Committee for Male Contraceptive Development and Regulatory Best Practices

Draft Recommendations

Quick Summary:

- Draft recommendations from the *Committee for Male Contraceptive Development and Regulatory Best Practices* are available for public comment*.
- We encourage you and others within your network to review these recommendations to ensure that the document is comprehensive and representative.
- Both general feedback on the document and targeted review and comments on specific sections are welcomed.

Dear Colleagues:

As you may be aware, Male Contraceptive Initiative has convened a committee of experts to evaluate the male contraceptive development space and make recommendations that will guide developers and regulatory authorities, ensuring the advancement and registration of safe and effective products. This committee (*Committee for Male Contraceptive Development and Regulatory Best Practices*), composed of basic scientists, clinical investigators, a bioethicist, consultants (pharma; regulatory; ex-FDA), device experts, and patient advocate(s), has been working since August 2024 to generate a comprehensive list of recommendations under the leadership of Committee Co-Chairs: Erin R. Gardner, PhD (Gardner Pharmacology, LLC) and Gregory S. Kopf, PhD (Sacyl Pharmaceuticals, Inc.).

We are pleased to announce that the draft report has been completed and is now available for public review and comment. This open call for comment is a critical step in shaping these recommendations. Your feedback will help ensure that the most comprehensive and relevant considerations are reflected, ultimately supporting more efficient and effective development and regulatory pathways for male contraceptive products.

A discussion forum has been established on the *Discourse* platform. To access the document and provide your feedback, please follow this link*. You will need to create an account to access the forum, after which point you will be directed to the forum page.

To help ensure a productive and organized review process, we kindly ask that you follow the instructions below when submitting comments:

- Please provide your feedback using the comment box on the forum page.

*Link: https://mci.discourse.group/t/request-for-comment-draft-guidance-from-the-committee-for-male-contraceptive-development-and-regulatory-best-practices/9

- Refer to specific line numbers whenever possible to help us accurately identify, understand and incorporate your input.
- Please include your name and affiliation with your comment.
- We welcome comments based on your area of expertise, including feedback on specific sections or topics. General feedback on the entire document is also appreciated.
- If you have extensive comments, a response letter, or supplementary materials, you may upload them using the paperclip icon in the comment box.

If you have further questions or any issues accessing the forum, please contact guidance@malecontraceptive.org.

We would like to thank the Committee and the Leadership Team for their extraordinary effort in support of this activity. We are truly grateful for your time, expertise, and partnership.

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Introduction and Background

The introduction of the first contraceptive pill in 1960 ushered in unprecedented agency for women to control their reproductive autonomy and resulted in a dramatic societal shift in proactive family planning.[1,2] Over the subsequent six decades, options for females have greatly expanded to include many hormonal (pills, patches, implants, rings, intrauterine systems) and nonhormonal (barrier methods, intrauterine devices, intravaginal gels) contraceptive modalities.[3] Despite these advances, nearly 50% of all pregnancies worldwide are still unintended,[4] and over half of these unintended pregnancies result in abortion.[5]

Unintended pregnancies cause a wide variety of long-lasting negative effects on the health and socioeconomic status of women, men, and the resulting children[6] and cost governments many billions of dollars each year.[7] One factor leading to the stubbornly high unintended pregnancy rate is limited contraceptive uptake among women, due to access barriers, improper product use, and early discontinuation. It is estimated that approximately 30-50% of women discontinue using hormonal contraceptives within the first year of use due to side effects (e.g. mood changes, weight gain, irregular bleeding, and reduced libido) or fear of long-term health risks.[8,9] Another critical but often-overlooked factor driving the high unintended pregnancy rate is the fact that men, half of the world's population, still have no pharmaceutical options for contraception. Even with conservative assumptions, modeling has shown that the introduction of male contraception would prevent hundreds of thousands of unintended pregnancies per year in the United States, Nigeria, and South Africa.[10] These statistics speak to the need for additional contraceptive options for all people at all stages of their reproductive lives, and this has been of interest to both international funding agencies and the pharmaceutical industry.[3]

Although there are a plethora of contraceptive options for females, the options for male contraceptives have not changed in over a century. The sole contraceptive options for males are vasectomy and condoms, and both have their limitations. Vasectomy is nearly 100% effective (failure rate ~0.15%)[11] but requires a surgical procedure and reversibility is not guaranteed.[12] Condoms offer user-controlled, on-demand contraception, but men and women often dislike their use, leading to a yearly failure rate of 13% largely due to non-adherence or incorrect use.[13] For these reasons, as with female contraceptives, there is a significant unmet need for new contraceptive options for males. Moreover, new methods would increase reproductive autonomy for males, provide additional contraceptive options for couples and would likely reduce unintended pregnancies and abortions.

Recognizing the need for new male contraceptive methods, funding organizations such as the Eunice Kennedy Shriver National Institute of Child Health and Development and the Male Contraceptive Initiative, among others, have provided funding for the development of new and innovative male hormonal and nonhormonal contraceptives. The development of new male contraceptive methods can be traced back to 1939 when testosterone supplementation was first shown to result in reversible suppression of sperm production.[14] Subsequent work has focused on androgens as single agents or in combination with progestins or hormone receptor modulators, administered through a variety of routes, and it has been reliably shown that these products can reversibly suppress sperm concentrations in humans to contraceptive levels.[15–17] Fast forward to today, a hormonal male contraceptive transdermal gel containing an androgen (testosterone) and a progestin (segesterone acetate, aka Nestorone®) has completed phase 2 clinical trials.[18] This formulation represents the furthest advanced new male contraceptive currently in development, but other hormonal male contraceptives are currently in earlier phases of clinical development.[19,20] Hormonal approaches to male contraception may result in systemic side effects consistent with their pharmacological mode of action which could ultimately limit market uptake, although similar side-effects are well accepted by women using hormonal contraceptives.

Advancements in biomedical science (e.g., animal and human genome sequencing and curation; a greater understanding of basic reproductive biology; reverse/forward genetic methods; new analytical methods) over the past decades have identified genes/gene products that play critical roles in both male and female reproduction.[21–23] *Such progress has allowed the biomedical community to develop highly specific non-hormonal male and female contraceptives that target gene products that play key roles in reproduction and that do not function by modulating the hypothalamic-pituitary-gonadal axis, and thus the regulation of systemic sex hormones.*[22] *Unlike hormonal methods that modulate the expression of many genes, nonhormonal approaches are anticipated to lack pleiotropic effects as 'on target' activity is expected to occur exclusively or primarily at the site of target protein expression, which for male contraceptives is often limited to or enriched in testes or sperm.*[24] *This has the promise of improved safety and side effect profiles, likely facilitating greater user uptake. Moreover, advances in drug development (e.g., screening platforms; medicinal chemistry; use of artificial intelligence) and biomedical engineering/materials science (e.g., drug delivery platforms) offer new and innovative approaches to develop and deliver new generations of contraceptives.*

Although the opportunities for the development of innovative nonhormonal contraceptives can be facilitated by the aforementioned scientific advances, a major question is whether there is a market for such products. Even a great product cannot succeed if there is no market for it. Several observations suggest that new classes of nonhormonal contraceptives, be they for males or females, would be widely adopted. First, the current societal and financial burden to economies of unplanned pregnancies is well known. According to a 2022 report of the U.S. Joint Economic Committee, of the over 47 million Americans aged 15-49 who relied on contraceptives, there is still a yearly unintended pregnancy rate of 45%, with an associated economic burden of the resultant births, abortions, and miscarriages of $21 billion.[25] *It has been clearly shown that access to modern contraceptives and their proper use has socioeconomic benefits not only in the US but globally (Finer and Sonfield, 2013).*[6] *In addition, several studies have demonstrated that there is global interest in new male contraceptive options, that women in stable relationships would trust men to share responsibility for contraception, and that the economics of male contraception would make it an attractive area for pharmaceutical development.*[26–29] *Moreover, discussions with male participants in recent male hormonal contraceptive clinical trials and their female partners have revealed a great interest in new male contraceptive products and an eagerness to continue using them if they were on the market. Despite this, appreciation by investors and the pharmaceutical industry is lagging behind. Towards this end it will be important to create Target Product Profiles that are commercially viable and are acceptable for insurance and reimbursement plans.*

The current pipeline of male nonhormonal contraceptives contains drugs and devices in various stages of preclinical and early clinical development. Two companies are developing reversible vas deferens occlusion devices.[30] Several drug programs are targeting gene products that play various roles in testicular sperm development and other programs are developing drugs that interfere with extra-testicular sperm function.[23] Discussions with developers have suggested that because of the uniqueness of the male contraceptive indication and the first-in-class nature of the products in development, the entire field could benefit from recommendations to guide their development pathways in a more time- and cost-effective manner. Regulators have had limited experience with male contraceptive products and often rely on the well-established regulatory guidelines governing hormonal female contraceptives, which are not necessarily applicable to male methods.

Recognizing the need for product development and regulatory guidelines for male contraceptive development, the Male Contraceptive Initiative initiated discussions with thought leaders in the contraceptive development space. A committee was formed, comprised of global experts in contraceptive research and development, academia, regulatory science, the pharmaceutical industry, and the global health spaces. The Committee for Male Contraceptive Development and Regulatory Best Practices (The Committee) has been meeting for the past 11 months and has developed the following guidelines for developers of male contraceptives and recommendations for regulators to consider as part of their engagement with developers. These guidelines and recommendations are intended to support developers and regulatory agencies in establishing official guidelines for male contraceptives. The Committee considers your input to its work as a critical part of its mission and would greatly appreciate your thoughts.

Comments can be submitted here any time before October 15th.

Thank you for your consideration.

Preclinical Evaluation of Male Contraceptives

There is a widespread perception among developers that the regulatory pathway for male contraceptives, especially non-hormonal methods, is unclear and overly burdensome compared to other product types. The lack of published male-specific regulatory guidance compounds that perception. The scientific bar is also unusually high: a preventive intervention for healthy men, targeting a physiological process that must be substantially, if not entirely, suppressed for efficacy and should be fully reversible. In addition, the most visible endpoint – prevention of pregnancy – occurs outside of the individual receiving the intervention.

To support the emerging field of non-hormonal male contraceptive development, the committee strongly recommends the publication of comprehensive guidance to assist early-stage product developers in designing rational, effective preclinical programs. Developers entering this space—often from academic or discovery research focused settings—face a steep learning curve, with limited infrastructure for regulatory support. Many are encountering Investigational New Drug (IND)-enabling requirements for the first time, and they would benefit from direction and shared learnings, particularly regarding animal model selection, mating study design, and reversibility assessment.

In the preclinical setting, developers must conduct animal studies to evaluate numerous domains, including: pharmacokinetics (PK); pharmacodynamics (PD), which includes efficacy and reversibility; reproductive and developmental toxicity; general toxicity (acute, subchronic, and chronic); safety pharmacology; genotoxicity; and sensitization. Not all of these studies must be fully completed before initiating first-in-human studies—nonclinical development is inherently iterative. However, demonstrating in vivo contraceptive efficacy and reversibility in at least one non-human species is a critical early milestone. The choice of animal models and endpoints should be thoughtfully aligned with the product's mechanism of action and route of administration.

Good Laboratory Practice (GLP)-compliant safety toxicology studies are required for IND submission and are designed to evaluate adverse effects at a maximum tolerated dose (MTD), to determine the no-observed-adverse-effect level (NOAEL) used to estimate the maximum safe starting dose in initial clinical trials and guide subsequent trial design, as described in the globally adopted ICH guidance M3(R2).[31]

Minimizing animal studies is an ethical and scientific imperative, as well as a financial one. Well-designed preclinical studies—those with clearly justified species selection, appropriate endpoints, and alignment with the anticipated clinical context—support both humane science and efficient regulatory progression. As male contraceptive

development evolves, developers should look to adjacent disciplines for insights—such as assisted reproduction, urology, and animal breeding sciences—particularly in areas like semen collection and fertility assessment. By sharing knowledge across disciplines and being more transparent about preclinical strategies, the entire field can benefit and avoid unnecessary duplication or wasted resources.

Given the limited number of male contraceptive products that have reached clinical trials, developers must be the experts in their targets, products, and animal models, as well as deepen their knowledge of key aspects of drug development. Clear, data-driven rationales are essential not only for study design but also for facilitating review by regulatory agencies that may lack specific familiarity with this product class.

Recommendation: Developers should prioritize target identification and mechanistic understanding to focus decision-making and streamline preclinical and clinical development.

- For potential male contraceptive drugs discovered via phenotypic screening or through repurposing after observations of infertility in other studies, gaining an understanding of the molecular target is critical to rational product development. Identifying the mechanism of action enables the design of studies that are appropriately tailored to the product's pharmacology and anticipated risks, allows for more efficient selection of relevant animal models, and supports the development of suitable biomarkers or surrogate endpoints.

- When the target is undefined, significant resources may be wasted as efficacy might be evaluated in animal models that may not even express the target, leading to inconclusive outcomes. Embarking on toxicity studies without an understanding of target expression, specificity, or how to distinguish on-target and off-target effects is likely to yield findings that are difficult to interpret. Without target-based justification for species selection, regulators may attribute an apparently non-toxic profile to poor model relevance rather than true safety and therefore request additional toxicity studies. While some agents may enter development based solely on compelling empirical efficacy data, continuing without mechanistic insight typically results in recurring challenges as development progresses. Whenever feasible, investment in target deconvolution should be undertaken as early as possible to inform downstream development decisions.

Recommendation: Following demonstration of *in vitro* activity, developers should conduct *in vivo* studies to evaluate contraceptive efficacy. Animal species selection should be guided by target expression, reproductive physiology, and feasibility of study endpoints. While mating studies are often considered the gold standard for assessing functional fertility, surrogate endpoints, such as sperm parameters, may also be appropriate.

- Once *in vitro* assays suggest potential efficacy, developers must transition to animal models to confirm contraceptive effects *in vivo*. Selection of an appropriate animal model is pivotal and should prioritize biological relevance (such as target expression), adequate PK and potency, comparable reproductive physiology, and logistical feasibility.

- For on-demand agents expected to require only one administration for activity, developers with validated targets often proceed directly to dosing animals and evaluating fertility outcomes after a single dose.

- For agents intended to inhibit the complex process of spermatogenesis, longer-term dosing is required. Developers should first conduct preliminary PK studies in the chosen animal model to optimize dosing frequency and ensure sufficient drug exposure to produce an effect. Additionally, animals will need to be monitored throughout at least one complete cycle of spermatogenesis, which can range from approximately 35 days in mice to approximately 60 days in dogs. These timelines are essential for interpreting reductions in sperm count.

- Rodents (e.g., mice and rats) are commonly used for early-stage evaluations of new drugs because of their small size (minimizing test article requirements), cost efficiency, and ease of handling. However, a significant limitation is that semen cannot be directly collected for *ex vivo* sperm parameter analyses without sacrificing the animal. In these species, sperm must be recovered from the cauda epididymis, making this a terminal procedure and precluding longitudinal monitoring within an individual animal. Additionally, epididymal sperm may not adequately represent ejaculated sperm, especially for products where the mechanism of action may be impacted via interaction with seminal plasma or accessory gland secretions. Alternatively, some researchers have retrieved sperm from the reproductive tract of female mice after copulation, but this is also a terminal procedure.[32–34]

- In larger animal species such as rabbits, dogs, pigs, and non-human primates (NHPs), true ejaculates can be collected using methods such as:
    - Electroejaculation**:** Applicable across multiple species, including rabbits, dogs, pigs, and NHPs; allows for collection with limited behavioral training, though may require anesthesia and has limits on frequency (typically once weekly) due to stress and sedation requirements, depending on whether penile or anal stimulation is utilized.[35]
    - Penile Vibrational Stimulation: Used in small NHPs such as marmosets and squirrel monkeys.[36]
    - Artificial vagina**:** Used primarily in rabbits, dogs, boars, and certain NHPs; yields physiologically representative samples but requires substantial training and handling. In rabbits, the use of this method (along with a teaser female) can allow for multiple collections per day, which may be highly beneficial for on-demand products requiring more frequent and precise time points.[37]
    - Manual stimulation**:** Feasible in species like dogs and boars; less commonly used elsewhere.[38]

- Although there are few publications detailing the use of different species in assessing the efficacy of novel male contraceptives, numerous animal species have been used broadly in medical research and can potentially be adapted to study contraceptives. For example, in addition to their routine use for IND-enabling toxicology studies, dogs have been widely used in urological research due to their comparable anatomy and physiology to humans. The similarity in size of the canine vas deferens to that in humans has led to the use of this animal model for testing vas occlusive devices.[39,40] Rabbits have been used extensively for reproductive health studies and are well-accepted by regulators for toxicology studies, as well as in vivo assessment of vaginal irritation.[41,42] Pigs, especially minipigs such as the Göttingen strain, are utilized for evaluating both transdermal absorption and dermal sensitivity (due to similarity with human skin), in addition to their use for testing medical devices, such as cardiac implants (due to comparable heart size).[43,44] There is additional relevant expertise that can potentially inform animal models for the development of male contraceptives, particularly from fields such as veterinary reproduction and farm animal husbandry, where semen collection, fertility assessment, and breeding optimization are routine practices. While outside the

traditional contraceptive domain, these practical methods and physiological insights can offer valuable lessons.[45]

- There is a perception in the field that demonstrating contraceptive efficacy in NHPs is superior to performing efficacy studies in other mammals, possibly based on historical usage and parallels with human physiology. Some potential male contraceptive targets (such as KLK3/PSA) only have orthologs in primates, so a justification could be made, but widespread use is typically not scientifically justifiable. The continued expectation of NHP data appears to stem from potential investors, despite regulatory discouragement.

- Mating studies are often considered definitive for demonstrating contraceptive efficacy, but their success can be highly variable. Key considerations for developers include:
    - Pregnancy rates in naïve animals: Untreated or placebo-treated controls must exhibit consistently high baseline pregnancy rates so that any reduction in fertility observed in the treatment group can be confidently attributed to the investigational contraceptive. However, there are numerous factors that impact the likelihood of mating success that developers must consider. For example, some species naturally achieve higher pregnancy rates due to repeat matings or prolonged mating windows, which may not be suitable for evaluating on-demand products. When untreated C57BL/6J mice were paired overnight, they achieved a pregnancy rate of 80%, but this fell to just 30% when mating was restricted to a 2-hour early evening window (4-6 pm).[46]
    - Variation in reproductive biology across species: This encompasses factors related to reproductive anatomy and physiology, including ovulation mechanisms (spontaneous in mice, while rabbits are reflex ovulators), sperm deposition and transport, semen viscosity and vaginal pH, frequency and duration of estrus, as well as seasonal breeding patterns.[47,48]
    - Behavioral compatibility and sexual receptivity: This can vary across strains and individual animals, and be affected by environmental conditions.[49,50]

  These factors introduce a risk of experimental failure that may not reflect a lack of efficacy, but rather suboptimal mating conditions or, worse, a successful study that does not consider critical biological differences

between humans and the species tested. For this reason, developers must carefully evaluate whether natural mating is appropriate and informative for their product. When not feasible, surrogate endpoints such as sperm concentration, motility, hyperactivation, capacitation competence, and acrosome status—collected from ejaculated semen—may be superior for evaluating contraceptive efficacy in the preclinical realm, provided they are mechanistically linked to the product's action.

