk of pregnancy is a higher priority, and stigma around HIV prevention often discourages women from accessing HIV prevention tools, such as pre-exposure prophylaxis (PrEP) [29–33].

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Multipurpose prevention technologies (MPTs) are biomedical prevention products which not only have the potential to increase protection but may also reduce stigma around HIV and STI prevention, improve acceptability of and adherence to contraceptive and anti-infective prevention products, and offer convenience by addressing overlapping risks with a single product [5]. The MPT development pipeline has grown substantially over the past decade, with a focus on combining hormonal contraceptive drugs and anti-HIV drugs into a single product [5]. Of the MPT approaches in the product development pipeline [5], the majority have a contraceptive component combined with protection against at least one STI, including HIV, HSV-2, and chlamydiasis. Given the side effects of hormonal contraceptives mentioned above and high rates of many STIs, there has been increased interest in the development of MPTs that are non-hormonal and have an anti-infective component to better provide a range of options and increase uptake.

## Materials and methods

The development of new contraceptive and STI prevention options is complex not only due to the science but also due to finite funding resources and limited funding mechanisms since most current R&D is funded by the US government with diverse mandates. Thus, additional strategic thinking is essential to address research and development challenges and to prioritize attributes that would optimize advancement to later-stage clinical trials and product licensure. Such strategies must balance explorations that are of scientific merit against fundamental research that must be conducted to achieve regulatory approval.

The Initiative for MPTs (IMPT) [5], a product-neutral global collaboration that advances the field of MPTs, was founded in 2009 by researchers, policy-makers, funders, and advocates working across the spectrum of women's global health to help facilitate strategic thinking for MPT development. With support from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), in 2019 the IMPT facilitated a process to inform strategic actions for advancing non-hormonal MPTs (the views presented in this paper do not necessarily reflect those of the agency). The process for developing this framework draws from the IMPT's earlier work developing a strategic action framework for hormonal contraceptive and HIV prevention MPTs[6]. Similar roadmaps have been developed for advancing the development of other prevention and treatment products, such as vaccines against STIs and cancer [34–36]. First, a landscape review of existing approaches to development of non-hormonal contraceptives for men and women was conducted. This review was informed by a search of relevant projects and research in both the peer-reviewed and grey literature, news articles, funding notices, and databases (e.g., grants.gov, NIH RePORTER, Calliope, and the MPT Product Development Database).

A series of over 30 in-depth semi-structured verbal key informant interviews (KII) were conducted with family planning experts, STI and HIV prevention experts, MPT product developers, and MPT funders from around the globe, with expertise ranging from basic science and clinical research to manufacturing and product introduction/implementation. This approach was based on the Delphi method, which is a process based on multiple rounds of questions discussed by experts, aggregation of results, and further vetting by groups of experts [37]. All but four of the KIIs were attended by two of the authors, and detailed notes were taken for all interviews. Following completion of all KIIs, these notes were reviewed for accuracy, then coded and key themes identified. From the key themes emerged a number of preliminary strategic action areas, which were presented and discussed in small groups by nearly 40 experts participating in a workshop during the November 4–6, 2019 NICHD Contraceptive Development Meeting in Houston, Texas. Workshop participants were provided a summary of findings and were asked to respond to specific discussion questions for each strategic action area. In the weeks after the workshop, the group discussion findings were captured in an updated summary, and workshop participants were given an opportunity to review this summary prior to the completion of this review.

## Results

The roadmap resulting from the process described above consists of seven primary action strategies, including the identification of key research gaps and priorities, to guide current and future MPT development that combines non-hormonal pregnancy and infection prevention products (Table 1).

### Action strategy 1

***Identify target populations and assess product preferences for non-hormonal MPTs.*** Lessons learned from the biomedical HIV prevention and other fields amplify the need to incorporate end-user perspectives from primary target populations early during product development (e.g., product conceptualization and preclinical stages) to inform non-hormonal MPT R&D (e.g., selection of appropriate polymers, delivery types, etc.) rather than wait until clinical stages of development when product modifications can be difficult and costly. Although research on end-user preferences exists for biomedical HIV prevention, including MPTs that provide hormonal contraceptive and antiretroviral HIV prevention [30, 32, 38–41], there is a paucity of research on women's desire for and preferences around non-hormonal methods.

