

**ASSESSMENT OF THE CONTRACEPTIVE RESEARCH ACTIVITIES OF THE
Eunice Kennedy Shriver NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN
DEVELOPMENT**

Executive Summary

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INTRODUCTION

The contraception program within *The Eunice Kennedy Shriver* National Institute of Child Health and Development (NICHD) faces a central paradox: contraception has such critical personal, medical and public health benefits, yet the pharmaceutical industry has almost entirely abandoned the field of contraceptive development. This disconnect represents a fundamental public health problem and market failure. As the preeminent leader in contraceptive drug development, the success of the NICHD's contraception programs is more critical now than ever.

In 2011, the NICHD conducted a scientific visioning process to identify the future research priorities of the Institute. This series of meetings engaged experts from multiple disciplines, Institute staff, and the National Advisory Child Health and Human Development (NACHHD) Council. Recommendations generated from these meetings were evaluated and prioritized by NICHD staff and then assembled into a single document summarizing the directions that the NICHD would take in the next decade. Contraception was highlighted as a priority area due to the domestic and global need for new and innovative contraceptive methods to provide a variety of effective and acceptable options across a range of settings and populations. To facilitate coordinated progress in contraceptive research and development, NICHD leadership engaged this review panel (the Panel) of experts in basic, clinical and behavioral research from academia, industry and non-governmental organizations (NGOs). The Panel was charged with assessing both the past accomplishments and impact of the contraceptive initiatives and the current status of contraceptive research and development at the NICHD. It was asked to identify areas for improvement and innovation, and to make specific recommendations for increasing the likelihood of future success.

The Panel worked over a six-month period, focusing primarily on the three NICHD branches most closely aligned with the contraceptive programs of the Institute, namely the Contraceptive Discovery and Development Branch (CDDDB), the Fertility and Infertility Branch (FIB) and the Population Dynamics Branch (PDB). The panel divided its assessment activities into two phases: 1) a review of the previous two decades of contraceptive research and development (R&D; defined in this report as research and development, and related behavioral research) activities at the NICHD with the goal of assessing the accomplishments and impact of the programs that could help inform future recommendations; and 2) a review of specific areas of research and product development with the goal of providing recommendations to improve NICHD-supported contraception R&D activities. Discussions between the Panel and NICHD staff, as well as interviews with experts in the field, were carried out during the assessment.

While the Panel's review of the NICHD's contraception R&D activities and accomplishments identified a number of distinct issues, an overarching concern is that

the NICHD's contraceptive R&D activities do not represent a sufficiently coherent and strategic response to the lack of private sector engagement within this field. The 2004 IOM Report, "New Frontiers in Contraceptive Research: A Blueprint for Action", identified this issue as well, and made multiple recommendations to reengage the pharmaceutical and medical device industries in contraception research and product development. The Panel determined that these recommendations were considered and discussed, but for a myriad of reasons, were not fully implemented. Moreover, the aforementioned 2011 NICHD Scientific Vision Workshop on Reproduction report was explicit in suggesting that NICHD should respond directly to the lack of private sector involvement and that "NICHD would now need to take the lead in contraceptive R&D and change the research paradigm in this field." (Section II.2.3). Despite taking a leading role in *funding* contraceptive research, the NICHD has yet to assume a leadership role in the development of new research paradigms or methods of operation that will achieve optimal success.

The Panel acknowledges the expertise and accomplishments of the NICHD staff working in contraceptive development and the diversity of the research portfolio. Nevertheless, there remains an urgent need for the NICHD to assume a more focused strategic and leadership role during the coming decade. Thus the Panel's report is a critical examination of NICHD activity in light of this new reality. The playing field for contraception R&D is dynamic and the NICHD's contraception R&D initiatives must evolve and adapt to the essential needs of a field desperately in need of guidance and leadership. Thus, the Panel urges the NICHD to assume this leadership role in the field, promoting cutting edge scientific discovery, product development and studies of end user needs and acceptance.

The Panel is pleased to present its recommendations to NICHD in this Executive Summary. Note that the recommendations in this document are not inclusive, but highlight the major areas that the Panel believes need to be addressed. The accompanying Full Report contains the complete process that the Panel used in its assessments and deliberations, all recommendations, the detailed analyses that informed these recommendations, and illustrative ways to operationalize these recommendations. Additional documentation (e.g., meeting minutes, results of interviews, reports of the subcommittees) that may be helpful to the reader is contained in the Appendices.

The Panel would like to thank the NICHD staff for their cooperation, professionalism and patience throughout this process. The Panel also extends its gratitude to both Christine Rogers, MA and Lisa Kaeser, JD for their assistance in planning the face-to-face meetings, scheduling and attending the teleconferences, taking minutes of all of the meetings, providing requested data, and overall guidance.

CROSS-CUTTING RECOMMENDATIONS

The Panel recognizes that the NICHD is now one of the few remaining entities supporting contraception research worldwide and, as a result, is a truly important international resource and standard-bearer in this area. The Panel strongly recommends that the NICHD/NIH continue to support all facets of this critical area of research, including basic research leading to target discovery; product development; and behavioral research to assess user needs, preferences and product acceptability.

The Panel identified several central cross-cutting themes common to all of the contraceptive development activities at the NICHD (*Recommendations 1-8*).