- Although *in vivo* evidence of efficacy is often valuable for bolstering developer confidence and supporting regulatory submissions, committee members emphasized that it should not be regarded as an absolute requirement. When no suitable animal model exists and a candidate drug shows no toxicological concerns, along with a strong scientific rationale for human activity, it may be reasonable to advance directly to first-in-human exploratory studies to observe the effect, rather than insisting on animal efficacy data of limited translational value.

Recommendation: Developers of drugs targeting outcomes other than azoospermia can advance decision making by establishing product-specific biomarkers and contraceptive thresholds of fertility, informed by PK-PD relationships and the biology of the selected test species.

- Most existing animal studies on male fertility have been designed either to maximize breeding success (e.g., in livestock production) or to detect reproductive toxicity, rather than to establish specific thresholds of sperm parameters, such as motility, below which fertility is predictably impaired. As a result, there is limited guidance on what constitutes a sufficient reduction in sperm count, motility, or function to achieve contraceptive efficacy in various species.

- While azoospermia (absence of sperm in semen) represents an unambiguous and broadly accepted endpoint, many male contraceptive candidates—particularly those that do not act via obstruction or inhibition of spermatogenesis—will benefit from alternative or more nuanced pharmacodynamic biomarkers. These biomarkers may include parameters related to motility, capacitation, acrosome reaction, or sperm-egg interaction. For products that suppress spermatogenesis, but may not entirely eliminate sperm from the ejaculate, sperm count thresholds that reliably prevent pregnancy have not been systematically defined and may vary considerably between species—and even between strains within a

species—due to inherent differences in reproductive physiology, mating behavior, and fecundity. Sperm morphology varies significantly between species, as does the regulation of motility; therefore, developers must also confirm the translational applicability of their chosen species.[51,52]

- Establishing surrogate biomarkers reflective of a contraceptive effect can accelerate both nonclinical and clinical product development. Biomarkers must be shown to correlate with significant contraceptive effect in vivo, through well-controlled natural mating studies or potentially through in vitro fertilization; a biomarker should display a clear dose-response relationship to support its validity. *See Biomarkers for a complete discussion of the clinical applications.*

Recommendation: Species selection for IND-enabling toxicology studies should not default to standard models but rather be guided by the goal of maximizing clinical translatability. Species selection must be rigorously justified based on the intended clinical use, including the pharmacologic target, mechanism of action, route of administration, and pharmacokinetics.

- The translatability of nonclinical findings to humans hinges on thoughtful species selection. The ICH M3 (R2) Guidance on Nonclinical Safety Studies for the Conduct of Clinical Trials and Marketing Authorization for Pharmaceuticals has been widely adopted by regulators, including the EMA and FDA.[31] This guidance requires new chemical entities (NCEs) to be tested in two mammalian species, typically including one rodent and one non-rodent species. While rats and dogs are often perceived as the standard species for general toxicology, developers should not default to these models without careful consideration and justification. No regulatory guidance mandates a particular strain or species; alternative models (e.g., minipigs, rabbits, different rodent species) may be more suitable, depending on practical and scientific considerations.

- Several publications describe the approaches and considerations employed in industry, with many developers prioritizing species based on homology, metabolite profile, and suitability of administration route. Many also base species selection on prior experience with chemical entities targeting the same pathway. For novel male contraceptives, there is sparse background knowledge or understanding of class effects to support decision-making, so it is even more critical to rationally and scientifically justify the selection of species.[53,54]

- Developers of male contraceptive drugs should consider:
    - Pharmacological relevance: For NCEs, it is required that at least one animal species used for toxicity testing (whether rodent or non-rodent) be "pharmacologically relevant." This is defined by considering the target expression, distribution, and homology, as well as the relative potency of the molecule against that target and known unintended targets in both the selected animal species and in humans.
    - Drug metabolism: Comparative *in vitro* metabolism data for a variety of animal species should be used to select the most metabolically relevant animal species for toxicity studies, ensuring similar exposure to metabolites expected in humans and increasing the likelihood of detecting meaningful adverse effects.
    - Protein binding: Readily assessed *in vitro* in a range of animal plasmas, ensuring that protein binding is comparable or lower than in humans will help ensure that adequate intracellular drug exposure can occur.
    - Route of administration: Some species are better suited than others for specific routes of administration, either due to the practical feasibility of repeat dosing, similarity to humans (e.g., minipigs for dermal administration), or the frequency of side effects that impact exposure (e.g., emesis in dogs).
    - Bioavailability: Developers should ensure that exposure in the animal model isn't limited by poor bioavailability via the planned route of administration.

- The use of efficacy models or species for toxicology should be carefully considered, as they are not always optimal for risk assessment. Importantly, alignment with the principles of the 3Rs (Replacement, Reduction, and Refinement) for animal use should be maintained by selecting species and study designs that reduce animal use while enhancing the predictive value of the data for human outcomes.[55] In the spring of 2025, the FDA announced its Roadmap to Reducing Animal Testing in Preclinical Safety Studies, intended to reduce animal use in toxicity testing, primarily through the use of *in vitro* and *in silico* tools.[56] Subsequently, the US National Institutes of Health (NIH) announced that it would no longer fund research performed solely in animals, aiming to advance progress on New Approach Methodologies and minimize animal

use.[57,58] Globally, regulators are actively discouraging the use of non-human primates (NHPs) for toxicology studies unless there are genuinely no alternatives. For example, in the European Union, the use of NHPs is restricted to new drugs for debilitating or life-threatening diseases, and only when other species are demonstrably unsuitable for the study's purpose.[59]

Recommendation: Reversibility should be demonstrated in at least one animal species prior to first-in-human studies, ideally through longitudinal monitoring of the relevant pharmacodynamic biomarker in semen following drug discontinuation or device removal. While mating studies may provide supportive data, pregnancy outcomes should not be required to demonstrate reversibility.

- Demonstrating reversibility of a contraceptive effect is a critical component of the preclinical evaluation of male contraceptives and should be established in at least one appropriately selected animal species. In many cases, reversibility can be adequately supported by the return of normal semen parameters—including sperm count and motility—following withdrawal of the investigational product. This approach reduces the variability and logistical challenges associated with mating studies, which are often poorly reproducible and confounded by species-specific behaviors.

- The chosen animal species should allow for repeat collection of ejaculates and be physiologically relevant to the mechanism of action of the investigational agent, enabling the demonstration of the contraceptive effect, followed by a return to fertility. For products inhibiting spermatogenesis or preventing sperm from being ejaculated, it is recommended that multiple samples be collected at pre-specified intervals during the suppression phase (to demonstrate a durable contraceptive effect), followed by additional samples collected after drug/device discontinuation to determine if sperm parameters have returned to normal ranges. Of note, these studies are considered primary pharmacodynamic studies and are not required to be performed under GLP conditions.

- The regulatory experience of committee members and others in the field suggests that reversibility based on semen analysis is generally acceptable when supported by precise, time-linked recovery data. Although mating

studies may be used as confirmatory or supplemental evidence, they are not expected to be required as the primary demonstration of reversibility.

Recommendation: Developers should clearly define expected and intended effects before initiating safety studies.

- The FDA provides comprehensive guidance on the evaluation of testicular toxicity, defined as "potential adverse effects on the testes," across multiple guidances, including "Testicular Toxicity: Evaluation During Drug Development Guidance for Industry."[60] Typically, the decision to implement a plan to assess testicular toxicity clinically arises if there are histopathological findings in repeat-dose toxicology studies and/or rodent studies that demonstrate an impact on male fertility. In the case of male contraceptive products targeting spermatogenesis, both findings would be expected—indicative of efficacy, not an off-target effect. It is crucial that this information is communicated to contract labs performing the IND-enabling toxicology studies, so that these histological changes (representing on-target effects in the intended tissues) are not misclassified as toxicity, thereby avoiding confusion in safety databases and preventing reviewer misunderstandings.

- Committee members recommend that developers clearly articulate to regulators the distinction between expected histopathologic changes (e.g., vacuolization, decreased number of spermatids) and off-target toxicity, emphasizing that providing reversibility data is critical to substantiating this distinction.

Recommendation: Developers of male contraceptive drugs should prioritize fully characterizing the pharmacokinetics of their product early in development, including an assessment of drug concentrations in semen.

- Establishing a comprehensive understanding of the PK of a clinical candidate at an early stage provides essential data that informs multiple aspects of product development. Early PK characterization supports rational dose selection, helps predict therapeutic windows, and improves the design and interpretation of PD studies, including an understanding of the duration of action. It also allows for early identification of potential liabilities—such as low oral bioavailability, rapid clearance, or high interindividual variability—that are not in line with the target product profile.

- Though regulators require non-clinical PK data to initiate clinical trials, this is typically limited to systemic exposure measured in plasma. Committee members have encountered concern from regulators over potential transmission of male contraceptive drugs through semen, resulting in exposure to the female partner and possibly impacting embryo/fetal development. Quantifying drug levels in semen provides a necessary foundation for assessing safety to secondary recipients, evaluating the potential for local pharmacologic effects, and designing appropriate nonclinical and clinical safety studies, if required. This quantification can be readily performed in the context of animal efficacy studies using a non-rodent model that allows for serial collection of ejaculates, with existing bioanalytical methodology adapted for the evaluation of drug concentrations in semen. By generating robust PK data—including concentrations in seminal fluid —developers will be better positioned to engage with regulators, support early modeling efforts, and ensure that their candidate advances through development with an evidence-based understanding of exposure and risk.

Recommendation: Developers of male contraceptives should consider conducting preliminary developmental and reproductive toxicity studies earlier than required by regulators and prior to entering the clinic.

- An extensive set of developmental and reproductive toxicity (DART) studies is required during drug development, but the timing of these studies often occurs after first-in-human trials and is mainly determined by regulators to ensure that the increasing risks to study participants at each stage of clinical development are supported by adequate nonclinical evidence. Given the significant cost and duration of these studies, regulators have recognized that it is often wasteful to perform them too early in development, with the ICH S5(R3) stating, "Since many clinical development programs are terminated prior to Phase 3, animal use can also be reduced by appropriately timing studies to support ongoing clinical development (e.g., embryo-fetal developmental toxicity data to support enrollment of women of childbearing potential) as per ICH M3."[61]

- Typically, assessment of DART involves three main *in vivo* study types: Fertility and Early Embryonic Development (FEED) studies, which assess adult male and female reproductive functions, gamete development,

mating behavior, and fertilization; the Embryo-Fetal Development (EFD) study, which aims to detect adverse effects on the pregnant female and on embryo- and feto-genesis; and the Pre- and Post-natal Developmental (PPND) study, which evaluates adverse effects following maternal exposure from implantation through weaning, monitoring the offspring's development up to sexual maturity. None of these components would be required before Phase I studies, given the male-only exposure and required use of another contraceptive method.

- For drugs designed to treat severe or life-threatening conditions, or where the risk of pregnancy can be severely minimized, an adverse finding during DART studies would not necessarily end clinical development. Conversely, in the field of male contraception, any DART findings beyond those that are intentional (i.e., suppressed fertility) would be expected to result in termination of development. Due to the nature of the product, typical risk management strategies are not applicable, and tolerance for biological developmental risk is essentially zero. Therefore, developers are encouraged to conduct preliminary DART studies to identify potential risks early and avoid initiating a costly clinical development program without sufficient confidence in an acceptable safety profile.

- For male contraceptives, which are only intended to be used by men, and should be discontinued once a pregnancy is recognized in a partner, two main concerns were discussed: possible drug exposure to women via semen and the risk of a small subset of sperm experiencing sublethal damage that could pose developmental risks if still capable of fertilization.

- Given the high cost of traditional DART studies, developers should consider initial screening utilizing alternative assays, designed to minimize cost and animal use, as described in Annex 2 of ICH S5 (R3).[61] These assays employ models such as zebrafish or embryo culture to provide an early assessment of developmental and reproductive toxicity.[62,63]

Drug Repurposing

Drug repurposing, also referred to as drug repositioning, is the process of identifying existing drugs or biologics that have already been clinically tested (and ideally approved) for one indication and re-testing them for a new indication. Often considered a compelling alternative to developing a new molecular entity, repurposing can leverage existing data, providing potentially shorter development timelines and considerable cost savings. The fields of oncology and neurology have found numerous successes in repurposing drugs originally developed for other indications, but sildenafil (Viagra) remains one of the most well-known success stories. Having failed in clinical development in 1993 as a treatment for angina, clinical development pivoted and sildenafil was approved for erectile dysfunction by both the EMA and the FDA in 1998.[64] *In 2005, sildenafil citrate was approved for another indication, pulmonary arterial hypertension, using a different strength and dosing frequency under the brand name Revatio.*[65]

Recommendation: Developers considering repurposing of drugs for an indication in male contraception should utilize a rational and selective approach, focusing on compounds for which there is a strong mechanistic rationale for contraception or case reports of infertility. Low– and medium–throughput screening of drug repurposing libraries is unlikely to be effective in identifying a successful candidate, given the stringent criteria for efficacy and low tolerance for side effects over the anticipated long-term use of these products.

- Identifying an existing drug that can be utilized either on-demand or chronically for contraception is appealing, given the availability of the 505(b)(2) approval pathway at the FDA and the hybrid medicine application at the EMA.[66,67] This ability to reference data generated by other sponsors can potentially result in shorter and less costly approvals. In addition, existing safety data on a drug may improve the likelihood of funding, whether through grants or investors. However, in comparison with therapeutic areas such as cancer, where the relative tolerance for off-target effects is greater, the likelihood of identifying a currently approved drug suitable for repurposing into a male contraceptive is much lower.

- One of the key challenges of drug repurposing is securing robust intellectual property (IP) protection. Because the active moiety has already been disclosed, composition-of-matter patents are usually unavailable.

Innovators therefore focus on formulation, method-of-use, dosing-regimen, or drug-delivery patents—especially when proprietary technologies or unexpected clinical findings create patentable distinctions. Most repurposed products are submitted to the FDA as 505(b)(2) new drug applications, which let sponsors rely on published literature or prior agency findings instead of duplicating all pre-clinical and clinical studies. A 505(b)(2) product that contains a previously approved active ingredient can obtain up to three years of regulatory exclusivity if new clinical studies essential to approval are provided. Conversely, if the application contains a New Chemical Entity (NCE), it remains eligible for the full five-year NCE exclusivity, even when filed under 505(b)(2). A recent example utilizing these strategies is Annovera—a contraceptive vaginal system that combines segesterone acetate (an NCE) with the previously approved molecule ethinyl estradiol. Approved in 2018 via the 505(b)(2) pathway, Annovera received five-year NCE exclusivity on the basis of segesterone acetate, while leveraging publicly available data for the estradiol component.[68]

- Developers using repurposed compounds should expect to perform numerous additional non-clinical studies. At a minimum, in vivo contraceptive efficacy and reversibility would need to be demonstrated. For drugs approved decades prior, often with a more limited dataset, developers may need to provide supplemental studies to meet current regulatory guidance. If the dose, route of administration, or planned duration of use differs from the original approval, additional non-clinical safety studies will be required, as described in the FDA Guidance, Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route.[69] Additional reproductive and developmental toxicology studies may also be required, if the repurposed drug was originally approved for a population or indication otherwise expected to be incompatible with fertility and therefore was not as thoroughly tested for these types of toxicity. For example, as described in ICH Guideline S5(R3), drugs originally approved for late-life-onset diseases or a presumptively infertile population typically may have evaluations waived due to minimal risk.[61] Clearly, these requirements are at the forefront when considering repurposing for contraceptive use in a younger, fertile population.

- Despite the clear challenges of repurposing existing drugs for male contraception, there were several areas of interest discussed by the committee. One approach may be the repurposing of acute medications into low-dose, chronically administered male contraceptives. It is plausible that there are approved agents that could impact spermatogenesis if dosed daily, without the effect being observed with periodic use. The reverse, utilizing a higher on-demand dose of an approved chronic drug, is unlikely to be successful; avoiding toxicity would likely require a cap to the frequency of use, limiting utility.

- Finally, a similar approach would be to utilize molecules that have failed during preclinical or clinical development, especially those that were discarded due to reversible fertility-related toxicity. Although these molecules would be expected to proceed via a more typical regulatory approval pathway, any available data could aid developers – either directly or by using the molecule for lead optimization. For example, the ReFRAME library, which stands for "Repurposing, Focused Rescue and Accelerated Medchem," contains approximately 12,000 molecules, including approved drugs, but also those that failed during clinical development.[70] This library has already been utilized in high-throughput screens searching for molecules that impair key sperm physiology parameters such as sperm motility and acrosomal exocytosis[71–73] and inhibit potential male contraceptive target proteins on sperm.[74] However, investigators are cautioned to carefully examine all hits arising from these screens to evaluate whether the selectivity, toxicity, and off-target effect profiles are compatible with a contraceptive indication,[75] especially when contraceptive use would require a change in delivery route or dosing, such as repurposing a molecule approved for occasional or topical use for chronic oral delivery. Further, developers should be aware that some hits from high-throughput screens may be pan-assay interfering compounds (PAINS) that provide false positives by reacting with components of standard assays rather than the intended target.[76] Molecules such as these are rarely amenable to development as pharmaceutical leads, so to avoid wasting time and resources, all screening hits should be reviewed critically by experienced medicinal chemists and confirmed using orthogonal experiments.[77]

- Commercial realities may also steer decision-making in drug repurposing. If an existing drug is found to act as a contraceptive as-is, its pricing would likely be dependent on the existing—often generic—product. Developers may wish to introduce a revised dose, regimen, formulation, or delivery system. Though this modification will necessitate additional pharmacokinetic and safety work, it still builds on the original dataset, reducing developmental uncertainty while enabling the product to be reviewed as a distinct submission. In turn, it can be priced independently of the legacy product.

On-Demand Contraceptive Drug Development

"On-demand" contraceptive drugs—designed to be used on an as-needed basis minutes or hours before sexual intercourse and be effective for a limited period of time—would represent an entirely new class of contraception; while many barrier devices and vaginally-administered spermicides can be used immediately before intercourse, and emergency contraception is approved for use after unprotected intercourse, there is currently no systemically-delivered pharmaceutical contraceptive available for males or females that is designed to be taken before each sexual encounter. To date, research into on-demand male contraceptives has centered around two general mechanisms of action: 1) inhibition of one or more necessary functions of mature spermatozoa, such as sperm motility, hyperactivation, capacitation, or sperm-egg fusion, and 2) inhibition of sperm release during ejaculation.