**Progress to date** As part of efforts to define target populations for products in development, the IMPT created the *MPT Target Population Identification Mapping Tool* [5]. This mapping tool uses epidemiological data on HIV prevalence, the total addressable market for contraceptives (defined as women currently using a modern method as well as those who plan to use contraception in the future), and the contraceptive method mix on the subnational level to identify geographical "hot spots" where HIV prevalence and contraceptive need among women overlap in 11 Sub-Saharan African countries. Inclusion of HIV incidence data is planned as it becomes available. This tool has been used by sociobehavioral researchers to inform where MPT end-user research may have most impact and to inform market introduction strategies for MPTs in development.

In the past, incorporating end-user research early and throughout biomedical HIV product development was rarely rigorously applied in academia, but has become increasingly recognized as a critical part of the product development process, as evidenced by a growing body of research in this area [38–41]. Also recognized is that, while there are limitations to conducting acceptability research focused on hypothetical and unfamiliar product types and these studies should not be the sole go/no-go criterion for a product, such data can provide guidance for early-stage product design. Early-stage end-user research is typically used in the pharmaceutical industry; however, standards for comparing and evaluating development and

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**Table 1.** Action areas for non-hormonal MPTs.

| | Action areas for non-hormonal MPTs |
|---|---|
| 1 | Identify target populations and assess product preferences for non-hormonal contraceptive MPTs |
| 2 | Utilize a systematic approach to stimulate innovative drug development |
| 3 | Maintenance of a pipeline containing the most promising product candidates |
| 4 | Optimize investments by defining an investment/business case and rethinking funding mechanisms |
| 5 | Define criteria to inform go/no-go decisions and an expanded non-hormonal contraceptive target product profile |
| 6 | Define criteria to inform go/no-go decisions and an expanded non-hormonal contraceptive target product profile |
| 7 | Define criteria to inform go/no-go decisions and an expanded non-hormonal contraceptive target product profile |

investment decisions for biomedical prevention products from the user perspective are complex and not consistently applied across stakeholders [42]. While some industry and philanthropic entities and nongovernmental organizations (NGOs) have internal standards that incorporate end-user perspectives in their product development and investment decisions, these standards for public sector funders are still in development.

## Recommended next steps

1. Identify primary target populations for non-hormonal MPTs in regions where these products may have the most impact, using epidemiological data on incidence of HIV and other STIs, the total addressable market for contraceptives, and the current contraceptive method mix. Due to varying market potential of the products, this could be stratified by LMICs and higher-income countries.
2. Use qualitative and quantitative research methods to evaluate end-user preferences within the target populations. End-user research should be used early in MPT product development to provide insights to researchers and developers into end-user lifestyles, drivers, and barriers to use of non-hormonal prevention products, as well as to inform preferred product attributes and go/no-go decisions. This research can also inform the feasibility of the product in development with regard to usability, acceptability, and product characteristic preferences, with the end result of informing product development decisions. Approaches used to characterize the target populations include the collection of qualitative data through in-depth interviews and focus groups within the target populations, followed by quantitative assessments, including conjoint analysis and discrete choice experiments. It is important to gather this information from both end-users and their influencers, including providers, family, and community members, as these groups may all have an impact on the end-user's decision-making process. Mathematical models are also useful tools, but accurate correlations between demand forecasting and future product performance, for example, directly correlate with the quality and accuracy of data used to generate the models [42]. Developers should consider the entire contraceptive journey of the end-user in order to design products that meet the user's needs, which vary throughout the life course. Stratifying end-users into those in high-income countries and those in low- and middle-income countries (LMICs) may also be useful.
3. Develop and implement appropriate messaging around non-hormonal MPTs. Messaging around non-hormonal MPTs needs to incorporate user-centered priorities as they are identified (outlined as part of #2 above), using culturally appropriate and inclusive language. Messaging must be stigma-reducing and promote understanding of fertility.

### Action strategy 2

***Utilize a systematic approach to stimulate innovative drug development.*** Past research efforts were often focused on a single molecular target, identified pathway, or existing drug. In some cases, leads fortuitously emerged out of unrelated research fields, such as the classic example of sildenafil (Viagra), which was identified as a potential treatment for erectile dysfunction while being tested in clinical trials for hypertension and angina pectoris [43].