Globally, men consistently rank time to onset of efficacy as one of the most important attributes driving their theoretical acceptance of a new male contraceptive,[28] so on-demand contraceptives might be embraced by a segment of users that are less interested in chronic or long-acting contraceptives. Other potential benefits of on-demand contraceptives are a reduction in the user's overall exposure to the active pharmaceutical ingredient (API) and the potential for the female partner to personally verify that the male user successfully took the contraceptive before intercourse. Further, it is possible that an API developed to impair sperm function within the male shortly before intercourse could separately be repurposed for vaginal or systemic delivery in the female before or immediately after intercourse, to impair the same sperm function upon arrival of the ejaculate in the female reproductive tract.

The potential benefits of this contraceptive modality are accompanied by unique challenges in its drug development process, which will need to be overcome for these products to reach regulatory approval. Further, because regulators currently have limited experience evaluating on-demand contraceptive drugs, in regulatory proceedings developers will need to be prepared to act as the experts on this novel modality, and suggest reasonable assays for the evaluation of these drugs and reasonable metrics by which to judge the results.

Recommendation: "On-demand" male contraceptives must require only one dose for full effectiveness, should offer effective pregnancy prevention within 1 hour or less after dosing, and should remain effective for at least several hours after dosing. The duration of action on the product label must be based on well-defined criteria and thoroughly investigated clinical data.

- Given that on-demand male contraception would be a first-in-class product, there are no real-world user data to define an ideal Target Product Profile. Preliminary end-user engagement by committee members suggests that both men and women prioritize the shortest feasible onset of action (unpublished); however, longer onset times (e.g., several hours) may be acceptable when paired with a substantially longer window of efficacy. The efficacy windows studied during human pregnancy-prevention trials should be chosen conservatively based on the observed PK/PD relationships seen in preclinical and early clinical studies, to reduce the incidence of users experiencing breakthrough pregnancies as a result of sex at the edges of the product's time window of efficacy, and the final product packaging must list an identical efficacy window that that which was studied in the pregnancy-prevention trials.

Recommendation: On-demand male contraceptives that block mature sperm functions but do not inhibit the release of sperm during ejaculation will be subject to dilution and potential washout of the API by the fluids in the female reproductive tract. To ensure that sperm do not regain fertilization competence after this dilution, developers of these drugs must consider API-target kinetics (e.g., K_{on} and K_{off}) and the duration of pharmacodynamic effects to create drugs that cause irreversible or extremely long-lasting inhibition of sperm function.

- Fertilization in humans has been recorded up to five days after the most recent episode of intercourse,[78] and inert spheres the size of sperm have been shown to traverse the cervix and enter the uterus during some phases of the menstrual cycle due to peristaltic fluid movement in the female reproductive tract.[79–81] Together, these data suggest that temporary inhibition of sperm parameters like motility may not be sufficient for successful contraception *in vivo*, because if the contraceptive API is only present in the semen, any sperm that traverse the cervix could survive for several days in the female reproductive tract, where uterine or fallopian fluid could dilute and/or wash out any API, allowing sperm to regain their fertilization capacity. To avoid this possibility, APIs used for on-demand male contraception must either remain durably bound to their targets in a dilutive fluid environment or utilize a mechanism of action in which temporary contact with the API causes irreversible loss of the sperm cells' fertilization capacity. Newer paradigms in drug design such as targeted degraders and covalent inhibitors could offer sufficiently durable inhibition

to prevent sperm from regaining fertilization capacity.[82,83]

Recommendation: For on-demand contraceptives that inhibit mature sperm function (e.g., motility, acrosome reaction), developers should be cognizant of the points of contact between sperm and the API – i.e. which male reproductive fluids contain the API and whether those fluids contact sperm before or during ejaculation. This information will impact drug design and preclinical/clinical experimental design.

- API distribution into various compartments of the male reproductive tract will dictate the extent of exposure to the sperm. APIs that distribute into the epididymis will have an extended opportunity to bind to their protein targets on sperm and inhibit sperm function, starting from as soon after administration as the API distributes to the epididymal fluid until the time of ejaculation. In contrast, APIs that do not enter the epididymal lumen but are present in fluids from the prostate, seminal vesicles, or other male reproductive glands will mix with sperm only at the moment of ejaculation, leaving very little time for the API to interact with its binding partner on sperm and inhibit sperm function, because within seconds or minutes of human ejaculation, sperm begin to leave the seminal pool in the vagina and swim into the cervical canal, where they are no longer in contact with the seminal plasma.[84,85] In such cases, standard semen analysis, which involves waiting up to one hour for semen liquefaction,[86] could overestimate the effect of the API on sperm function by extending the sperm's time of contact with seminal plasma beyond what occurs *in vivo*. The pharmacokinetic distribution of APIs can be measured in various reproductive fluids in preclinical model species[87] and can potentially be estimated in humans using split ejaculate collection.[88,89]

NOTE: Several topics relating to on-demand contraceptive development are discussed in other sections of this document:

- Necessary semen sample frequency for on-demand products in clinical trials is discussed in the Clinical Sperm Parameters section.
- The necessity of pharmacokinetic and toxicity studies to investigate the effect of frequently repeated dosing is also discussed in the Clinical Sperm Parameters section.
- A recommendation relating to pharmacodynamic biomarkers for on-demand contraceptives is included within the Biomarkers section.

- A discussion of statistical measurements for efficacy that may be applicable to on-demand products is included in the Evaluation of Clinical Efficacy section.

Biomarkers

The use of biomarkers has become commonplace in both medical research and clinical practice. Biomarkers are frequently used as diagnostic tools (e.g., hemoglobin A1c for Type 2 diabetes), to assess risk or susceptibility (e.g., BRCA1/2 for breast cancer), or to monitor drug safety (e.g., liver function tests).[90] *In addition, pharmacodynamic, or response, biomarkers are frequently employed at various stages of drug development and as surrogate endpoints in clinical trials.*[91] *Biomarkers also have the potential to greatly benefit the development of novel male contraceptives. The U.S. Food and Drug Administration (FDA) defines a biomarker as "a measurable indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic intervention."*[92] *Within the context of these recommendations, we will focus on pharmacodynamic (PD) biomarkers–those that measure the response to an intervention–and their eventual use as surrogate endpoints, able to replace a direct measure of clinical benefit in a trial. This type of biomarker is a critical tool in understanding the pharmacodynamic effect of a new investigational agent and can be leveraged to support efficacy claims, enable dose selection, and monitor reversibility.*

The most widely used pharmacodynamic biomarker in male contraceptive research is sperm count. It serves as a surrogate endpoint for pregnancy prevention in both nonclinical studies and early-phase clinical trials and is the established clinical measure for assessing the efficacy of vasectomy. Despite broad utility and acceptance, no contraception-specific biomarkers—male or female—have yet been formally qualified through the FDA's Biomarker Qualification Program (BQP), nor utilized as a surrogate endpoint for drug approval.[92,93] *Individual developers who wish to use a potential biomarker in clinical trials must therefore propose and justify to regulators the choice of biomarker (and the suitability of its assay). Biomarker qualification through the BQP—a rigorous, multi-year process typically pursued by a consortium—is not required for clinical trial use. However, without qualification, regulatory acceptance of a proposed biomarker (and associated assay) is IND-specific and does not extend beyond that submission.*[94,95] *The FDA provides a detailed list of considerations for developers who intend to use a biomarker as a new surrogate endpoint that has not been previously used as the primary basis for product approval.*[96] *Formal qualification of one or more response biomarkers for male contraception could be highly valuable to the field. Once qualified, either as a pharmacodynamic biomarker to directly assess drug effect, or as a surrogate endpoint for contraceptive efficacy, that biomarker can be used across multiple development programs by any developer, thereby lowering development barriers for new product developers and improving consistency in regulatory expectations.*

Despite the lack of qualified biomarkers to this point, well-justified pharmacodynamic biomarkers already support decision-making throughout the development of male contraceptives—from early efficacy assessments in Phase 1/2 studies, to dose optimization and evaluation of time to effect onset—and are critical to assessing suppression of fertility before initiating pregnancy-based trials. Biomarkers are also a vital tool for evaluating the reversibility of contraceptive methods in humans. Natural pregnancies following a trial can offer definitive evidence of recovery, but requiring couples to conceive for the sake of data collection is ethically unacceptable, necessitating the use of a biomarker to assess a return to normal fertility.

Although sperm-based biomarkers have attracted growing interest as surrogate endpoints for pregnancy prevention, only post-vasectomy azoospermia has achieved universal acceptance. While sperm count—particularly severe oligozoospermia and azoospermia—is employed as a pharmacodynamic biomarker to support clinical development, its acceptance as a standalone surrogate for contraceptive efficacy remains limited. Continued data collection, assay standardization, and regulatory engagement are essential to advance sperm count toward potential formal qualification under frameworks such as the FDA's Biomarker Qualification Program.

In parallel, there is a critical need to identify, validate, and standardize additional biomarkers tailored to products that operate through novel mechanisms beyond the inhibition of spermatogenesis or obstruction of the male reproductive tract. These efforts should include the development of reliable and robust assays, as well as clinical evidence that biomarker changes are predictive of contraceptive efficacy. Emerging evidence suggests that composite biomarkers—such as metrics incorporating multiple sperm parameters (e.g., total progressive motile sperm count,[97] calculated by multiplying semen volume, sperm concentration, and the percentage of progressively motile sperm)—may offer enhanced power to predict contraceptive effect. These multidimensional readouts may prove superior to single metrics, such as sperm concentration, particularly for products targeting sperm function rather than sperm production or transmission of sperm.[98,99] For more discussion of these sperm parameters, see the Clinical Sperm Parameters section.

Qualifying the established pharmacodynamic biomarker of azoospermia as a surrogate endpoint for pregnancy prevention, as well as validation of new pharmacodynamic biomarkers for novel targets, could represent a paradigm shift in male contraceptive development, facilitating earlier, more efficient demonstration of efficacy in male-only studies and reducing dependence on large, complex pregnancy trials in partnered couples.

Recommendation: Developers of products that impact sperm function, rather than spermatogenesis or sperm transmission, must identify reliable, biologically relevant biomarkers and establish reproducible laboratory assays to measure them. For a first-in-class product (based on a novel mechanism of action or drug target), this biomarker should also be measurable in relevant animal models, so that its correlation with pregnancy prevention can be demonstrated prior to clinical use.

- Developers of male contraceptive products that impact sperm function have greater challenges in biomarker development than developers of products that lead to azoospermia or severe oligospermia. The latter can rely upon the World Health Organization's Laboratory Manual for the Processing and Examination of Sperm, which details well-established procedures for counting sperm and is used worldwide.[86] Developers of products that impact sperm function will have to develop, validate, and standardize new methods applicable to their mechanism of action. The multi-step process of developing and validating one or more biomarkers and their associated assays is challenging, but the male contraceptive field benefits significantly from the non-invasive nature of semen sample collection and analysis. In contrast, many efficacy biomarkers in other therapeutic areas are measured in blood or even tissue, requiring invasive procedures such as repeated venipuncture or biopsies, which add discomfort, risk, and logistical complexity, and may limit patient acceptability. For male contraceptive products targeting sperm function, it is expected that a direct biomarker (measuring the effect of the drug on the target) can be measured. In addition, a downstream or indirect biomarker (such as sperm motility) may also be readily measurable. For example, the activity of a drug targeting soluble adenylyl cyclase (sAC) could be measured in semen both directly (by monitoring the reduction of the intracellular concentrations of cAMP within spermatozoa) and indirectly (by monitoring sperm motility).

- After identifying a potential pharmacodynamic sperm biomarker indicative of measuring direct or indirect activity of the target, developers of novel male contraceptives will have to develop and validate an assay capable of generating accurate, precise, and reproducible data to measure the biomarker. The extent of assay validation should follow a fit-for-purpose approach, suitable for the intended use of the data.[100] Once the biomarker assay is validated for a species, developers should plan to

demonstrate a dose-response relationship between exposure and change in the biomarker. Subsequently, validation of the biomarker itself, by comparing pregnancy rates in the same species with the biomarker measurements, will ensure that it correlates well with the contraceptive effect. Developers may want to validate both a direct and an indirect biomarker. A direct biomarker may be more useful in preclinical development, aiding in the establishment of a PK-PD relationship (as well as comparing potential lead compounds). A direct biomarker may also be more sensitive than an indirect biomarker, potentially allowing for the detection of a pharmacologic effect even at the low initial doses typically administered in first-in-human studies. However, the indirect biomarker may be more clinically applicable in later trials, since there might be an existing knowledge base (for example, published data on the typical motility observed across a population) and greater acceptance of its correlation with fertility.

- In a Phase 2a clinical trial of a male contraceptive product, the use of a response biomarker is critical to inform PK/PD relationships for dose selection. The biomarker (and its assay) must be high quality and properly implemented to ensure that the resulting data can justify and inform the design of subsequent couple-based trials evaluating pregnancy prevention. The onus will be on the developer to convince regulators that the chosen biomarker is sufficiently sensitive to detect differences in response at various dose levels, is suitable for clinical use, is expected to correlate with contraceptive efficacy, and can be measured reliably and accurately. Preclinical validation of a new biomarker, as described above, is typically required to establish a correlation between changes in the biomarker and fertility outcomes, thereby supporting its use clinically. It should be noted, however, that numerical thresholds of efficacy (e.g., the percentage of sperm affected by a functional change that correlates to contraceptive effect) may not translate directly from animals to humans, given the significant variation in reproductive biology, including sperm parameters, across species and even strains of animals.

- For on-demand contraceptives that impact sperm function such as capacitation, acrosome reaction, or sperm-egg fusion, the identification and validation of a well-defined biomarker that can be measured accurately, precisely, and reproducibly will be critical. In comparison with agents designed to suppress spermatogenesis and administered daily for

prolonged periods, on-demand agents are expected to display markedly more transient effects. Consequently, PD biomarker assays for these types of products will likely require greater assay performance to adequately define the product's time to onset and the duration of sufficient contraceptive activity. For example, in trials of a product that suppresses spermatogenesis (e.g., male hormonal methods), there may be no meaningful difference in outcome between sperm concentrations of 100,000 and 200,000 per milliliter, since both are well below the established threshold associated with male contraceptive efficacy. In contrast, assays of functional changes in sperm may need to detect significantly smaller shifts in the pharmacodynamic biomarker. For example, following administration of a sAC inhibitor to mice, an average of 1-2% of sperm were motile at timepoints up to 2.5 hours, with approximately 10% of sperm motile after six hours.[101] This example underscores the importance of highly sensitive, accurate, and precise assays to determine whether the subject (or animal) is within or beyond the window of contraceptive efficacy for on-demand products.

Recommendation: Pregnancy should not be the only endpoint evaluated in Phase 3 / pivotal trials of male contraceptives. For products that suppress sperm production or prevent sperm emission, a male-only cohort should be included, utilizing sperm count as the efficacy endpoint.

- The committee extensively discussed the limitations of relying solely on pregnancy prevention as the primary endpoint in pivotal trials for male contraceptives. While pregnancy remains the regulatory gold standard for establishing contraceptive efficacy of female methods, members emphasized the scientific, ethical, and logistical benefits of focusing on direct measures of biological activity—particularly sperm count.

- Within this context, the committee agreed that currently, azoospermia is the only sperm-based endpoint with enough mechanistic plausibility and precedent to be considered a surrogate marker for contraceptive effect. It is also accepted as the endpoint for vasectomy efficacy.[102] Similarly, severely suppressed sperm concentrations (<1 million/mL) have been associated with very low pregnancy rates in hormonal male contraceptive trials.[103] For other sperm biomarkers, additional clinical data are needed before an assessment of the threshold required for contraceptive efficacy can be made.

- The inclusion of male-only cohorts in pivotal trials—particularly for products that suppress sperm production or block sperm transmission—was broadly supported by the committee as a scientifically valid and strategically advantageous approach. While efficacy data from such cohorts may not yet support a full contraceptive indication and will potentially introduce study design and statistical challenges, male-only studies or arms provide several critical benefits, both for the product under development, as well as long-term male contraceptive development. These benefits include:
    - Direct pharmacodynamic assessment**:** Male-only cohorts allow for precise evaluation of sperm suppression (e.g., onset, consistency, duration of suppression) aligned with the product's mechanism of action.
    - Expanded safety data in a more diverse population**:** Studying uncoupled men enables developers to collect safety and tolerability data in a broader population that more accurately reflects a substantial portion of likely end users. It also allows for evaluation of whether real-world adherence or usage patterns vary with relationship status, given the autonomy in contraceptive decision-making.
    - Ethical and practical feasibility**:** Male-only cohorts reduce or eliminate pregnancy risk, decrease the burden on females, and may be a more judicious option when enrolling participants in jurisdictions lacking abortion access. In addition, male-only cohorts provide data and experience that can be applied to required studies in adolescent males.
    - Operational efficiency**:** Male-only studies and male-only arms of larger trials can likely be enrolled more rapidly and performed at lower cost than traditional trials with pregnancy as the only endpoint, an important consideration for resource-limited developers. In contrast with study arms that only include men, pregnancy-based trials require prolonged participation of both partners, a willingness to rely only on the experimental product and risk pregnancy, and the need for the participants to remain coupled for the duration of the trial.

  By generating robust safety and pharmacodynamic data in broad male populations, male-only cohorts can contribute greatly to the long-term

data, including the likelihood of suppression and frequency of sperm rebound in studies of agents that suppress spermatogenesis.

- The use of a sperm-based biomarker such as azoospermia as a primary efficacy endpoint in Phase 3, or even Phase 2b, represents an aspirational shift in how male contraceptive efficacy may be assessed—moving from indirect outcomes (pregnancy in a partner) to direct biological effect in the male user. This paradigm could streamline development, improve ethical alignment, and create a clearer scientific bridge between mechanism and outcome. However, committee members widely agreed that the current depth and breadth of clinical data and level of regulatory and public acceptance are not yet sufficient to fully support this shift. While sperm count is accepted and utilized as a pharmacodynamic biomarker to assess vasectomy success, its use as a surrogate efficacy endpoint in regulatory submissions will require a concerted, multi-product, data-rich effort—likely spanning many years and significant investment. Importantly, any departure from the traditional pregnancy-based efficacy standard will require educating prescribers and end users on the rationale and validity of azoospermia as a predictor of pregnancy prevention to ensure understanding of the mechanism and trust in the product. As an illustrative example from another therapeutic area, statin drugs are approved based on a surrogate endpoint (LDL-cholesterol reduction), rather than direct clinical benefit (i.e., improvement in cardiovascular outcomes).[90] Now one of the most widely prescribed drug classes, with 92 million people in the US reportedly using a statin in 2019, public acceptance arose not only from prescriber guidance, but also from a dramatic increase in common knowledge of cholesterol through direct-to-consumer advertising, health campaigns, and media interest.[104] Until a surrogate endpoint is validated for male contraceptives and public awareness of azoospermia as a contraceptive mechanism increases, the strategic use of male-only cohorts in pivotal trials offers a feasible and scientifically sound pathway to advance the field—enabling rigorous data collection to support ongoing and future development, while minimizing the risk of unintended pregnancy.

- The unconventional concept of male contraceptives seeking a label indication for azoospermia rather than contraceptive effect was also discussed by the committee. This approach would eliminate the need to formally establish azoospermia as a surrogate endpoint. This approach

might be most applicable to vas occlusive devices, given the current use of azoospermia to classify a vasectomy as successful. However, this approach would mark a profound departure from established regulatory precedent and would almost certainly require a dramatic shift in how consumers think about and choose contraception.

Global Considerations

In the current global landscape, contraceptive product developers have many options when deciding where to initiate clinical trials. To choose clinical sites, decision makers must consider and balance factors including cost, timeline, data acceptability by regulatory agencies in markets of interest, participant diversity, experience and capabilities of the on-site trial team, logistics of delivery of test articles and necessary equipment, local legal and political landscape, structures of participant payment plans, etc. Because of these multifactorial considerations, different clinical locations may be appropriate for different development programs, or even for the same development program at different stages of development. In the recent history of male contraceptive development, clinical trials have been held in many different countries, including various US states, Australia, Chile, China, the European Union, India, Indonesia, Kenya, the United Kingdom, and Zimbabwe.[105–110]

Currently, several American companies that are developing male contraceptives and planning to seek regulatory approval in the US and EU have chosen to conduct early studies in countries outside of these regions. In part, this highlights the role that governmental policies have in making particular locations more or less appealing for contraceptive clinical trials.

Recommendation: Jurisdictions may be made more attractive to contraceptive developers by shortening review timelines, streamlining and simplifying data submission formats, and offering R&D tax credits.

- The decision of where to conduct a clinical trial is frequently driven by the sponsor's business concerns, particularly costs and timelines. As examples of attractive policies, members of the working committee cited Australia's Research & Development tax incentive[111] and the reduced timeline for first-in-human study approval from the Australian Therapeutic Goods Administration (TGA). As examples of dissuasive policies and systems, committee members cited the time necessary to convert preclinical datasets into the US Food and Drug Administration's required 'Standard for Exchange of Nonclinical Data (SEND)' format. However, this should not preclude developers from engaging with the US FDA, even if they do not

plan to initiate an early clinical trial in the United States. Notably, the FDA offers scientific advice meetings at no cost—unlike in Europe, where fees for similar meetings can exceed €50,000.[112] If the goal of the sponsor is to ultimately enter the US market, these FDA pre-submission meetings can be helpful to ensure that data from trials performed outside of the US will be acceptable by the FDA as future justification for a later-stage clinical trial in the US.

Recommendation: Male contraceptive efficacy trials that utilize pregnancy as an endpoint should prioritize clinical sites in states or countries with stable legal access to first-trimester abortion care.

- Any experimental male contraceptive carries an unknown level of risk of breakthrough pregnancy, whether through method failure or poor user compliance. Early phase clinical trials that only enroll males and do not track pregnancy generally require participants to use a backup method of contraception, but in later stages of development, where the trial contraceptive is being used as the only form of pregnancy prevention, it is critical that the study organizers develop and implement a well-formed plan that prioritizes the female participants' care in the case of a pregnancy. Any study participant who becomes pregnant while on study should have easy and immediate access to safe pregnancy termination, should they choose it, both because of the imperative to provide complete care for all study-related events, and because assurance of the availability of pregnancy termination in the case of pregnancy is likely to significantly increase successful participant recruitment rates. Consistent access to safe pregnancy termination may be made difficult by the changing legality of abortion care in different jurisdictions, and so states or countries in which legal challenges to first-trimester abortion are ongoing should be considered with caution, to avoid a situation where early-stage pregnancy termination becomes illegal in that jurisdiction midway through a study. If it is not possible to avoid jurisdictions lacking stable early-stage abortion protections, developers may wish to delay performing clinical trials in regions with limited abortion access until later stage trials when a better estimate of pregnancy risk is known and can be adequately communicated to potential participants.

- Currently, many US federal government funding appropriations carry a restriction stating that they cannot be used to pay for pregnancy

termination except in rare circumstances.[113,114] Developers utilizing any US federal funding should seek legal counsel if they wish to cover pregnancy termination on-study using non-governmental funds, and all developers should carefully develop and implement study protocols to ensure complete care for study subjects in the case of breakthrough pregnancies while remaining compliant with local regulations at all clinical sites.

Recommendation: Participant compensation structures should be carefully considered to ensure equitable compensation within a local context, prevent financial coercion, and maximize patient compliance. Participant compensation structures without a significant up-front payment should be used wherever possible.

- In recent contraceptive efficacy trials, considerable compensation at study intake or before entry into the efficacy period has sometimes led to unusually high rates of participant withdrawal prior to the start of drug administration, which can artificially inflate participant discontinuation rates. Study sites should be prioritized if they allow for minimal reimbursements early on, with more significant payments mid-study and beyond.

- Developers have relied upon local experts to help navigate delicate decisions around participant compensation rates and structures. It is important to tailor compensation structures to local economic standards and levels of risk and effort incurred by participants at each step of the process, so the study is sufficiently attractive to potential participants and enables their participation by covering needs like transportation costs or childcare but does not encourage participants to overlook potential risks or remain on study when they would otherwise wish to withdraw.

Recommendation: Developers should utilize study sites that have clinicians and support staff who are experienced in both the practice of reproductive health and participant intake/evaluation for clinical trials, to help ensure genuine participant interest in the study.

- Clinical trials for male contraceptive drugs and devices outside of the US have been performed in collaboration with local physicians and contract research organizations (CROs) that specialize in clinical research. Committee members stressed the importance of utilizing a local team that

is experienced at screening and consenting subjects thoroughly, carefully following study protocols, and recording data while delivering excellent patient care. For example, urologists who routinely perform vasectomies and have experience with consenting patients and managing and documenting adverse effects in clinical trials may be ideally suited for vas-occlusive device development programs.

Study Participants

Explicit guidance on inclusion and exclusion criteria for study participants is limited. The principal reference for regulators and clinicians remains the widely adopted ICH E8(R1), General Considerations for Clinical Studies.[115] *Updated most recently in 2021, the overall objective of this document is to protect the rights, safety, and well-being of study participants. However, little specific guidance is offered with respect to participant selection. The document states, "The population to be studied should be chosen to support the study objectives and is defined through the inclusion and exclusion criteria for the study. The degree to which a study succeeds in enrolling the desired population will impact the ability of the study to meet its objectives. The study population may be narrowly defined to reduce the risk to study participants or to maximize the sensitivity of the study for detecting a certain effect. Conversely, it may be broadly defined to more closely represent the diverse populations for which the drug is intended."*

In the context of female contraceptive methods, FDA guidance[116] *offers the following directive on participant age: "The primary efficacy results should be calculated using the trial population of women younger than or equal to 35 years old at study enrollment because the likelihood of pregnancy decreases with advancing age. Include additional efficacy analyses for the overall trial population and a subgroup analysis for those older than 35 years old." Regarding the age of the participants for safety evaluations of these trials, the document states, "The safety evaluation should include data from all enrolled subjects (from all participating countries), including those older than and younger than 35 years old."*

Conversely, the EMA guidance[117] *for female hormonal contraceptive methods merely provides participant factors to consider, stating "The demography of the group of women included in studies should be carefully described, especially regarding factors thought to be relevant for the overall contraceptive efficacy of the method (e.g. weight, height, BMI, age, education, sexual relation/activity, parity, smoking, alcohol use, menstrual related symptoms, concomitant use of condoms to protect from sexually transmissible disease etc.). Where heterogeneity of fertility is likely (e.g. a study group containing a subgroup of breastfeeding mothers or older women), separate estimates or specific studies of the Pearl Index should be presented for important subgroups."*

In addition to the adult population, developers in the US are legally required to clinically evaluate most new drugs in pediatric populations to comply with the Pediatric Research Equity Act (PREA). Two FDA guidances are available to aid developers in this effort, specifically Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act[118] *and Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations*.[119] *Though the PREA mandates that New Drug Applications include a pediatric assessment, mechanisms for waivers or delays exist. Specifically, "FDA recognizes that in certain cases, scientific and ethical considerations dictate that pediatric studies should not begin until after adequate safety and efficacy data are available in adult subjects; for example, where a drug has not shown any advantage over other approved drugs in the class, the therapeutic gain is likely to be low, and the risks of exposing pediatric subjects to the new drug may not be justified until the drug's safety profile is better established in adult subjects. In these cases, the applicant can request a deferral of required pediatric studies (see section III. A., PREA)."*[119] *The EMA has a comparable option to petition for a Pediatric Investigation Plan deferral*.[120]

Recommendation: Clinical trial sites should be chosen to ensure ethnic and racial diversity of the study population. Furthermore, to ensure study participants are representative of future users, studies should include males not in committed relationships, as well as those in long-term monogamous relationships.

- Though regulators encourage, or even require, clinical study populations to be racially and ethnically diverse, developers should ensure that the study population represents the demography of future users (i.e. a mix of coupled and single men) and prioritize countries with greater interest in male contraceptives. Practically, the enrollment of un-partnered males in efficacy studies will require the establishment of a male-only endpoint (such as sperm concentration, or total motile sperm count; *See Biomarkers section*), so that men's participation is not limited to the evaluation of safety.

Recommendation: Clinical trials of male contraceptives should enroll a broad age range of adult males. Proven fertility should not be required, but participants should have sequential normal semen analyses demonstrating adequate motility, morphology, and count as described in the most current edition of the World Health Organization Laboratory Manual for the Examination and Processing of Human Semen.[86]

- Recent trials of male contraceptives have utilized an upper age limit for men ranging from 50-65.[106,121] Though less striking of a decline than female fertility, a decrease in male fertility also appears to occur with age, with the likelihood of couples with a male partner 35 or older conceiving in one year half that of men under 25.[122] Increasing paternal age is also associated with higher miscarriage, stillbirth and birth defect rates. Though minimal correlation between age and sperm count has been observed, semen quality, especially motility, has been shown to decline with age.[123,124] If enrollment age skews towards older men, there is concern that efficacy would not adequately represent a younger population with greater fertility.[122] However, the committee was unified that male contraceptive trials should (1) utilize a representative group of intended users, and (2) perform multiple semen analyses during screening so the study population can be selected via adequate baseline sperm parameters, rather than the more arbitrary age brackets.

- To account for intraindividual variation in ejaculate volume and quality, eligibility should be based on at least two -optimally three- samples, with each collection preceded by 2-7 days of abstinence (i.e., serial samples should be collected <u>at least</u> 48 hours apart).

Recommendation: First-in-human studies of new molecular entities for male contraception should be performed in men who do not desire to father children in the future, in case of unexpected adverse effects on fertility or lack of reversibility. Additionally, developers may want to consider offering the cryopreservation of a semen sample for the duration of the trial at no cost to the study participants.

- Though comprehensive animal studies will have demonstrated reversibility prior to a new agent being used in humans, enrolling men who do not intend to father children in the future is a simple and rational de-risking strategy. The potential of using vasectomized men for Phase 1 was

discussed at length by the committee, but is suboptimal for methods that target extra-testicular sperm function, since it precludes evaluation of ejaculates for early pharmacodynamic evaluation. Most importantly, limiting study participation to vasectomized men will narrow the pool of potential participants too severely and exclude willing participants such as gay men who do not intend to father children but may not seek a vasectomy due to lack of pregnancy risk.

- However, for some studies, an alternative approach has been used, with the intentional recruitment of men already planning for a vasectomy. This strategy was used in previous studies of drug combinations, with the collection of post-treatment testicular biopsies at the time of vasectomy.[125,126] A current trial of a vas-occlusive device also provides a vasectomy to the user, allowing for tissue collection and analysis.[121]

- Short-term safety studies should not expect, nor require, male participants to be partnered. However, all study participants would be expected to utilize backup contraception if engaging in intercourse with a partner at-risk for pregnancy.

Recommendation: Developers should carefully consider the acceptable minimum sperm parameters for enrollment, with consideration for the stage of development and the mechanism of action of their drug or device.

- Significant discussion occurred within the committee regarding what should constitute "normal" or sufficient sperm/semen parameters for enrollment. The WHO Laboratory Manual for the Examination and Processing of Human Semen (6th ed.) lists lower reference (5th-centile) values of 39 million total sperm per ejaculate, 16 million sperm per mL, 42 % total motility (32 % progressive), and 4 % normal morphology in men whose partners conceived within 12 months of unprotected intercourse.[86] A recent study of a hormonal male contraceptive combination gel (NES/T) employed an enrollment criterion of 15 million (M) sperm/mL (based on two analyses), additionally requiring that at least one of these samples was "… without gross abnormalities of sperm motility and morphology."[127] Developers will need to consider, based upon their own product's mechanism of action, whether meeting the reference value for a single parameter is sufficient or multiple parameters should be required for enrollment. For example, for products targeting azoospermia, the total

number of sperm per ejaculate might be a superior indicator of testicular function, as opposed to sperm concentration, since it incorporates both volume and concentration.

- For any novel male contraceptive whose primary effect is on a functional sperm endpoint not captured by the WHO semen parameters (e.g., acrosome reaction), developers will need to define and justify the lower threshold acceptable for enrollment. These functional thresholds should ideally be based upon demonstrated correlations with actual fertility outcomes, even though robust, population-level data for many novel endpoints may be lacking. This threshold would additionally be used to demonstrate reversibility and a return to fertility. As clinical and epidemiological evidence accumulates, these cut-offs should be periodically re-evaluated and refined to ensure they continue to accurately predict contraceptive efficacy and reversibility.

- For dose-finding trials of novel therapeutics, developers should aim to enroll participants whose baseline values span the entire reference range for the key parameter/biomarker. Demonstrating efficacy across this spectrum of physiological variability provides confidence that the chosen dose will be effective in the broader target population.

- For efficacy studies with a pregnancy endpoint, developers may consider a requirement to exceed a specific centile for all WHO-defined parameters, or utilize another composite measure, to ensure efficacy can be attributed to the product and not the sub-fertility of the participants. For example, in one study of sub-fertile couples, male partners with a total progressively motile count (TPMC; calculated as total sperm count multiplied by the proportion of cells showing progressive motility) ≥50 M had a 45% greater chance of conception and achieved pregnancy earlier compared to those men with TPMC <50 M (median 19 months versus 36 months, after accounting for female factors.[128] Consideration of alternative sperm/semen parameter thresholds may be particularly important for developers of on-demand contraceptive methods, as the risk of pregnancy in these approaches is more directly influenced by participant fertility, with even a single missed dose.

- The intention is not to create additional barriers to enrolling appropriate participants, but to ensure developers gain an accurate understanding of

their product's efficacy, assess the alignment with the goals established in the Target Product Profile and make well-informed decisions about future development.

See Clinical Sperm Parameters for more information.

Recommendation: For efficacy studies with pregnancy as the primary endpoint, female partners should be aged 18-35, with a reported cycle length of 21-35 days. No proven fertility should be required.

- Trials of female methods typically utilize an age range of 18-35 for calculation of efficacy when submitting to the US FDA, with no consideration of the age or fertility of the male partner in pregnancy studies. Similarly, trials of non-hormonal female methods enroll women with a "normal" menstrual cycle, defined as having a reported duration of 21-35 days.[116] To ensure that end-users and clinicians can readily compare male and female methods, it is expected that efficacy statistics of male contraceptives will need to utilize the same age range (18-35) for female partners. For male contraceptives with little to no expectation of female exposure to the drug, the partner safety metrics collected during late-stage clinical trials will likely be minimal, and it would be superfluous to enroll female partners over the age of 35 as efficacy outcomes cannot be utilized in the primary calculation of effectiveness.

Recommendation: When enrolling couples for studies with a pregnancy endpoint, the only social criteria that should be applied is an expectation of remaining in a monogamous relationship for the duration of the study.

- Unlike efficacy studies of female contraceptives, which merely require the female participant to record at least one occurrence of unprotected sex each month, independent of partner or relationship status, accurately measuring pregnancy risk of a male contraceptive requires enrolling a couple that intend to remain partnered and monogamous for the duration of the study. Additional non-scientific barriers to participation, such as requiring the couple to have been in a relationship for a minimum duration prior to enrollment, should be avoided, since they can hinder clinical trial recruitment and enrollment unnecessarily.

- If a couple does separate during the efficacy portion of the study, the male partner may opt to transfer to a male-only cohort and continue to provide safety and sperm-based efficacy data, rather than having his participation truncated.

Recommendation: Clinical trials for initial approval of a new male contraceptive method should be limited to adults (defined by the FDA as 18+ for drugs and 22+ for devices). Male contraceptive developers should seek a deferral from regulators to delay enrolling adolescent males on trials of male contraceptives until safety and efficacy has been established in adults. Studies in adolescent males are important and should utilize a sperm-related endpoint that has been well-characterized as a surrogate for efficacy in adult studies.

- The committee strongly agreed that regulators would be likely to grant a deferral for studying a novel male contraceptive in adolescents until safety and efficacy are well-established. Ideally, these studies would take place after marketing approval for adult males is granted. Though there is a clear need for additional contraceptive options to decrease unplanned teen pregnancies, there is potentially added risk with the use of male contraceptives during puberty, especially with hormonal agents. While adolescent females are routinely prescribed hormonal contraceptives for pregnancy prevention and menstrual disorders, drugs and dosages have been refined for decades in this population. Male puberty is typically considered to have both a longer duration and to occur later. Therefore, usage in late adolescence (18+) may also need to be evaluated carefully, possibly through sub-group analysis of a larger adult study. Ultimately, study protocols for pediatrics will need to be developed in close consultation with regulators, tailored to the drug's mechanism of action and potential safety signals identified in adult males.

- By first establishing a surrogate endpoint in adult males, such as a sperm count threshold correlated with pregnancy prevention in adults, this can then be utilized to assess direct efficacy in adolescent males. *(See Biomarkers)*

Clinical Sperm Parameters

Before a male contraceptive can be clinically evaluated for pregnancy prevention, the successful onset and reversibility of effects on sperm production, ejaculation, or sperm function will have to be demonstrated in human males. Then, in pregnancy-prevention clinical trials for chronically dosed contraceptives with delayed efficacy, each male participant should be tested to demonstrate that his sperm count or sperm functional parameters have decreased to a threshold that developers expect will prevent pregnancy before he and his partner rely on the contraceptive as their only form of pregnancy prevention.

Therefore, standardized measurement of sperm parameters will be critical to the success of male contraceptive clinical trials. Since the assays used to measure many sperm parameters are not standard practice at every hospital and clinical trial site, developers should design and implement plans for standardized sperm analysis throughout the clinical trial process.