**Progress to date** Development of new non-hormonal contraceptive MPTs will likely benefit from emerging technologies that now allow for a large-scale systematic approach to drug discovery utilizing new high-throughput technologies for a systematic screening of targets. One such method is utilizing DNA barcoding technology for genes critical to reproductive pathways, a technique that allows for orders of magnitude more compounds to be screened compared to traditional methods. Eventually, all discovered non-hormonal contraceptive MPT compounds need to be administered via suitable drug delivery systems. With the convergence of engineering, biology, chemistry, and materials sciences, in recent years, there has been promising innovation in the area of drug delivery (e.g., long-acting vaginal rings, vaginal films, smart tampons) and in the area of device manufacturing such as 3D printing, which could be used to manufacture unique dosage forms of non-hormonal MPTs.

## Recommended next steps

1. Boost basic science efforts in reproductive biology to identify and refine non-hormonal reproductive targets for fertility regulation. These efforts need to be complemented with assay development and bench/in silico screening methodologies to facilitate the identification and validation of novel targets. Both topical and systemic approaches should be considered for non-hormonal contraception, and technologies to support this development should be pursued. These include but are not limited to understanding the range of potential targets, understanding how non-native molecules can traverse the blood–testis barrier, development of novel methods for perturbing gametogenesis and evaluating compound function in vitro, and the development of novel screening methods (e.g., DEC-TEC, phenotypic screening of sperm motility).

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2. Access to regulatory experts and documented guidelines that can inform the best paths to harmonize and advance new drugs, devices, and combined drug/devices in the pipeline should also be prioritized.
3. Identify and stimulate research for STI prevention approaches and targets that can be combined with non-hormonal contraceptives.
4. Foster innovation in systematic drug development to build, maintain, and share with the scientific community joint-access compound libraries. Recognizing proprietary considerations, it is nevertheless critical to facilitate information sharing in the scientific community to advance research and field-wide success. The development of approaches that address a critical need currently unfulfilled (e.g., non-hormonal drugs for contraception in men and women) should be prioritized among funding agencies.
5. Invest in the concurrent development of new platforms for drug delivery, and leverage technological advances in other fields such as HIV and hormonal contraception for this.

### Action strategy 3

***Maintenance of a pipeline containing the most promising product candidates.*** Biomedical prevention product development requires significant investment and amalgams of funding from public and private sectors to bring prevention products with the greatest potential global public health impact to market. Drug development pipelines are filled with promising technologies that ran out of steam or money early on or that presented an unacceptable side effect profile or manufacturing challenges in later development stages. Standards for comparing and evaluating development and investment decisions for such products are complex, but such go/no-go decision-making is critical.

Other fields have successfully developed models for independent, objective product prioritization processes. An example is the Paediatric Antiretroviral Drug Optimization (PADO) aimed to inform the most promising antiretroviral formulations for children, led by the World Health Organization (WHO) [44].

## Recommended next steps

1. Accelerate the progress of new compounds through the drug development pipeline into stages of clinical research and ultimately the clinic. Such a concerted effort among funders and stakeholders also needs to include innovations in study design to respond to challenges such as of non-inferiority requirements and post-market effectiveness assessment.
2. Development of a global authoritative body with no financial interests to provide an evidence-informed priority list and a clear and consistent message to guide industry and interested stakeholders on the lead non-hormonal and MPT product candidates. This expert body should be comprised of multidisciplinary experts to ensure robust evaluation from different perspectives, including basic science, clinical feasibility, end-user preferences, and regulatory, manufacturing, and product introduction. Given limited resources and the extremely high cost for clinical trials and market introduction, this product neutral expert body would provide a data-driven review process of the non-hormonal MPT product candidates with greatest public health impact potential. Such a list could be a critical tool to focus research and development efforts and resources. The WHO has experience moderating these processes in other sectors of global health and could become a valuable resource [44].

### Action strategy 4

***Optimize investments by defining an investment/business case and rethinking funding mechanisms.*** Our landscape assessment revealed extensive research on biological pathways and drug candidates, especially early in discovery and the preclinical development phase. However, over the last several decades, many of these approaches have faltered—often due to limited resources to continue the research. While academic research centers often build the foundation for a scientific breakthrough with government and philanthropic funding, historically these institutions have not been well equipped for the challenges of taking research onward through the preclinical IND-enabling safety and toxicity studies (following good laboratory practice standards [GLP]), drug manufacturing, and costly clinical testing. The pharmaceutical industry is built on a business model that tends to license programs once they have completed discovery and early- to mid-clinical drug development stages which are prone to failure, thereby de-risking investments.

Funding of basic science that supports the early drug development pipeline is well spent, despite an anticipated high attrition rate of early-stage product development. Basic science such as target validation and screening is not very expensive compared to late-stage preclinical work and clinical studies.