Recommendation: Recent hormonal male contraceptive trials have settled on reducing sperm concentration below a threshold of 1 million sperm per mL, but contraceptives that work through mechanisms other than hormonal inhibition of spermatogenesis may need to propose different thresholds for sperm concentration, count, or other relevant parameters that are expected to correlate with clinical efficacy.

- Though there is clear consensus that absolute azoospermia would result in full contraceptive efficacy, the presence of any motile sperm in semen could potentially result in a pregnancy.

- Previous male hormonal contraceptive trials have established that male participants with sperm concentrations ≤1 million per mL experienced an unintended pregnancy rate of roughly 1 per 100 person-years,[129] similar to that of existing female hormonal contraceptives,[130] while earlier trials with thresholds of up to 5 million sperm per mL observed somewhat higher rates of pregnancy.[129,131] However, these trials did not assess whether the residual sperm produced by the men in the study had any functional

defects, so this incidence of unintended pregnancy may not translate equivalently to non-hormonal methods that result in similar sperm counts.

- For contraceptives that do not result in inhibition of spermatogenesis, different target values for sperm parameters such as motility, morphology, acrosome reaction, etc., need to be developed. Unfortunately, due to the limited clinical history of contraceptives with these novel mechanisms of action, there is little existing data that can be used to predict the risk of pregnancy associated with a given level of alteration of particular sperm parameters by potential contraceptive molecules. The committee unanimously agreed that sperm parameter distributions in the fertile population, such as those compiled by the WHO,[86,132] should not be directly extrapolated to create predictions or criteria of contraceptive efficacy, given that these values have been generated by evaluating fertile couples and sperm parameters may co-vary with one another, leading to statistical confounding factors. Furthermore, due to the inherent differences between the human reproductive system and those of common preclinical species, as well as the limited knowledge about the *in vivo* behavior of human gametes in the female reproductive tract, caution should be taken when predicting human effectiveness based on preclinical animal studies.

- Vasectomy alternatives and vas-occlusive devices may choose to use the American Urological Association's guideline for successful vasectomy (≤100,000 non-motile sperm per mL)[133] as a target value.

- Committee members stressed the importance of Total Progressively Motile Sperm Count (TPMC) as a potentially superior predictor of pregnancy risk, as compared to single-parameter measures of sperm count such as total sperm count or sperm concentration, since TPMC reflects a combination of sperm concentration, motility status, and ejaculate volume.[128,134]

Recommendation: Reversibility and post-treatment recovery should be defined by a return to sperm parameters above the 5th percentile of the reference population range for fertile men as described in the most current version of the World Health Organization Laboratory Manual for the Examination and Processing of Human Semen, as opposed to individual baseline values.[86,132]

- Males can display significant fluctuations in their semen parameters between subsequent ejaculate samples.[135–137] Though the establishment of an accurate initial baseline is strongly recommended to ensure participants meet the inclusion criteria, using a minimum of two semen samples (see the 'Study Participants' section), a return to this individual baseline should not be required to deem a participant recovered. Classifying a contraceptive as successfully reversible only if each man returns to semen parameters that are not statistically different from his baseline values would likely cause many false positives for supposed contraceptive irreversibility, due to the natural background variation in semen parameters over time. Further, this requirement could necessitate significantly more semen samples at study completion, which would unnecessarily prolong trial duration and increase study cost and burden on participants.

Recommendation: To ensure accurate and reproducible measurements, all semen preparation and analysis for male contraceptive clinical trials should be conducted by experienced andrology laboratories that regularly conduct high-complexity semen analysis, and throughout the trial technicians must utilize consistent equipment and protocols that are compliant with the most current version of the World Health Organization's laboratory manual for the examination and processing of human semen.

- Though the WHO laboratory manual for the examination and processing of human semen provides standardized guidance on methodology,[86] andrology labs that routinely perform quantitative semen analysis are better positioned to maintain technician proficiency and ensure consistent, high-quality results.

Recommendation: Studies recording sperm count as an endpoint should utilize Computer-Aided Sperm Analysis (CASA) machines if possible. If CASA is not feasible, well-trained technicians at each study site can perform manual sperm counting. As a less desirable option, it is possible to ship semen samples to a central lab for sperm counting, but shipping introduces potential sources of variation that must be managed with care.

- If study budget and logistics allow, developers should utilize modern

Computer-Aided Sperm Analysis (CASA) machines to record sperm count, operated by well-trained technicians using consistent consumables and protocols. Quantifying sperm count using CASA machines is considered "moderate complexity" in the Clinical Laboratory Improvement Amendments (CLIA) test rating system.[138]

- Manual sperm counting requires less expensive equipment but is a skill that requires training and experience and can show significant variation between technicians if they are not well-trained. As a result, manual quantification of sperm count is considered "high complexity" in the CLIA rating system.[138] Developers should be aware that some andrology laboratories only evaluate semen qualitatively for presence or absence of sperm and motility. Presence/absence measurement is rated as "moderate complexity" in the CLIA system[138] but will not provide sufficient detail for the purposes of a contraceptive clinical trial. If otherwise-promising clinical sites do not possess technicians with experience in manual sperm counting, these technicians need to be trained to perform the test in advance of the clinical trial and undergo regular proficiency testing to ensure output of high-quality data.

- In general, best results in semen analysis are obtained when the analysis is performed locally, soon after sample collection. Further, as stated above, Total Progressively Motile Sperm Count, which requires measurement of motility within an hour of ejaculation, is a preferred measurement over Total Sperm Count. However, as a less desirable option, if developers decide to measure only Total Sperm Count, it is possible to ship semen samples to central laboratories for counting because this measurement does not require the cells to be living. This could lead to greater standardization of analysis for multi-site trials, but also introduces potential sources or variation that could lead to degradation or agglutination of sperm cells, which could cause inaccuracies in counts. Because proteases and bacteria in semen can degrade sperm cells over time, if living sperm cells are transported in the original semen samples, shipping temperature and time between sample collection and analysis must be standardized. If sperm cells are diluted into extenders or fixatives before shipping, great care must be taken to accurately record original semen volume and volumes of any diluents to allow for accurate calculation of original sperm concentration values.

Recommendation: For studies measuring sperm function as an endpoint, developers should utilize Computer-Aided Sperm Analysis (CASA) at each study site.

- Functional parameters such as motility and hyperactivation are negatively impacted by shipping time and sample storage conditions, so these parameters must be measured locally at each clinical site, within an hour of semen sample collection. The committee recommends the use of Computer-Aided Sperm Analysis (CASA) machines, which provide automated assessments of semen parameters such as concentration, many different motility measurements, and hyperactivation. Some models can also assess parameters like sperm morphology, vitality, DNA integrity, and more. However, it is worth noting that each model of CASA machine may use different algorithms to calculate these parameters, and so multi-site trials should ensure that all sites are using the same model. These instruments can speed data collection and reduce inter-observer variation, though careful setup, calibration, and training is still necessary. Additionally, the instruments are susceptible to error in certain cases, such as samples with dense cellular debris or significant sperm agglutination, and so experienced technicians should still review the videos captured by CASA to check for such issues.[139] As such, measurement of sperm motility using CASA is rated "moderate complexity" in the CLIA rating system, while manual motility analysis is rated "high complexity".[138] Importantly, modern CASA machines can also record all of their video and photo measurements for digital sharing with a central lab, which offers the possibility of centralized analysis and quality control through remote verification of measurements.

Recommendation: Subtle abnormalities in sperm morphology should not be used as indicators of contraceptive efficacy. Only significant defects such as pinheads, globozoospermia, lack of functional flagella, etc. are reliably linked with male infertility.

- Humans have a high baseline rate of sperm morphological abnormalities, with the 5th percentile of fertile men having only 4% of their sperm showing normal morphology when measured using the criteria in the 5th and 6th editions of the WHO laboratory manual for the examination and processing of human semen.[132] Because of the experimental difficulty of proving which sperm cell subpopulations are actually capable of reaching and

fertilizing an egg in humans, it remains unknown whether moderate morphology defects, such as large heads or residual cytoplasmic droplets, actually prevent fertilization *in vivo*. Therefore, potential male contraceptives that work through inducing sperm morphology defects should be designed to cause significant defects in nearly all sperm in the ejaculate, both to maximize chances of these defects preventing pregnancy and to facilitate easy identification of the intended cellular phenotype by clinical andrology lab technicians.

- Morphology can be measured either manually or by certain models of CASA machines, though both methods are rated "high-complexity" in the CLIA standards.[138] Since morphology is measured on slides of fixed sperm cells, it is possible to ship these slides to a central lab for analysis if desired.

Recommendation: At-home sperm tests, such as lateral flow tests for sperm antigens, may be useful as adjunct diagnostics but formal andrology lab tests are needed to assess key clinical trial decision points, such as entering an efficacy stage or classifying a participant as recovered.

- There has been a recent increase in the development of at-home sperm analysis tools of various formats, such as rapid antigen tests and smartphone microscopy tools,[16] and at least one of these tools has been evaluated as an adjunct measurement in a hormonal male contraceptive clinical trial.[140] The committee concluded that none of these tools have yet been proven reliable enough for use as a primary measurement tool in a contraceptive clinical trial. However, they can be a useful tool for interim analyses during clinical trials – for example, providing an added confirmation for study participants that their results remain durable between clinic visits once they have reached the efficacy stage of the trial.

Recommendation: The schedule of semen evaluations in clinical trials of male contraceptives should be chosen based on the mechanism of action, anticipated time to contraceptive onset and recovery, and clinical trial phase, with the expectation of less frequent collections later in development as the objective shifts from characterization to confirmation.

- **Screening:** Semen analyses are initially performed during the participant screening phase of each trial to ensure participants meet the minimum criteria for inclusion. The 6th edition of the WHO laboratory manual for the

examination and processing of human semen recommends that "The ejaculate should be collected after a minimum of 2 days and a maximum of 7 days of ejaculatory abstinence" to minimize variability arising from ejaculatory frequency.[86] However, some committee members recommended a maximum of 5 days of ejaculatory abstinence, based on reports of increases in sperm count and declines in motility after this point.[141]

- **Drugs and devices targeting spermatogenesis or causing azoospermia – Phases 1 and 2:** The frequency of collections is expected to be greater in earlier phase trials as developers seek to characterize the onset of efficacy and time to recovery. For example, Phase 2a trials of agents that suppress spermatogenesis may wish to sample every two weeks in order to sufficiently characterize the time course of onset and reversibility for the primary parameters of interest, such as suppression of count or motility. Once those dynamics are well understood, Phase 2b trials of the same agents might only sample monthly. For methods with a concern about sperm count rebound, increased sampling frequency may also be necessary in the first few months of a study, with decreased frequency later in the efficacy phase. Any long-acting devices with a planned end-of-life may also require more frequent monitoring as the expiry date of the device approaches.

- **Drugs and devices targeting spermatogenesis or causing azoospermia – Phase 3/Pivotal:** In Phase 3 or pivotal studies, there is a need to balance the required "actual use" scenario and participant burden with data collection for efficacy. In these studies, quarterly semen analyses are likely to be sufficient, with targeted assessments after three and six months of suppression to ensure maintenance of contraceptive effect and to detect late rebound for drugs targeting spermatogenesis. However, developers must also consider how on-study sampling plans may impact the use of the product once it is marketed. For example, if regulators place a requirement for frequent semen sampling as a requirement on the product label (based on Phase 3 data and study plan), this requirement might become a potential impediment to product adoption. However, at-home self-tests may make such a requirement more acceptable to end users.

- **On-demand products – Phases 1 and 2:** For on-demand products with a short onset or duration of action, trial sampling schedules must be uniquely tailored to the product's pharmacokinetic and pharmacodynamic profile.

Standard schedules for sampling and follow-up used in chronic or long-acting contraceptive trials, such as WHO's recommended 2-day interval between subsequent ejaculations, are likely too widely spaced to capture the pharmacodynamics of onset, peak activity, and return to fertility. However, developers hoping to collect numerous timepoints to fully characterize these effects should be aware of the impact of frequent ejaculation on the semen parameters of interest. Meta-analysis has shown that in fertile men, duration of ejaculatory abstinence has significant effects on ejaculate volume, total sperm count, and sperm concentration, but no significant effects on the percentages of progressive motile sperm, morphologically normal sperm, or living sperm.[142] Only very limited data are available on the impact of more than two ejaculations within the same day, but the trend of sperm parameters agrees with that found in the meta-analysis mentioned above.[143] Therefore, for drugs acting primarily on sperm motility, daily or more frequent semen collections from each participant may be appropriate, as long as motility is quantified using metrics that do not use sperm count or concentration as an input value (such as percent motile or percent progressive). On-demand drugs with mechanisms of action targeting hyperactivation, acrosome reaction, or other functions that are not measured in standard semen analyses will likely require preliminary studies to characterize the effect of high-frequency semen sampling on these functional parameters.

- **On-demand products – Phases 2 and 3:** In later-phase clinical trials, it is expected that on-demand agents will need to be evaluated as chronically administered agents, as regulators apply ICH Guidance E1, "The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions" to all drugs expected to have repeated intermittent use for longer than 6 months.[144] For drugs designed for frequent use, a clear understanding of pharmacokinetics and pharmacodynamics, as well as whether accumulation is occurring systemically or in semen, is necessary. This understanding is not only crucial for selecting recovery time points but also for defining the maximum anticipated usage.

Acceptable Efficacy

There are currently no published regulatory guidelines related to efficacy for male contraception.

Regulatory agencies have published guidance on the expected efficacy of contraceptives in Phase III or pivotal trials, but these guidelines are clearly directed at hormonal female contraceptives with an expectation of near-perfect efficacy. The EMA states in the Guideline On Clinical Investigation Of Steroid Contraceptives In Women, "The key studies, carried out in a sufficiently representative population, should normally be at least large enough to give the overall Pearl Index (number of pregnancies per 100 woman years) with a two-sided 95% confidence interval such that the difference between the upper limit of the confidence interval and the point estimate does not exceed 1 (pregnancies per 100 woman years)."[117]

For novel products which presumably do not utilize a hormonal mechanism of action and may have a greater Pearl Index (i.e., lower efficacy), the guidance notes the potential use of a comparator and a potential willingness to approve a product with a higher Pearl Index in exchange for greater end-user acceptance: "For a new product utilising a mechanism of action which may result in a relatively high pregnancy rate (PI>1), comparative studies may be necessary… Comparative safety data provide important information for the user and the prescriber in the choice between different methods. A higher Pearl Index may under certain circumstances be acceptable if, e.g. tolerability is very high."

Health Canada and Australia are in accordance with the EMA guidelines for female hormonal contraception.[145,146]

The US FDA specifies, "Combined hormonal contraceptives are very effective at preventing pregnancy, typically having an upper bound of this 95% confidence interval (for the Pearl Index) below 5 in adequately designed and conducted trials. For hormonal contraceptives with fewer risks, such as oral progestin-only contraceptives, a slightly higher upper bound of this 95% confidence interval may be acceptable."[116]

Recommendation: Developers should set a clear efficacy target at the outset of development—anchored to the envisioned target product profile—rather than defaulting to benchmarks established for existing female contraceptives.

- The future of male contraception will span a wide range of use cases. Standalone products designed to be the only form of contraception used by

a couple are currently under development, but secondary methods designed to be adjunctive to other forms of contraceptives (e.g., condoms or female methods) will arise. There was strong agreement by the committee not to advocate for a "one size fits all" benchmark for efficacy. This view arose from a disagreement among the committee as to what methods might generate commercial interest and end-user acceptability.

- Given that the existing male options are either permanent (vasectomy) or have marginal efficacy (condoms with an actual-use failure rate of 8 to 13%), there is clear unmet need.[147,148] Additionally, a 2023 survey of over 3000 men in the US found that 11% relied upon withdrawal for pregnancy protection.[149] Global market research suggests that a wide range of efficacies are acceptable to men and that tolerance for different benefit:risk ratios exist.[149] For example, couples uninterested in permanent methods, due to a future desire for children, but for whom highly efficacious female methods are contraindicated, may accept any product with efficacy superior to a condom. Additionally, there is interest in alternatives to condoms for use in a layered approach, where each partner utilizes their own method, for maximal pregnancy prevention.

- In recent years, the FDA has approved several female products with a PI>1, concluding that the benefit of new options for decreasing the risk of unintended pregnancy outweighed any method-related risks. For example, Opill[150] (norgestrel, a progestin-only product) was approved as the first non-prescription hormonal oral contraceptive, with the review stating that, "…the Pearl Index in real-world use after a nonprescription approval will likely be higher, perhaps in the range of 7% or somewhat higher." This is comparable to published historical data for progestin-only pills.[151] Similarly, Phexxi, a non-hormonal, on-demand vaginal gel, was approved, despite 13.7% of participants becoming pregnant over just seven menstrual cycles on study, resulting in a calculated PI of 27.5.[152]

- If regulators, such as the EMA, were to apply the efficacy thresholds designed for the most effective female hormonal products to new male contraceptives, and the efficacy is not anticipated to result in a PI < 1, the size and scope of clinical trials may be prohibitive for developers. To meet the statistical requirements of the EMA guidelines (referenced above) with 90% power, using the calculations of Gerlinger et al., greater than 1300 and 1700 year-long study participants would be required to generate assumed-

true Pearl Indexes of 2 and 3, respectively.[153]. Alternatively, if comparator studies are required, condoms would be the sole reference option. Such a comparison study would also require a substantial number of subjects, and the costs and enrollment timeline would be considerable, especially considering the minimal scientific value a condom-only arm would likely add.

- For the reversible vas-occlusive devices under development, vasectomy might appear to be an obvious comparator. However, surgical procedures are not devices, and vasectomy is not regulated by the FDA. Therefore, it is expected that vas-occlusive devices would need only to establish stand-alone efficacy. Even if a vas-occlusive method falls short of vasectomy-level efficacy, the product could still be attractive to users if it offers the meaningful advantage of reversibility, meeting the unmet need among men who do not desire permanent sterilization.

- Ultimately, developers should establish minimum and preferred efficacy goals in the context of the product's intended use, user group, safety, and tolerability as they develop a Target Product Profile. Regulatory strategy should also be considered, especially for male methods likely to be used in a layered manner with female contraception. Regardless of where initial studies are performed, developers may opt to perform pregnancy trials in the US and seek initial market approval from the FDA, given the apparent wider acceptable efficacy range as compared to other regulatory agencies.

Pregnancy Testing and Management

Pregnancy testing and management in male contraceptive clinical trials must balance the regulatory requirement to accurately assess pregnancies that occur due to method failure or user non-compliance, while minimizing potential burdens on the female partner —including risks to reproductive health, safety concerns, and time demands. Though the committee envisions a future where one or more sperm parameters (e.g., total progressively motile sperm count) are qualified as biomarkers of contraceptive efficacy, assessing the efficacy in preventing pregnancy in couples will remain the norm for clinical trials in the near term.

Recommendation: Clinical efficacy trials must design and implement a comprehensive and participant-centered informed consent process. The integrity of the informed consent process must not be compromised by pressures to meet recruitment goals or timelines.

- The committee emphasized the importance of ensuring that participants — particularly female partners — fully understand the risk of pregnancy during study participation. Clear communication during the consent process is essential to uphold ethical standards and may also reduce the emotional impact associated with the occurrence of an unexpected pregnancy on-study.

- All participants, male and female, should be consented both jointly and individually. Consent forms should be explained to participants in person (or via videoconference) and also provided to them for review at their convenience. Participants should have the opportunity to ask questions and receive clear, thoughtful answers to support genuine understanding of any potential risks.

- Consent documents should explicitly describe the experimental nature of the method under study and the real possibility of pregnancy. Early efficacy trials will need to clearly state that the risk of pregnancy is unknown. For later-stage trials, information about expected risk (based upon earlier efficacy trials) can be provided, as well as a risk comparison with existing contraceptive methods. Consent documents should explain what will happen if a participant becomes pregnant—including required testing, clinical follow-up, and counseling—and highlight any limitations on available management options, especially if access to legal abortion is

restricted in the trial site jurisdiction. Consent documents should also specify which procedures and associated costs (e.g., ultrasounds, laboratory tests, or termination services) are covered by the trial and which will remain the participant's responsibility.

Recommendation: **Enrolled female partners should undergo pregnancy testing in the clinic at key timepoints and be provided with urine pregnancy tests for interim use at home.**

- Female partners typically undergo pregnancy testing at study transition points such as enrollment and at the beginning and end of an efficacy phase (if applicable). During the efficacy phase, some trials of male contraceptives have included additional testing at periodic clinic visits, but this should be balanced with the participant burden of additional visits.

- Participants should be provided with home urine pregnancy tests and encouraged to test whenever they have concerns about a possible pregnancy. In addition, developers may wish to schedule at-home testing at specific intervals between clinic visits or set criteria such as requesting that participants utilize a pregnancy test if menses do not occur within 7 days of the expected onset. Given that female participants have naturally variable cycle durations and are included if they have cycle lengths between 21 and 35 days, this latter criterion will ensure that testing is performed at home no later than 42 days (6 weeks) after the first day of the last menstrual period, minimizing the delay between conception and detection, which is critical for timely intervention and accurate dating of conception.

Recommendation: Clinical teams should ensure a prompt, participant-centered response to any positive pregnancy test, prioritizing timely follow-up and support tailored to the couple.

- Clinical visits should be initiated as soon as possible after a positive pregnancy test to provide rapid access to options, including medical abortion, if desired. Visits should include blood hCG testing to confirm pregnancy, ultrasound (if needed), and discussion of next steps with the couple—all ideally occurring during the same visit. However, participants should retain full agency in the pace and extent of evaluation, including the option to delay decision-making or decline ultrasound, if preferred.

- Overall, the committee focused on the emotional complexity of unintended pregnancy and ethical care for participants. Ideally, studies should provide counseling; however, in the absence of on-site support, facilitated referral to an OB/GYN or appropriate external counseling services should be the standard protocol.

Recommendation: Pregnancy should be defined by a single clinical hCG test result and not require serial, quantitative sampling.

- A single positive urine or serum human chorionic gonadotropin (hCG) test performed by the clinical laboratory should be considered sufficient to define pregnancy for evaluation of study outcomes. While sequential serum beta-hCG testing offers quantitative data that may aid in dating or assessing ectopic pregnancies, they are not strictly required for documenting pregnancy.

- A negative clinical test, following a positive at-home test, would not be counted as a pregnancy. However, if a subject is lost to follow-up after reporting a positive home pregnancy test, U.S. regulators have generally required that case to be counted as a pregnancy, even in the absence of clinical confirmation (such as ultrasound or beta-hCG measurement).

Recommendation: Male contraceptive product developers must define a reasonable pregnancy efficacy window to classify whether pregnancies should be attributed to failure of the investigational drug/device. Additionally, clinical protocols should include a plan to identify failure due to non-compliance.

- For female hormonal contraceptive methods, both the EMA and the FDA provide guidance on when pregnancies are considered related to product use.[116,117] These timeframes are informed by known pharmacodynamics and are tailored to the mechanism of action, expected duration of effect and reversibility of the specific product, and aim to provide consistent and comparable measures of efficacy across products. These EMA and FDA guidelines serve to delineate which pregnancies are "on-treatment" or attributable to the investigational product, as distinct from those occurring after the expected return of fertility. Specifically, the FDA guidance states, "On-treatment pregnancy should be defined as any pregnancy that occurs during use of the product or within a specific timeframe after last use of the

product."[116] For example, conception calculated to have occurred within 7 days of the last day of treatment with a daily oral combined hormonal contraceptive would be considered on-study, while for intrauterine systems or devices, only those pregnancies detected within 7 days of removal would be considered associated with the failure of the product, with the assumption that conception must have occurred while the device was still in place. Conversely, the EMA states, "Pregnancy rates should be described by Pearl Index and life table analysis including all pregnancies during treatment. Pregnancies following premature discontinuation of study medication should also be included in the calculations, unless the date of conception determined by a valid method (e.g. ultrasound, beta-hCG) is without doubt after the premature discontinuation."[117] Historically, the differing windows utilized by regulators have led to notable differences in efficacy calculations.[154–156]

- For male contraceptives currently in development, the mechanisms of action and timelines for onset and recovery of the contraceptive effect vary widely, necessitating the careful development of product-specific "on-study" parameters. Developers will need to accurately identify the expected onset and duration of contraceptive protection and propose methodology to regulators accordingly. In recent Phase II trials of the combination Nestorone/testosterone gel (NES/T), subjects did not enter the defined "efficacy stage" until serial confirmation of two sperm concentrations below the target threshold of 1 million/mL. Pregnancies conceived within 7 days of the last dose were considered to be on-study.[157] Conversely, an on-demand, single-use male contraceptive product would have a much shorter window after discontinuation for pregnancies to be considered on-study.

- For user-dependent methods, developers must justify the exclusion of any on-study pregnancy. Objective evidence of non-compliance could be identified through review of participant diaries or pill counts. It is also possible that pharmacokinetic sampling or semen analysis at the time of pregnancy confirmation could be insightful. However, if a participant has subsequently resumed dosing after a lapse, the delay between missing one or more doses and sampling may mask earlier non-adherence. (See the Evaluation of Clinical Efficacy section)

Recommendation: Ultrasound should only be used when necessary for pregnancy dating.

- Transvaginal ultrasound should be used only when pregnancy dating is necessary to determine whether conception occurred during the treatment period, or the defined "on-study window." To avoid unnecessary burden on the pregnant partner, ultrasound use should not be mandated universally upon positive pregnancy test. Rather, investigators should assess the need for ultrasound based on the product's mechanism of action, the couples' duration on study, as well as study diaries and beta-hCG test results. Female participants must retain full agency in deciding whether and when to undergo transvaginal ultrasound, even if declining the procedure results in counting of an on-study pregnancy that might have otherwise been excluded.

Recommendation: Paternity testing should not be utilized in contraceptive efficacy trials.

- In female contraception studies, pregnancies clearly arise from the fertility of the participant receiving the investigational drug or device, regardless of how many sexual partners the woman may have. Unique to male contraception, the female study participant could still become pregnant as a result of intercourse with a partner external to the study, even if her male partner in the study was compliant with the contraceptive method and the method was functioning perfectly. As such, the overall calculated efficacy of a product may be underestimated based on pregnancies arising from non-participatory partners. While this is unfortunate for the product developers and study sponsors, attempting to assign paternity is ethically problematic and may breach participant confidentiality and undermine trust between investigators and study subjects. Moreover, paternity testing may disrupt a relationship and could result in targeting of the female partner emotionally, physically or legally. Additionally, legal and regulatory barriers related to genetic testing in many countries likely hinder the use of paternity testing in clinical research settings.

- Emphasis should remain on timing of conception, not genetic attribution, when determining whether a pregnancy constitutes a product failure. The committee unanimously agrees that prioritizing the privacy of participants outweighs the limited likelihood of a meaningful shift in efficacy statistics.

Evaluation of Clinical Efficacy

Efficacy statistics in contraceptive development serve numerous critical purposes—satisfying regulatory agency evaluation, enabling direct comparison across contraceptive methods, supporting clinician recommendations, and guiding informed end-user decision-making. These statistics, such as the Pearl Index or life table cumulative probability estimates, express failure rates (i.e., the number of pregnancies) and provide a standardized means of quantifying the likelihood of pregnancy under defined conditions of use. For clinicians, these statistics optimally translate complex clinical trial data into actionable information that can be readily communicated to end users weighing contraceptive options. For end users, efficacy statistics are intended to clarify the relative risk of unintended pregnancy, facilitating choices aligned with individual preferences and reproductive goals. From a regulatory perspective, standardized statistical endpoints enable the comparison of benefit-risk profiles across product types and are essential for establishing claims of contraceptive effectiveness.

FDA regulatory guidelines are focused on the development of female hormonal contraceptives and indicate a requirement for the Pearl Index (PI) to be calculated as the primary pregnancy efficacy endpoint.[116] This metric is defined as the number of pregnancies per 100 person-years of exposure. Recognizing the historical use of 28-day cyclic methods, such as oral contraceptive pills, the FDA traditionally recommends that the duration of contraceptive exposure be broken into 28-day cycles (resulting in 13 cycles per year) as follows:

$$PI = \frac{\text{Number of pregnancies} \times 13 \text{ cycles} \times 100}{\text{Number of 28-day cycles in analysis}}$$

However, for female contraceptive methods that do not pharmacologically constrain the menstrual cycle to 28 days in length, such as the non-hormonal female contraceptive gel Phexxi[158], an alternative calculation, based on the total number of days at risk (i.e., days on study) has been utilized:

$$PI = \frac{\text{Number of pregnancies} \times 365.25 \text{ days} \times 100}{\text{Total number of days exposed/at risk}}$$

The FDA additionally instructs developers to include a life table analysis as a supportive analysis to provide monthly and cumulative failure rates.[116] Rather than presenting a simplified average of all participants, regardless of their duration on study, as the Pearl Index does, life table analyses calculate the probability of pregnancy per cycle or month, based on the number of study participants at risk during that interval. For example, a life table analysis can directly provide the risk of pregnancy in the first month of use. Additionally, the cumulative risk is calculated, allowing for comparison of studies of different durations and helping users understand their risk of pregnancy over time.

The EMA guidelines[117] (also adopted by the Australian TGA[159]) state that both Pearl Index and life table analysis calculations should be performed and included in submissions, with no superior weighting given to the Pearl Index.

Neither the Pearl Index nor life table analyses adequately characterize the efficacy of male contraceptives.

Recommendation: Male contraceptive efficacy studies of products targeting spermatogenesis should implement a standardized reporting framework to comprehensively assess method performance and allow for direct comparison between products. This framework must separately report individual components of contraceptive failure—suppression failure, sperm rebound, and unintended pregnancy.

- Male contraceptive efficacy studies present unique considerations compared to female methods as the product is taken by the man to prevent an unwanted effect in his female partner, necessitating a standardized and comprehensive approach to reporting outcomes. Unlike female

contraceptives, many male methods—particularly those that suppress testicular sperm production—follow a distinct clinical trial structure that includes a suppression phase, an efficacy phase, and a recovery phase.[129] In contrast, on-demand male contraceptives do not require a lengthy suppression phase, as they are inherently developed to be fast-acting and reversible after each use. These differing pharmacologic approaches introduce distinct timelines and outcome categories, all of which must be clearly defined and systematically reported to ensure consistency and comparability across products.

- To provide a clear and complete picture of a male contraceptive's performance, Amory (2025) has detailed a framework to standardize reporting of the multiple components of total contraceptive failure:
- Suppression failure refers to the number of men who do not achieve the defined threshold of sperm count (or functional sperm parameter) suppression during the initial phase of treatment. Separating this metric is vital because it informs potential users about the likelihood of being a "responder" to the method, which is a critical piece of information for men and clinicians. For instance, a product might be highly effective once suppression is achieved, but if a substantial percentage of men fail to suppress, this must be clearly disclosed.

- Sperm rebound accounts for instances where sperm parameters rise above the contraceptive threshold during the efficacy phase, indicating a loss of contraceptive protection. This can arise naturally, as observed in a small percentage of men treated with long-acting hormonal methods of male contraception.[129] Sperm rebound could also result due to insufficient drug exposure, whether arising through shifts in pharmacokinetics over time or due to non-compliance with self-administered contraceptives. The incidence of sperm rebound can inform future users and clinicians of pregnancy risk, but also highlight if routine monitoring is needed to ensure adequate and durable suppression.

- Unintended pregnancy is the final component of method failure, indicating a pregnancy occurred while the method was in use, after an initial suppression threshold had been met.

- Importantly, the first two measures–frequency of sperm suppression failure and sperm rebound can–be assessed in all male clinical trial participants,

regardless of whether they have a female partner. These data can be pooled across all studies of a given product, provided they were conducted at the same dose for an adequate duration, enabling the detection of meaningful trends.

Recommendation: In studies of male contraceptives that evaluate pregnancy, the primary efficacy endpoint should be calculated using the life table approach, rather than the Pearl Index.

- Though the Pearl Index is the traditional measure of contraceptive efficacy used by regulators to evaluate the performance of contraceptive methods, it is of limited utility to users and providers. Perhaps most troubling is that it suffers from a form of selection bias; individuals who are at less underlying risk of pregnancy tend to contribute more time to the analysis. Therefore, the Pearl Index will vary as a function of the duration of the study from which it was estimated, and so it is not generalizable to any individual. For example, in long-term studies of contraceptive methods, the Pearl Index decreases over time, with those most likely to conceive experiencing early pregnancies (whether due to coital frequency, naturally higher fecundity, or perhaps less practice with using the method correctly).[4] As a result, shorter trials often appear to have a significantly higher PI than longer trials.

- In contrast, the cumulative probability of pregnancy obtained from life table methods provides a clear interpretation for users of the chance a woman has of becoming pregnant when using the method over a given period of time. Therefore, to adequately define the likelihood of pregnancy, the standard for male contraception should be life table analyses that provide cumulative (monthly) pregnancy risk to a couple. For example, in clinical trials of the female contraceptive vaginal ring Annovera, containing segesterone acetate and ethinyl estradiol, there was a 1.1% likelihood of pregnancy over the first six cycles and a 2.6% likelihood of pregnancy over 13 cycles of use. The Pearl Index for this same group was 2.98, which provides no indication of how risk changes over time.[160] An excellent review and discussion of the issue and related statistics can be found in Mauck et al. (2023).[161]

- Nevertheless, several committee members emphasized that developers should anticipate that regulators will still require the calculation of the

Pearl Index as a secondary endpoint.

- An additional consideration in the evaluation and interpretation of male contraceptive efficacy (as well as in female non-hormonal methods) is the variability in menstrual cycle lengths. When female partners are enrolled in male contraceptive trials, cycle lengths are typically permitted to range from 21 to 35 days, resulting in a potential range of 10 to 17 cycles over a year. Developers should keep in mind that, unlike female oral contraceptive trials—where participants typically experience 13 pharmacologically-regulated cycles per year—this broader range introduces variability in the number and timing of potential fertile windows. Such differences should be carefully considered when designing studies and interpreting statistics.

Recommendation: Developers of male contraceptives should pre-specify a comprehensive set of detailed reasons for discontinuation and implement reporting systems to systematically collect, classify, and report participant data, clearly distinguishing why participants did not complete a study, whether due to adverse events, contraceptive failure, lifestyle factors, non-compliance, or other causes.

- While unintended pregnancies are the typical primary efficacy endpoint in contraceptive trials, participant retention and reasons for non-completion are equally critical in understanding a product's real-world utility. High dropout rates are common across all types of clinical trials and occur for a variety of reasons (e.g., intolerance to side effects; personal lifestyle changes such as relocation or a change in relationship status; challenges related to study requirements).[162] This can obscure the true rate of ongoing effective contraception, a metric that reflects both biological efficacy and user adherence or tolerability.

- Reporting systems can be designed to include more than one level of classification, as well as investigator notes, allowing for enhanced data collection, rather than relying only broad required terminology, such as "Withdrawl by Subject."

- It will also be necessary to pre-specify how study participants who are not fully adherent will be managed and classified for reporting. For clinician-

administered products, such as injections, participants who miss a scheduled re-injection can be classified as non-compliant. For self-administered methods, however, the criteria for censoring participants are more complex–especially when brief "drug holidays" may not lead to a meaningful loss of contraceptive effect.

- Regulators, including the FDA and EMA, expect developers to fully account for missing data and discontinuations in efficacy analyses using appropriate censoring and sensitivity methods. However, a more detailed understanding of the reasons for dropout also informs method acceptability—a key determinant of real-world use. Precise categorization and transparent reporting of dropouts will allow for better-informed decision-making for potential users and clinicians. This is particularly important in the male contraceptive space, where public trust is still being established. By investing in robust dropout tracking and transparent reporting, developers can provide the information needed to aid clinicians and users in assessing both the likelihood of continued use and the long-term effectiveness of the method.

Recommendation: Developers should consider utilizing data on the frequency of sexual activity for exploratory efficacy analyses in their clinical studies.

- There is a clear need to improve the understanding users have of contraceptive efficacy, especially as new products enter the market. Numerous studies, primarily focused on women, have shown that while efficacy is a primary concern, the understanding of comparative effectiveness is inadequate.[163,164] There are concerns that men, whose contraceptive options have historically been minimal, have markedly less knowledge of the effectiveness of various methods. Additional tools and metrics are needed to aid users (or the clinicians counseling them) in selecting the most suitable method for the individual at a given point in their life.

- The standard methods used to estimate pregnancy risk in clinical trials—namely, the Pearl Index and life table analysis—do not account for coital frequency, despite clear evidence that increased intercourse frequency is associated with shorter time to pregnancy.[165–167] Current FDA guidance typically requires only one or more sexual acts per cycle/month for inclusion in efficacy calculations[116], resulting in wide variability in baseline

pregnancy risk and potentially underestimating failure rates for users with more frequent intercourse.

- The POP100, calculated as the probability of at least one pregnancy in 100 sexual acts, is a recently introduced male-centric contraceptive measure designed to communicate frequency-based risk to men in a format that may be more intuitive.[168] The POP100 can also potentially be viewed as a more personalized risk evaluation, especially for users of on-demand products, since the cumulative risk of an unplanned pregnancy for a couple infrequently having intercourse compared to a couple that is engaging in daily intercourse is dramatically different, and this is not reflected in a population measure such as the Pearl Index or a life table analysis. A frequency-based measure such as the POP100 is potentially most informative to users of on-demand methods, given the expected variation in usage, as well as those with very low or very high sexual frequency. However, exploratory analyses using the POP100 will need to evaluate whether a selection bias occurs, as is the case with the Pearl Index.