**Progress to date** The National Institutes of Health (NIH) has recognized these challenges and recently expanded the existing grants platform with funding instruments targeted for product development and manufacturing (U19, U54, U01, SBIR) to include new mechanisms such as the X01 and a reconfigured R61/33 [45]. These mechanisms and funds are welcome additions to the portfolio but remain limited in scope for larger-scale product development instruments and initiatives. Furthermore, the NIH Commercialization Accelerator Program (CAP) is available to NIH and Health and Human Services (HHS), Small Business Innovation Research (SBIR), and Small Business Technology Transfer (STTR) Phase II awardees to provide them commercialization training which can help bring their technologies to market [46].

## Recommended next steps

1. Develop new funding models that can be used for large-scale collaborative approaches in order to take advantage of advances in technology that allow the systematic screening of libraries with billions of potentially druggable targets and matching compounds to efficiently tailor innovative drugs with few side effects.
2. Build a robust investment framework and business case for non-hormonal MPTs to engage the private sector early on in product development for advice and support in order to accelerate basic science and preclinical and clinical research. A compelling novel product idea or a modification to an existing approach (such as hormone-free contraception and combining contraception and STI prevention) may generate considerable excitement among investors in a women's health market with an estimated worldwide market for contraceptives alone at $15.6 billion dollars in 2018 [47]. Enthusiasm

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may be increased if non-hormonal contraceptives are combined with anti-infectives, but sociobehavioral research and market data are needed on this.

3. Develop a more complete understanding of market size for non-hormonal MPTs for men, women, and couples, and assess competing markets such as current hormonal contraceptives users. These activities are critical to estimate the social impact of innovations and potential return on investment. When costing a future intervention, higher prices and increased revenue in high-income countries can help subsidize the use in low- and middle-income countries, as practiced with the Bill & Melinda Gates Foundation's (BMGF) Global Access Clause [48].

### Action strategy 5

***Define criteria to inform go/no-go decisions and an expanded non-hormonal target product profile.*** During the drug development process, a target product profile (TPP) for each specific product needs to be developed to inform the establishment of milestones and define go/no-go criteria for continued development. A TPP outlines the intended product attributes and other critical details for a specific product in development and describes the intended use by the end-user [49]. The general structure of a TPP resembles a product label, or product insert, that would be found associated with a regulatory licensed commercial product or device, and it provides information on the desired product's indications, dosage, mechanism of action, target populations, efficacy, storage/shelf life, preclinical and clinical safety, pharmacokinetics, contraindications, and relevant data pertaining to each of these attributes. A general TPP framework for non-hormonal contraceptive products and non-hormonal MPTs would provide helpful guidance for the field.

**Progress to date** In 2012, the IMPT moderated an expert think tank to define general target attributes for specific MPT product dosage forms (i.e., long-acting injectables, intravaginal rings, and on-demand products) [50]. Through our more recent discussions with key experts in the field, additional important considerations emerged regarding safety, efficacy, and pricing. Determining acceptable thresholds for minimum contraceptive and anti-infective efficacy will be important, especially in comparison to highly effective hormonal contraceptives as regulators will compare any new products to those for similar indications already available. For safety, side effects and off-target effects need to be considered. Products with a better safety profile compared to hormonal contraceptives are highly desirable. Many experts cautioned against overestimating the initial unit price at market introduction, as this figure tends to down-correct rapidly as market penetration increases.

## Recommended next steps

1. Develop an expanded target product profile (TPP) for non-hormonal contraception. An expanded TPP for non-hormonal contraception could add select aspects to the attributes currently included in a TPP. These could include additional assessments for feasibility of the approach, complexity of manufacturing processes and manufacturing capacity in global regions, access, logistics of procurement, and burden on the health-care delivery system (e.g., storage requirements, frequency of administration by trained personnel, user education and counselling needs, over-the-counter availability.) Further, the ecological impact of drug production, fast reversibility of a method, as well as design characteristics that can affect ease of use and user behavior will drive acceptability by the end-user. Many characteristics that could be included in an expanded TPP for non-hormonal contraception are flexible and may not warrant specific go/no-go criteria but could inform the design of a product to ensure the highest degree to success. Acceptability of a product in different target populations and cultural contexts may differ, as can the desired degree of user autonomy during administration and reversibility of method. Additional noncontraceptive benefits of a product (e.g., improving skin and post-menstrual syndrome effects, enhancing the sexual experience) could significantly increase the attractiveness to users. Some criteria such as the political and ethical climates surrounding technological approaches were seen as too fluid across time and geographies to merit significant concerns.
2. Build a general go/no-go framework for non-hormonal MPTs based on stakeholder consensus to support an objective decision-making process and guide the field toward using its limited resources on approaches with the most potential for reaching markets and impact for change. This resource can help to assess the feasibility of multiple approaches and set criteria to determine when a specific approach has reached a no-go decision. Academic research often seeks a general contribution to knowledge, whereas a commercial approach to drug development needs to measure time and resources needed to systematically turn science into a cost-effective licensed product. Such a framework can aide in conceptualizing what designates a highly desirable product and/or delivery mechanism and drive target selection accordingly. Researchers in small companies and academia need to access or build expertise for following FDA guidance for toxicity and efficacy standards and industry standards for drug quality. Finalizing a go/no-go framework for non-hormonal contraception should involve an interdisciplinary team of experts including researchers, end-users, regulatory experts for different global markets, decision-makers in the health insurance fields, and funders.