- Trials of contraceptive products routinely collect diary data, which can be utilized for exploratory analyses, such as the POP100, but implementation may present challenges. These statistics rely upon accurate reporting of sexual activity, which may necessitate improved digital tools with reminder functionality. Collecting this level of sexual activity detail may also present challenges in certain cultures.

Clinical Safety

The clinical safety evaluation of male contraceptive drugs is expected to follow the harmonized regulatory guidance (ICH E1) applicable to all investigational new drugs intended for long-term use with non-life-threatening conditions.[144] *These guidelines are applicable based on the expected chronic dosing of novel male contraceptives, whether due to daily dosing requirements or regular periodic usage (of 6 months or more) for on-demand products. Across all therapeutic areas, early-phase clinical studies are designed to identify dose-limiting toxicities, characterize pharmacokinetics, and establish an initial safety and tolerability profile through standard assessments, including physical examination, vital signs, and clinical laboratory panels (e.g., hematology, liver and renal function). These evaluations are equally applicable to male contraceptives.*

However, male contraceptive products differ in several key respects. Most notably, they are administered to healthy volunteers of reproductive age, with the primary therapeutic goal of transiently suppressing sperm production, sperm transmission (preventing the ejaculation of sperm), or sperm function. Unlike most drug development programs, the intended pharmacodynamic effect of male contraceptives—suppression of male fertility—would be classified as an adverse outcome in other therapeutic contexts. This distinction has implications for both study design and safety interpretation, and developers must clearly communicate to regulators the delineation between intended contraceptive effects and unintended safety signals.

As an investigational new drug or device progresses into later-stage clinical trials, study objectives will transition from dose-selection to efficacy, but safety remains the primary consideration in all clinical trials. As described in FDA guidance, "Safety monitoring in a clinical trial serves two purposes: (1) to protect the safety and well-being of individual trial participants; and (2) to obtain safety information to be used in the assessment of the risk profile of the investigational medicinal product."[169] *First-in-Human/Phase I trials provide the first opportunity to assess safety in humans, characterize drug disposition, and, wherever possible, generate early evidence of product efficacy. Early Phase II studies (sometimes referred to as Phase 2a) should support rigorous exploration of dose-response and dose-duration relationships for both efficacy and adverse events. These data inform the selection of dosing regimens and monitoring strategies for later-phase trials. Over the progression of Phase I and Phase II clinical trials, the frequency and depth of evaluations typically decrease, as a safe and effective dose is defined, and product evaluation moves towards more real-world usage scenarios. The goal of Phase III studies is to gather sufficient high-quality data to determine whether*

the investigational product, under actual-use conditions, can be used safely, effectively, and reliably as a sole method of contraception.

Regulators will expect a tailored, risk-informed approach to evaluating safety in clinical trials, rather than relying solely on standard clinical laboratory blood panels and vital signs. Developers should proactively address potential product-specific safety concerns before initiating clinical trials, rather than relying on prompting from regulators. The detailed guidance Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products, published by the EMA,[170] states that "Uncertainty may arise from particular knowledge, or lack thereof, regarding the mode of action of the IMP [Investigational Medicinal Product], the presence or absence of biomarkers, the nature of the target, the relevance of available animal models and/or findings in non-clinical safety studies… The process of designing a set of studies in a development programme is governed by the attempt to reduce this uncertainty step-by-step by gathering relevant knowledge. Sponsors and investigators should identify, a priori for each clinical study, the potential risks that might arise and apply appropriate risk mitigation strategies."

Developers will need to ensure they are considering all sources of existing safety data for their product and how this scientific information can be translated into the design of subsequent clinical development:

- *Mechanism of Action: Potential on-target/off-tissue biological effects based on the drug's pharmacologic pathways. If a target is expressed in tissues beyond the reproductive system, developers should ensure that tissue expression is understood and anticipate possible effects. In addition, interaction with molecules closely related structurally and functionally to the intended molecular target should be considered.*
- *Known Class Effects: Safety profiles from related agents, even if not previously used as contraceptives, can inform expectations regarding potential side effects. (e.g., ion channel modulators, hormonal agents, enzyme inhibitors).*
- *Non-Clinical Toxicity Findings: Preclinical data from safety pharmacology, general toxicology, and reproductive toxicology studies may identify specific organ systems or safety biomarkers of concern; however, not all of these may be clinically relevant. The EMA states, "An evaluation as to whether the target organs identified in the non-clinical studies warrant particular monitoring in the CT [clinical trial] should be undertaken. Serious toxicity should lead to a more cautious approach when setting doses and applying risk mitigation strategies in the clinical setting… Some serious toxicities are poorly translated to humans, e.g.,*

species-specific immune reactions with monoclonal antibodies. Such toxicities may be categorised as not clinically relevant with the appropriate data and/or rationale."[170] Realistically, for male contraceptive drugs, serious nonclinical toxicities—especially when observed near projected efficacious exposures—can lead to termination of development. Model selection should therefore prioritize human translatability (target orthology/distribution, comparable exposure–response and metabolism) to generate credible safety margins and data that can inform the clinical program. (See the Preclinical Evaluation section.)

The EMA states explicitly that, "Experimental and/or literature-data should be taken into account when defining the degree of uncertainty of the IMP."[170] Given that non-hormonal male contraceptive targets are novel and there is limited to no clinical experience with many of the targets, the degree of uncertainty is higher than when new drugs in an existing class begin clinical trials. Accordingly, developers may wish to proactively mitigate safety concerns identified in the literature by performing additional animal studies or incorporating assessments into compulsory studies.

Regulatory expectations regarding clinical safety exposure for new molecular entities (NMEs) are harmonized across many agencies, including the FDA and EMA, and are outlined in ICH E1.[144] Developers should plan for cumulative exposure in at least 1,500 men, including 300 exposed for six months and 100 for one year, at doses equal to or higher than the dose planned for marketing, prior to submission of an application. These population sizes are designed to ensure the adequate detection of uncommon but clinically meaningful adverse events (AEs), with the expectation that many common AEs will occur within the first few months of treatment. However, some may only become detectable after longer-term use.

As clinical development proceeds, safety monitoring will continually evolve based on clinical findings. Adverse Events of Special Interest (AESIs) will need to be carefully monitored. AESIs are predefined adverse events that are of particular interest due to their likely link to the investigational product, which are either severe or occur frequently. If preclinical data or literature suggest the potential for AESI that may only emerge with prolonged dosing or in a larger population (due to its low frequency), it should not be omitted from the IND submission. Instead, developers should communicate their intent to assess the risk in later stages of development, when appropriate study conditions allow for its adequate evaluation.

When evaluating the frequency and severity of adverse events to assess the overall risk-benefit profile of a new male contraceptive, it is expected that regulators may be accepting of certain adverse effects if those effects are readily monitorable. This is because

events that can be identified through routine clinical assessments—allowing for timely intervention, treatment, or discontinuation—are generally considered less concerning than those that are abrupt, unpredictable, or irreversible. When adverse effects can be detected and addressed before causing significant harm, they are often viewed as more manageable within a clinical development program. For example, the use of combined oral contraceptives has resulted in hypertension in a subset of women, potentially leading to an increase in the risk of cardiovascular disease, including acute myocardial infarction and ischemic stroke.[171] *These risks can be minimized through regular blood pressure monitoring and discontinuation of the product where warranted.*

The committee's recommendations focus primarily on concerns that are amplified with male contraceptives—the clinical assessment of potential reproductive toxicity, especially for agents that alter sperm structural or functional attributes (e.g., morphology or DNA fragmentation) and the evaluation of female partner exposure.

Recommendation: Clinical safety and pharmacokinetic assessments of male contraceptives should only be conducted in the female partner when preclinical and/or early clinical pharmacokinetic studies demonstrate that the active drug is present in the ejaculate at meaningful concentrations.

- Protection of the sexual partner is an essential consideration in the development of male contraceptives. However, current regulatory expectations do not require routine measurement of drug concentrations in semen or partner exposure assessments for most investigational products. Requirements for such evaluations are generally reserved for compounds with known or suspected reproductive toxicity based on nonclinical studies. Historically, the FDA and EMA have required seminal pharmacokinetic (PK) assessments only in cases where preclinical findings suggest the potential for semen-mediated exposure leading to teratogenic or embryo-fetal effects.

- A stepwise, risk-based decision-making process should be used to determine whether semen testing and subsequent female partner safety assessments are warranted. If non-clinical studies demonstrate measurable concentrations of active drug or its metabolites in the semen of the treated animal species, this finding may justify measurement of semen concentrations in human males during Phase I trials. If drug is detected in human semen, the potential for systemic exposure in a female partner can be mathematically modeled using standard assumptions regarding

ejaculate volume and sexual frequency. The resulting estimates of potential female exposure can then be evaluated in combination with known pharmacokinetic properties of the drug (e.g., bioavailability, volume of distribution, and clearance) to assess the likelihood of systemic uptake and the plausibility of toxicologically meaningful exposure. If these modeled estimates indicate that the maximum theoretical partner exposure is significantly below the no observed adverse effect level (NOAEL) derived from reproductive toxicology studies in animals (typically with built-in safety margins), no further female safety monitoring is warranted. Conversely, if predicted exposures approach or exceed thresholds of concern, clinical partner safety assessments may be justified.

- This structured approach will ensure that evaluation of partner risk remains scientifically grounded and proportional to actual exposure risk, while minimizing unnecessary burden on female trial participants and use of resources.

Recommendation: Developers of male contraceptive drugs should plan to follow all on-study pregnancies through outcome—whether live birth (with neonatal assessment), spontaneous abortion, elective termination, stillbirth, or ectopic pregnancy—and conduct postnatal follow-up of any resulting offspring for at least 6 months and up to 12 months to assess for developmental effects and ensure compliance with regulatory expectations.

- Regulators have widely adopted ICH E8 (R1), applicable to all clinical trials regardless of indication, which states, "…a participant becomes pregnant while participating in a clinical study, follow-up evaluation of the pregnancy and its outcome, and the reporting of outcomes are necessary."[115] Where a live birth occurs, committee members noted that regulators, such as the FDA and EMA, typically recommend follow-up of infants from birth for six months to one year to evaluate postnatal development and detect any adverse effects potentially attributable to the investigational product, although formal guidance is lacking. Practically, this is often managed by requesting that the participating couple provide details of their pediatric well-visits.

- In the context of male contraceptives, developmental toxicity risks potentially arise from drug exposure to an embryo (via semen after conception, but before awareness of the pregnancy), or directly if a sperm

cell with a drug-induced defect can fertilize an egg. Regulators may therefore expect more significant follow-up for male contraceptive drugs that impact sperm structural or functional attributes, such as sperm morphology or sperm DNA integrity, as compared to those that decrease sperm concentration or prevent sperm release during ejaculation. Pregnancy registries may be needed in the post-approval phase to gather additional data, since it is likely that few pregnancies will occur on-study with a highly effective contraceptive.

Benefit-Risk Considerations

Benefit-risk analysis is of paramount importance in the context of male contraceptive development, given that no novel male contraceptive products have yet been approved, and unique considerations are involved. Although this topic was discussed at length by the committee, the absence of established regulatory precedent and the complexity of the issues involved led to a decision not to issue a set of recommendations at this time. Instead, the committee compiled a structured summary of challenges, uncertainties, and background considerations to foster and catalyze further discussion and refinement of a regulatory framework. One unanimous recommendation did emerge: that developers should engage meaningfully with end users, as this can yield critical insights into user priorities, motivations, and unmet needs—factors essential to both product development and regulatory evaluation.

Benefits of male contraception

The intent and benefit of all contraceptives is the prevention of unintended pregnancies. Even with conservative uptake assumptions, novel male contraceptive methods could meaningfully reduce unintended pregnancies, particularly in regions with low current contraceptive use. A male contraceptive pill or reversible vas occlusion device is modeled to decrease unintended pregnancies by 3.5% to 5.2% in the United States, 3.2% to 5% in South Africa, and an astounding 30.4% to 38% in Nigeria.[10]

One of the complexities of evaluating male contraceptives is that the primary benefit—pregnancy prevention—occurs in a person other than the user. However, emerging male methods have the potential to offer substantial advantages for both partners, extending beyond pregnancy prevention alone:

- *<u>Reduced contraceptive health risks and side effects for female partners:</u> New male contraceptive options used in lieu of female methods will significantly reduce female partners' exposure to risks and side effects associated with female contraceptives. Male methods will offer an alternative method of preventing pregnancy for women with medical contraindications to hormonal methods. Additionally, the efficacy of many female hormonal contraceptive options, including emergency contraception, is lower in women with higher BMI, placing these women at greater risk of pregnancy and restricting their contraceptive options.*[172,173]
- *<u>Enhanced contraceptive efficacy through method pairing:</u> Novel male contraceptive methods offer the potential to maximize pregnancy prevention when*

both sexual partners use their own independent contraceptive method simultaneously. This layered approach may be especially impactful when the female partner is using a less effective method of contraception due to contraindications or lack of tolerance to the most effective female contraceptives. By providing a reliable alternative to condoms as a secondary line of protection, new male methods may serve as a safeguard in contexts where preventing pregnancy is critical and reliance on a single method is insufficient, but prevention of sexually transmitted infections is not a concern.[174]

- *Opportunity for shared responsibility: Male contraceptives may lead to more equitably shared responsibility in family planning, reinforcing mutual decision-making and trust within partnerships.*[175] *By assuming a direct role in pregnancy prevention, men utilizing male methods will reduce the burdens currently placed almost entirely on the female partner, such as scheduling medical appointments, managing prescription refills, and enduring side effects. The redistribution of responsibility will allow balanced participation in contraceptive management.*
- *Enhanced reproductive autonomy and control: Male contraception empowers men to independently prevent pregnancy, expanding their options beyond condoms or abstinence. This autonomy lets men make proactive choices to avoid unintended fatherhood, treating contraception as a fundamental tool for aligning their reproductive choices with their personal values and long-term goals.*[172]
- *Improved sexual experience, compared to condoms: Novel methods of male contraception, whether drugs or devices, will likely eliminate common drawbacks associated with condom use, such as decreased sensation or spontaneity.*[176]
- *Increased Healthcare Engagement: Prescription-based male contraceptives could lead to more routine healthcare visits, especially among younger men, addressing an existing care gap where young men often lack a routine provider. For example, in the US in 2012, the preventive care visit rate for men aged 18-44 was a mere 18.5 per 100 men, as compared to 87.1 visits per 100 women in the same age range.*[177] *These visits offer opportunities for preventive care, early detection of chronic illnesses, mental health issues, and sexually transmitted infections (STIs), and also serve as an entry point for comprehensive male sexual and reproductive health (SRH) services, which are sadly lacking.*[173]

New male contraceptives will increase the range of options available, improving the likelihood of finding and consistently using a method that aligns with a couple's health needs, lifestyle, and personal preferences—ultimately improving outcomes for the entire family through pregnancy prevention. Unintended pregnancy is associated with higher odds of maternal depression during pregnancy and the post-partum period, as well as a decline in physical health, as compared to planned pregnancies.[178,179] *Unintended*

fatherhood also has mental health consequences, with an increased likelihood of depression compared to those who father a planned pregnancy.[180] *Unplanned pregnancies are associated with poorer birth outcomes, including preterm birth and low birth weight, especially in low- and middle-income countries.*[181] *This has often been attributed to insufficient preconception care and late initiation of prenatal care. Pregnancy intendedness is strongly associated with mother-infant bonding, which has long-term impacts on child development.*[182,183] *The likelihood and duration of breastfeeding are also decreased for women with unintended pregnancies.*[184,185]

On a population level, novel male contraceptive options have the potential to decrease maternal mortality and morbidity. Globally, 260,000 women die as a result of pregnancy each year,[186] *and an even larger number of women (1.8%) experience significant morbidities during delivery (e.g., major obstetric hemorrhage requiring a blood transfusion, acute kidney failure).*[187] *In the United States, women still regularly die as a result of pregnancy, at a national rate of 18.6 deaths per 100,000 live births in 2023, rising to 50.3 deaths per 100,000 live births for Black American women.*[188] *In Nigeria, where novel male contraceptives are modeled to have a dramatic impact on unplanned pregnancies, women have an estimated lifetime risk of maternal mortality of 1 in 19.*[189] *Ultimately, male contraceptives will benefit couples (and their future children) by supporting planned pregnancies and adequate birth spacing—factors closely linked to improved maternal health, healthier pregnancies, and better outcomes for infants and children.*[190,191]

Risks of male contraception

On the other side of the equation lies risk. Male contraceptive developers are seeking to balance efficacy with acceptable risk—yet as novel products with unique mechanisms, these drugs lack established standards or known class effects that set a threshold for approval. In the context of evaluating clinical risk, two main categories emerge: 1) adverse events requiring medical intervention or drug cessation and attributable to the product (with regulators considering the frequency and severity) and 2) tolerability—the extent to which mild side effects are acceptable to users and do not interfere with continued use. Although regulators may place greater weight on adverse events with clinical significance, tolerability has a direct impact on adherence and, consequently, real-world product effectiveness. To minimize risk, most non-hormonal male contraceptive drug developers are pursuing mechanisms that act selectively within the male reproductive system, aiming to reduce off-target effects and avoid broader systemic impact. Acceptable risk will ultimately be defined by regulators. Still, the perspectives of both male users and their partners will hopefully help shape those

boundaries, especially given the ethical complexity of introducing risk to healthy individuals who do not bear the direct physical consequences of pregnancy.

Benefit-risk frameworks

Historically, there has been a lack of transparency in benefit-risk evaluations by regulators, leading to concerns about subjective and inconsistent processes.[192] *However, the assessment of benefit-risk (BR) profiles for medicinal products has undergone significant transformation over the last two decades, shifting towards more structured and objective approaches to enhance clarity and consistency in regulatory decision-making. Both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have adopted more systematic methodologies, acknowledging the critical need to meticulously weigh desired outcomes against potential harms.*

For new drug and biological products, the FDA primarily advocates a structured qualitative approach, emphasizing that quantitative analysis supports, rather than replaces, expert judgment.[193] *This framework is integrated into clinical review templates and is used to communicate BR assessments to advisory committees. The Benefit-Risk Framework for new drugs identifies key decision factors, each with two components– Evidence and Uncertainties, along with Conclusions and Reasons. In the context of contraceptives, this typically encompasses:*

- *<u>Analysis of Condition:</u> This addresses the therapeutic context for the proposed indication, including the intended medical use and patient/user population, impacts, and public health implications. For contraceptives, this section highlights the negative consequences of unintended pregnancy.*
- *<u>Current Treatment Options:</u> This section outlines current FDA-approved treatments and the standard of care, including efficacy, safety, tolerability, and any limitations (e.g., subpopulations that are unresponsive or intolerant to treatment). The medical need for a new drug in terms of efficacy, safety, or tolerability is also assessed. For female contraceptive options, this list often includes a broad range of available options, including male condoms.*
- *<u>Benefit:</u> This assesses the clinical endpoints, detailing the nature of the effect (i.e., protection against pregnancy) and associated uncertainty (e.g., confidence interval, clinical importance), distribution of treatment effects (e.g., percent of users experiencing substantial benefit), and the time course and durability of effect.*
- *<u>Risk and Risk Management:</u> This evaluates observed adverse events or safety signals, assessing their clinical importance, including severity, likelihood of occurrence, reversibility, and impact on drug tolerability or adherence. It assesses*

the level of certainty for a causal association, the potential impact of product quality issues, anticipated post-marketing differences, the potential for misuse or accidental exposure, and the likely effectiveness of proposed risk management approaches.

For medical devices, the FDA's Center for Devices and Radiological Health (CDRH) also employs a structured approach for benefit/risk analysis of premarket approval (PMA) applications and De Novo classifications, guided by similar factors.[194] *Their assessment includes the following sections:*

- *Assessment of Benefits: This evaluates the extent of the probable benefit(s) by considering the type of benefit (e.g., pregnancy prevention), the magnitude of the benefit (e.g. contraceptive efficacy observed in pivotal studies), the probability of the patient experiencing a benefit, and the duration of effect (how long the benefit lasts).*
- *Assessment of Risks: This examines the extent of the probable risk(s)/harm(s), including the severity, types, number, and rates of harmful events (serious, non-serious, procedure-related complications), the probability of a harmful event, and the duration of harmful events.*
- *Additional Factors: This section is designed to capture other relevant considerations that should be included in the assessment, such as:*
    - *Uncertainty (e.g., study design, generalizability of results, repeatability)*
    - *Patient-centric assessments and patient-reported outcomes (PROs)*
    - *Patient perspectives*
    - *Availability of alternative treatments (including non-device therapies)*
    - *Risk mitigation (e.g., labeling, specialized training)*
    - *Postmarket data needs*
    - *Novel technology (whether the device addresses unmet medical need).*

The Patient Perspectives category, distinct from clinical assessments, is a unique feature of the CDRH benefit-risk evaluation, with guidance stating, "FDA recognizes that patient perspectives on benefits and risks may reveal reasonable patients who are willing to tolerate a very high level of risk to achieve a probable benefit, especially if that benefit results in an improvement in quality of life." Additionally, the guidance emphasizes the importance of capturing a comprehensive understanding of the patient perspective, stating, "Rather than one-sided evaluations, patient preference assessments should take into account both the patient's willingness and unwillingness to use a device or tolerate risk in exchange for probable benefit, and/or evaluate how patients view trade-offs between benefits and risks of various treatment options."[194]

In Europe, the EMA initiated its "Benefit-Risk Methodology" project in 2009 to develop a more structured approach, emphasizing transparency and consistency. Their primary recommendation is a two-level evaluation: a qualitative approach, which is sufficient for most cases, primarily utilizing the 8-step generic decision-making guide addressing the Problem, Objectives, Alternatives, Consequences, Trade-off, Uncertainty, Risk tolerance, and Linked decisions (PrOACT-URL) model, similar to the analysis framework used by the FDA's CDER and CBER.[195] If the qualitative analysis is insufficient, the EMA then applies a quantitative approach using Multi-Criteria Decision Analysis (MCDA) for more complex or "marginal" situations.

Shared risk and responsibility

Male contraceptives present unique challenges in assessing benefit and risk because the primary, direct benefit of preventing pregnancy occurs in the female partner, rather than directly in the male user. The concept of benefiting someone other than the user is rare for drug and device approvals. There are, however, parallels to vaccine usage, where the benefit to public health, or even family members, often outweighs the benefit to the individual. For example, pertussis vaccines are encouraged for parents and close caregivers to protect infant health, through a "cocooning" strategy.[196] Although the direct benefit to the adult receiving the booster may be small, the rationale for immunization is compelling, as the direct benefit is realized in a family member. Finally, when assessing risk, it is crucial to recognize that choosing not to use a male contraceptive does not eliminate risk for men; rather, it increases the likelihood of fathering an unintended pregnancy and enduring the associated potentially deleterious consequences.

The concept of "shared risk and responsibility" has been introduced as an ethical framework for considering the benefit-risk of male contraceptives.[197] This framework acknowledges that contraception is relational and defines risk as the sum of risks to both members of a sexual dyad associated with contraceptive use by either partner, compared to the risks of unintended pregnancy for the couple as a whole. This contrasts with the traditional "individual framework," which focuses solely on the benefit and risk to one individual. An example provided by Campelia et al. proposes that if a female combined oral contraceptive (F-COC) has a risk of 7.5 deaths per million user-years due to thromboembolism, applying the "shared risk" paradigm means the couple accrues this risk.[197] If a male contraceptive had a lower risk of death, e.g., 1 death per ten million user-years, the overall "shared risk" for the couple would be significantly reduced, making the male contraceptive strongly favored from this perspective. This framework allows developers to reframe the risk assessment for male contraceptives, justifying medical risks

to the male user while reducing overall risk to the couple. It also aims to alleviate gender-based disparities in risk and responsibility related to family planning.

Lessons from the regulatory approval of female contraceptives

Regulatory precedent for female contraceptives demonstrates a willingness by the FDA to approve products despite known risks, limitations in use, and sub-optimal efficacy, to expand contraceptive options (and forms) and support broader efforts to reduce unplanned pregnancy. Female combined hormonal contraceptives (CHC) carry a boxed warning for cardiovascular risk, yet this has not prevented regulators from continuing to approve new female methods. Recent approvals, utilizing the benefit-risk framework described above, offer insight into regulatory considerations. For example, Nextstellis (drospirenone and estetrol tablets) was approved in 2021.[198] Its benefit-risk analysis considered the significant risks and consequences of unintended pregnancy in healthy reproductive-age women, balancing them against the risks of hormonal contraception, including serious thromboembolic adverse reactions. The approval acknowledged that the risk of unintended pregnancy provides justification for CHC approval. Nextstellis had an acceptable overall Pearl Index (PI) of 2.65 (with an upper bound of the 95% confidence interval at 3.88). Still, its PI exceeded 5 for women with increasing BMI, suggesting it may be less effective than other currently approved oral contraceptives. As justification, the Analysis of Condition stated, "Unintended pregnancy remains a significant reproductive health problem for females and their families in the United States due in part to compliance, access and affordability," concluding that, "Additional modifications of contraceptives in regard to ease of use, effectiveness and safety are warranted to continue to reduce the unintended pregnancy rate."

Twirla, a transdermal hormonal contraceptive patch for females, received approval from the FDA in 2020.[199] For women with a BMI between 25 and 30, the PI was 5.7 (95% CI: 3.0–8.4); however, the product was approved, presumably due to the limited number of transdermal or weekly options available. In the obese (BMI $\geq$ 30) subpopulation analysis, a Pearl Index of 8.64 (95% CI = 5.79, 11.50) was observed, resulting in an indication only for women with a BMI less than 30. The benefit-risk analysis stated that, for the obese sub-population, "the lower bound exceeded the upper bound of every previously approved CHC."

Phexxi, a non-hormonal contraceptive vaginal gel, was approved by the FDA in 2019, following a pivotal 7-cycle trial.[200] The cumulative pregnancy rate was 13.7% with a 95% CI of (10.0%, 17.5%) based on 101 on-treatment pregnancies. The Pearl Index was calculated as a required secondary efficacy endpoint. Based on 101 on-treatment

pregnancies over seven cycles (with exposure counted in days), the Pearl Index was 27.5 (95% CI: 22.4%, 33.5%). The approval package states that, "These effectiveness results are in the same range as nonoxynol-9 spermicidal Tier 3 products on the market and, therefore, are acceptable. Although the contraceptive benefit of Phexxi in terms of pregnancy rates is significantly less than that of hormonal methods, it does provide another contraceptive option with less side effects. The safety profile is consistent with other topically applied vaginal products. The vaginal application just prior to intercourse allows for on-demand use, which may benefit women with infrequent intercourse or if concomitant use with a barrier method is being considered." The benefit-risk analysis subsequently states that "Non-hormonal products offer contraceptive options for women who cannot tolerate hormone therapies or have a history of health problems that contraindicate hormone use."

These examples indicate a tolerance of risk and acceptance of a range of effectiveness in female contraceptives by the FDA, seemingly driven by the significant need for pregnancy prevention and the provision of diverse options.

Conversely, the EMA has centrally approved only a single contraceptive in the last decade. Drovelis (the same drospirenone and estetrol product as Nextstellis, marketed under a different name) was approved in 2021.[201] *Although a trial including US-based sites observed lower efficacy, with the European Public Assessment Report (EPAR) highlighting the failure to meet the expectations of hormonal contraceptives, it was ultimately approved based on adequate efficacy in the European pivotal trial, which resulted in a PI of 0.44. The EPAR states, "The requirement for precision of the PI (2.42, 95% CI: 1.58, 3.54) was not met in accordance with the EMA Guideline on Steroid Contraceptives, since the difference between the upper limit of the corresponding 2-sided 95% CI for the Pearl Index and the point estimate was > 1."*

Lessons from the regulatory approval of products for men

Given that no male contraceptive drugs have yet been approved, we must look elsewhere for indications of the regulatory perspective on drugs to treat non-life-threatening conditions in men. The FDA has approved numerous drugs for men that could be classified as "quality of life" products, such as those to treat male pattern hair loss and erectile dysfunction (ED). The approval of ED drugs like sildenafil citrate (Viagra), tadalafil (Cialis), and vardenafil (Levitra) predates the usage of the current risk-benefit framework for assessment.[202–204] *These products, all phosphodiesterase type 5 (PDE5) inhibitors, are also authorized by the EMA. The Scientific Discussion of the original EMA authorization documents states, "Although erectile dysfunction is*

regarded as a benign disorder, it has a medical and social impact due to its high prevalence, costs, and implications for quality of life for many men (and their partners)."[205] *In addition to the primary efficacy endpoints related explicitly to erectile function, secondary endpoints utilized a range of quality of life measures, including the Fugl-Meyer Quality of Life Questionnaire and the Centre for Epidemiological Studies Depression Scale (CES-D) Questionnaire. PDE5 inhibitors have several accepted class effects, including headache, flushing, nasal congestion, and dizziness. The labeling for Levitra also warns of rare but serious side effects, including vision loss and sudden hearing loss.*

There are a number of testosterone-replacement products, in a range of forms, currently approved by the FDA and authorized by the EMA. Widespread and increasing use of testosterone to address symptoms of low endogenous testosterone is considered off-label, though clearly recognized by regulators.[206,207] *For example, Xyosted was approved by the FDA in 2018 as a subcutaneous injection form of testosterone enanthate.*[208] *The review states, "TRT [testosterone replacement therapy] is the current standard of care for hypogonadal men with primary or secondary hypogonadism due to conditions associated with a genetic or structural disorder. Nonetheless, despite a drug class Limitation of Use (LOU) in approved product labeling, TRT products are often prescribed to older men with "low T" for the treatment of "age-related hypogonadism." There are a host of FDA-approved TRT products available, including a variety of formulation types. Xyosted would be another therapeutic option in the armamentarium for TRT." Regulator concerns about depression and suicide risk, as well as increases in blood pressure, potentially leading to major adverse cardiac events, were primarily handled via labeling, with a boxed warning detailing the hypertensive effects (as well as additional post-marketing work to assess patient understanding of the warnings contained in the medication guide).*

Finasteride, initially approved by the FDA as Proscar, was approved in 1997 at a lower 1 mg dose under the name Propecia for the treatment of male pattern baldness.[209] *Though it demonstrated cosmetic improvements in hair growth, the FDA later required the addition of a warning on the package insert stating "Increased Risk of High-Grade Prostate Cancer with 5α-Reductase Inhibitors." This product is also approved in the EU, but a recent review by the EMA has identified an increased risk of suicidal ideation.*[210] *The EMA states, "Most cases of suicidal ideation were reported in people using 1 mg finasteride tablets, which are used to treat androgenetic alopecia (hair loss due to male hormones). A warning about mood changes, including depression, depressed mood, and suicidal ideation, is already included in the product information for finasteride medicines. Patients who experience mood changes should seek medical advice and, if taking*

finasteride 1 mg, should also stop treatment. The product information for finasteride 1 mg tablets will now also alert patients about the need to seek medical advice if they experience problems with sexual function (such as decreased sex drive or erectile dysfunction), which are known side effects of the medicine and may contribute to mood changes."

Overall, regulatory precedent suggests a tolerance for rare but serious AEs in products that support improved quality of life for men, including appearance, vitality, and sexual function, if these risks can be clearly communicated and adequately understood by the end-user.

Patient experience data

Both the EMA and FDA are placing a growing emphasis on patient-based drug development and integrating the patient perspective into benefit-risk evaluations, recognizing patients as both experts in their own experiences and the ultimate stakeholders in treatment outcomes. Per the EMA, "Patients have valuable insights and perspectives from living with a condition and its treatment. This includes symptoms, natural history, quality of life, unmet needs, which outcomes are important, and preferences for future treatments. Input from patients, as users of medicines, can inform medicine development, enhance regulatory decision making, and result in more patient-relevant outcomes."[211]

Patient Experience Data (PED) encompasses information collected from a wide variety of sources, including patients, family members, and patient advocacy organizations, to detail unmet needs, experience with products, and user preferences. These types of data can be critical in a benefit-risk assessment, as they help identify the potential benefits or features that are most meaningful to users and evaluate the acceptability of risk trade-offs and uncertainty. PED includes:

- *<u>Patient-Reported Outcomes (PROs):</u> Direct measures of how patients feel and function, and key components of patient-focused outcome measurement approaches in clinical trials. Identification and selection of PROs worthy of evaluation in male contraceptive trials may be challenging, given the preventive nature of the products. In female contraceptive trials, the most common PROs assessed are satisfaction (also applicable to male methods) and side effects such as bleeding/spotting.*[212]
- *<u>Patient Preference Information (PPI):</u> Captures explicitly the value patients place on important attributes (benefits and risks) of a medical product. Well-designed PPI studies can elicit which attributes are important to patients, their relative importance, and the trade-offs patients are willing to make between benefits and*

risks. PPI is considered to be particularly valuable when significant risks or uncertainty exist, when patient views vary considerably within a population, or when patient views are expected to differ from those of healthcare professionals.

The FDA's Center for Devices and Radiological Health (CDRH) was a pioneer in incorporating quantitative patient-preference data, using it to inform regulatory review and approval decisions for medical devices as early as 2012. CDRH revised its guidance in 2016 to include PPI as a factor explicitly. Additionally, they provide a detailed guidance on how PPI can be utilized in device approvals.[213] Unfortunately, the formal inclusion of these data in the analysis of benefit-risk for drugs remains challenging.[214,215] The FDA has generated four methodology guidances for assessing and submitting patient experience data, several of which remain open for public comment.[216]

Summary

The approval of male contraceptives will require a nuanced and modernized approach to benefit-risk analysis—one that moves beyond the traditional, individual-focused framework to embrace a model of shared risk and responsibility. Such a paradigm recognizes the relational nature of contraception and addresses longstanding gender disparities in family planning. New male methods offer the potential to expand contraceptive choice and better align with users' individual health needs, lifestyle preferences, and cultural values. Regulatory precedent for drugs that address non-life-threatening conditions in men—such as erectile dysfunction, hair loss, and testosterone deficiency—demonstrates a willingness to approve products with recognized risks, provided those risks are clearly conveyed and well-understood by users. The committee emphasizes the importance of balanced risk tolerance, supported by clear, comprehensive, and patient-friendly safety information in the labeling, to enable individuals to make informed decisions based on their own circumstances. The FDA has already shown flexibility in the approval of female contraceptives by accepting a range of effectiveness and risk profiles in service of broader public health goals. The committee hopes that this same spirit of regulatory pragmatism—centered on unmet need and user perspective—will extend to male contraceptive products.

While many aspects of male contraceptive development remain uncertain—particularly how regulators will approach benefit-risk—there was unanimous agreement that early and sustained engagement with end-users is both feasible and essential. These efforts will inform product development, assess acceptability, and lay the groundwork for future regulatory decisions.

Recommendation: Male contraceptive researchers and developers should prioritize the collection and use of patient experience data throughout the development process and consider how this can be used to support regulatory benefit-risk assessments.

- Given the novel nature of male contraceptives beyond condoms, public perceptions about their acceptability, required attributes, and likely adherence vary widely. Contrary to the common assumption that men will only consider a contraceptive method if it is completely free of side effects, emerging evidence suggests otherwise. Analysis of data from a trial of an injectable hormonal male contraception found that while the frequencies of side effects were comparable to female contraceptive trials, the discontinuation rates were lower for men.[217] In a large, multi-country study by Kaur et al., over 18,000 men were surveyed using a discrete choice experiment that assessed preferences across 11 product attributes, including impact on sex drive, testicular size, ejaculate volume, energy, weight, and mood. The analysis revealed that product form (e.g., pill, transdermal gel, etc.) and timing of administration (e.g., on-demand, daily, etc.) were by far the strongest drivers of men's decision-making – 2 to 4 times more influential than any potential side effect across all countries studied.[28] As such, the initial analysis focused on likelihood of uptake by potential product form and time of use, i.e., on-demand pill, daily pill, on-demand transdermal gel, daily transdermal gel or long-acting vas-occlusive hydrogel. However, subsequent analyses are in process to further investigate the nuanced trade-offs men are willing to make regarding different side effects (unpublished, Kretschmer, 2025).

- The committee had the opportunity to engage in discussions with men and couples who had participated in a Phase 2 study of the male hormonal contraceptive gel combining Nestorone (segesterone acetate) with testosterone (NES/T).[157] These participants offered a range of compelling perspectives. Many were young couples who wished to delay having children for several years. The men often expressed a desire to begin shouldering the burden of contraception. Many had seen their wives try multiple female contraceptive options yet discontinue them due to intolerable side effects. This implies that in the model of shared risk and responsibility, new male contraception methods may be a second- or third-line approach for some couples, where men might be willing to try a product because female products have failed their partner. Formal end-of-

study surveys were collected for this study but have not yet been published.

- Given the absence of precedent for the development and use of male contraceptive drug products, it is essential that developers and researchers proactively characterize user preferences and expectations across a broad spectrum of end-users. These insights can be utilized to establish tolerability ranges—acknowledging that acceptable side effects and risk-benefit trade-offs will differ across individuals, cultures, life stages, and partner dynamics—rather than aiming for a single universal threshold. This includes early and ongoing engagement with potential users through structured approaches such as focus groups and trial-integrated surveys—conducted both prior to and following study participation. In parallel, developers should collect formal patient experience data, including patient-reported outcomes (PROs) and patient preference information (PPI). These data will be critical for articulating the public health need and user acceptability to regulatory authorities. Early dialogue with regulators regarding the design and intended use of these data is strongly encouraged to increase the likelihood of their influence on benefit-risk evaluation.

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