### Action strategy 6

***Enhance research collaborations, and leverage expertise from other fields and engagement with advocates and other stakeholders.*** Building global research collaborations can be challenging in a climate that often encourages scientists and developers to balance conflicting professional and institutional directions related to their particular funding source and specific project objectives with the overarching goal of supporting MPT development. Transdisciplinary and trans-institutional research collaborations could be facilitated by independent coordinating bodies. Engaging new stakeholders and instituting strategic collaborations will catalyze scientific discovery and the movement of products through the regulatory approval process. Broad collaborations are important, including not only scientists engaged in contraception, HIV, and STI treatment and prevention. Non-hormonal MPTs may have additional health benefits outside of contraception or HIV/STI prevention, such as reduced risk for infertility, which could leverage resources from related fields and engage new researchers in the MPT space. Building a collaborative network of scientists, clinicians, developers, regulators, advocates,

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funders, and other stakeholders could aid advocacy and awareness-raising efforts, expand the messaging around MPTs, and create an ecosystem of innovation for small centers and biotech developers.

**Progress to date** Over the past decade, there has been an increase in valuable multidisciplinary dialogue, as demonstrated by new communications and bridges built between US government funders and private foundations as well as sociobehavioral and basic scientists and clinical researchers supporting HIV prevention, other STI prevention, and contraception. Further, the FDA has increasingly participated in scientific MPT development meetings as a collaborator, which has immensely helped to clarify the regulatory requirements and goals that had previously been viewed as a "black box" for product development. This FDA guidance on regulatory issues is critical, especially for MPT development since it often involves more than one active pharmaceutical ingredient and multiple indications.

Existing research libraries and databases have a wealth of information about approaches that have been previously explored and since abandoned, which may be excellent targets for potential non-hormonal MPTs. With most new technologies in early phase development, there is a critical need to leverage expertise and facilitate collaborations within the scientific and funding communities that enable transition of lead products from preclinical to clinical testing.

## Recommended next steps

1. Facilitate early, ongoing conversations among collaborators with diverse areas of expertise and interests critical for non-hormonal MPT development, advocacy, and stakeholder engagement. Multidisciplinary collaborations will also be critical for delivering clear and effective product information, messaging, and dissemination to optimize access to and uptake of new products.
2. Prioritize strategic alliances. Multidisciplinary teams are needed to facilitate connections and collaborations between parties involved in all stages of the MPT product development and introduction process. Such strategic alliances should include those with expertise in medicinal chemistry; basic, clinical, and behavioral science from diverse disciplines (e.g., contraception, infertility, HIV, other STIs); regulatory (e.g., FDA, EMA); translational science to enable passage of products through preclinical to clinical trials; manufacturing; and product introduction and procurement.
3. To advance these strategic alliances, formalize programs to facilitate connection and collaborations between various areas of drug development and implementation science that traditionally have not interacted, particularly between scientists, product developers, and pharmaceutical companies.
4. Build nurturing training environments that will encourage a pipeline of trained scientists that can increase the workforce available for small centers and biotech firms.

### Action strategy 7

***Address challenges with planning a regulatory pathway, the patenting process, and manufacturing and commercialization.*** Several additional challenges in successful and timely product development are unfamiliar territory for most small developers or academic researchers, but critical to navigate proactively as they can make or break a product candidate.

The development of a viable regulatory pathway to licensure in the United States is guided by the FDA, where devices and drugs are reviewed separately. Many developers focus on the lucrative US market first. However, regulatory requirements may differ in Europe or other global markets, and a sound regulatory strategy addressing these differences early on will greatly accelerate later global introduction of a product. In recent years, the WHO has supported building regulatory expertise in developing countries, including efforts to increase prevention of HIV.

Contraceptives must be studied in healthy women and men of reproductive age, the most challenging study population for regulatory approval. Since highly effective hormonal contraceptive methods such as oral contraception, IUDs, and implants are on the market, the non-inferior efficacy and safety of a new method would have to be established to gain regulatory approval. Combining multiple independently validated active pharmaceutical ingredients (APIs) that are small molecular weight molecules into one product requires testing for potential drug–drug interactions (DDI) between APIs combined in a single product. Different absorption levels and DDIs may be found when APIs are coadministered systemically versus topically. APIs of different chemical properties (e.g., hydrophobic and hydrophilic) may be challenging to combine into singular products. Combination products often face more complicated regulatory requirements in order to demonstrate safety and efficacy. Cocktails of same class biologics, e.g., antibodies or mRNA, may have different or reduced DDI or absorption concerns, but may be immunogenic. Furthermore, combined compounds may vary in potency by several magnitudes. For example, many current anti-HIV products are not potent enough for long-term drug release out of a small volume of product.

Trial design must be considered early on and intermittently as product development progresses. Given the multiple indications inherent in MPTs, perspectives of a large group of collaborators involved must be considered in these discussions. Toxicity requirements for MPT drug development should also be addressed during the screening stage for targets and compounds.

The patenting process also requires careful consideration. Patent rights are usually retained and sold in stages—first for the completion of preclinical development process, then for the conduct of clinical research and licensure, and then again for the commercialization of the product. Once a patent is filed, the clock starts ticking, and a slow development process shortens the time frame for recuperation of development costs during exclusive commercialization. Publishing avenues for scientific results may be limited for some patent holders. Large academic institutions are usually equipped to complete the patent application process for the United States, but rarely submit international patent filings which may require global partners with expertise and investments in foreign markets.

Important areas of expertise for drug development, such as medicinal chemistry or biotechnology, as well as expertise in conducting preclinical animal model testing suitable to support an investigational new drug (IND) need to be adequately represented in research institutions and the pharmaceutical/biopharmaceutical industries. Challenges for manufacturing of reproductive health drugs need to inform the development pathway in times of limited global manufacturing capacity and financial resources for contraceptive development by biopharmaceutical and pharmaceutical companies.

It is important to consider barriers and incentives for commercialization early on. Drug products with delivery methods that are easy to use with relatively little burden on distribution and health-care

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providers will have a commercialization advantage. Since products for treating healthy populations have high safety standards, and product liability risks, this will be an ongoing challenge. Prescription requirements and reimbursement by health insurance providers are important considerations for planning commercial success.

Having expertise in all of these areas above is very difficult for small companies and most academic settings. Providing a centralized resource of expertise in toxicology, pharmacology, statistical, and regulatory sciences to support academic institutions and small businesses will accelerate drug development efforts and reduce the likelihood of costly mistakes.

### Recommended next steps

1. Build a network of expertise to advise researchers on realistic pathways to licensure and commercialization for non-hormonal contraception or non-hormonal MPT products. Continue engagement with regulatory agencies to further map out requirements for products combining multiple APIs.
2. Build a network of expertise regarding global patenting to support small developers and research institutions devising contraceptive intellectual property strategies.
3. Evaluate experiences in other fields where governments help offset liability.

## Discussion

MPTs containing a non-hormonal contraceptive component are an exciting avenue into a market for women who require alternatives to existing methods of contraception and protection from HIV and other STIs. The seven strategic action areas outlined here define an actionable way forward to guide progress for the field of non-hormonal MPTs. Given limited resources for this field, these action areas aim to identify gaps and priorities which can help guide individual funders and facilitate collaboration and innovation.

While the focus of this article is to advance the development of female-initiated non-hormonal MPTs, the identified strategic action areas will also inform the development of single indication non-hormonal female and male-initiated contraceptive methods. It is important to remember that end-user prevention preferences will vary between cultural settings and throughout the life course of users. We need to expand prevention options for women, catering to individual preferences for contraceptives and their impacts on users' lives. As global health priorities shift to encompass more self-care and overall wellness, the role of non-hormonal MPTs, including their noncontraceptive benefits, could reach women who are not currently protected against STIs and unintended pregnancy.

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## Conflict of interest

The authors have declared that no conflict of interest exists.

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