Recommendation #1: Improve Communication

The Panel recommends that improved and more formalized communication be established for all aspects of contraceptive R&D activities (e.g., nonclinical and preclinical development, clinical trials, behavioral research). Specifically, improved communication is needed among the branches focused on contraceptive R&D (i.e., CDDB, FIB, PDB); between these branches and NICHD leadership; and between these branches (especially the CDDB) and other NIH institutes, the scientific community, private industry, and the non-profit sector. The current deficiencies of effective communication and interactions were perceived as a significant weakness, and rapid and dramatic improvement in this area will be critical to the success of the NICHD contraceptive mission. Specific recommendations include:

- It is critical that the CDDB communicate effectively across the branches of the NICHD, and with the NIH, the scientific community, the non-profit sector, industry and relevant regulatory agencies. This role is critical, as the CDDB needs to routinely engage these sectors in order to establish and maintain leadership in contraceptive R&D.
- Increase frequent and formalized communication between NICHD Leadership and the CDDB, FIB and PDB to discuss strategy, the pipeline, and alignment of activities with the 10-year NICHD strategic plan.
- Increase communication among the three branches and potential grant applicants prior to application submission in response to RFAs/RFPs to ensure alignment of proposed research activities with the needs, missions and practical limitations recognized by each of the branches.
- Vet competitively scored contraception-related applications from one branch by the other two branches to ensure optimal alignment with research and/or programmatic needs.

- Improve communication with industry to maximize alignment of interests and objectives, as well as recognize limitations of potential commercial partners.
- Improve communication with non-commercial entities to maximize alignment with domestic and global end user needs and preferences.
- Improve communication of the NICHD's mission to peer review panel members and the scientific community to ensure that reviewers and applicants are aware of the unique needs and requirements associated with contraceptive R&D, and that applications and application reviews are aligned with this mission.
- Convene and support meeting(s) of small and large pharmaceutical companies, foundations, NGOs and NIH-supported investigators to identify needs and develop strategies around early to mid-stage contraceptive development, encouraging focus on later stage clinical development, and aligning regulatory strategy to ultimately increase the likelihood of commercial partnership and product approval.

Recommendation #2: Restructure the Application and Peer Review Process

The Panel recognizes the difficulty inherent in scientific peer review of projects related to contraceptive R&D, as product development involves a vastly different approach and set of disciplines from those normally used by scientists studying basic research or clinical questions. Similarly, the approaches and disciplines of behavioral researchers may not be sufficiently familiar to investigators focused on product development or clinical issues. The Panel was in uniform agreement that a new system of application review is needed to ensure that the mission of contraceptive R&D within the NICHD is fulfilled. A new mechanism of peer review, if developed properly, would also afford the NICHD staff greater input and oversight over the resulting contraceptive development pipeline; this lack of oversight was perceived by the Panel as a major problem. Specific recommendations are as follows:

- Add greater specificity of language in the writing of future RFAs/RFPs to increase the likelihood of receiving applications aligned with the CDDB mission that address the programmatic needs of the contraceptive portfolio.
- Create a standing peer review subcommittee within the NICHD with the proper composition and leadership to ensure alignment of activities with the CDDB mission and goals of the respective RFAs/RFPs.
 - For example, person(s) with a thorough knowledge of reproductive science/medicine as well as drug development should chair peer review panels of drug development applications.

- Develop dedicated Contraceptive Development Review Panels assembled under the auspices of the NICHD similar to the current arrangement for the Reproduction, Andrology and Gynecology Subcommittee charged with well-defined areas for review of research proposals (as opposed to an ad hoc Special Emphasis Panel assembled by the NIH Center for Scientific Review). Such panels would be tasked with reviewing applications that span the nonclinical, preclinical, clinical and behavioral research/product development activities related to contraceptive development, and therefore reviewer expertise could be aligned with the subject material of the respective application pools. Dedicated internal review panels would ensure a more consistent review process aligned with the contraceptive development mission and would give the NICHD program staff greater input over panel composition.

Recommendation #3: Foster Closer and More Productive Interactions with Industry

As stated in previous recommendations, it is advantageous for the CDDB to become more actively engaged with industry, since the NIH does not have the manufacturing and marketing capabilities that industry has, and these capabilities are essential for the full development, dissemination and adoption of new contraceptive methods. Engagement with industry needs to occur at all levels of contraceptive R&D to maximize the opportunity and possibility that a product in development might be licensed out to industry for ultimate distribution in the marketplace, as well as to reinvigorate the interest of industry in this field. The Panel proposes the following recommendations:

- Make more aggressive and effective use of SBIR and STTR funding pathways to stimulate collaborations between investigators and entrepreneurs in order to facilitate contraceptive development and FDA approval and marketing of contraceptive compounds and devices.
- Explore the indemnification of products (i.e., through a product liability exemption) supported and developed through the NICHD.

Recommendation #4: Foster Training in Reproduction Relevant to Contraceptive Development

The Panel acknowledges the significant commitment that the NICHD has to training and workforce development through its T, K and F funding mechanisms, and its investment in training programs where contraception research is the primary focus. For the NICHD to be successful in its mission to develop new and innovative contraceptive products

that are acceptable to industry and used by consumers, there must be a long-term commitment to the training and development of new generations of basic and behavioral scientists and clinicians in the field of family planning. To aid in achieving this goal, specific recommendations are as follows:

- Increase the annual salary caps of the scientists supported by training programs from \$75,000 to at least \$100,000 and preferably to \$125,000.
- Continue and increase funding of training programs specifically devoted to family planning and contraception research. Strategic partnering with organizations devoted to training such as the Society of Family Planning and the American Congress of Obstetricians and Gynecologists could offset costs and organizational responsibility.
- Increase the number of K24 grants for mid-career basic and clinical scientists whose research targets contraception development and related behavioral issues. In addition, consider loosening the eligibility criteria to include those who have a track record of independent research funding in patient-oriented research without specification of the source of funding or the type.

Recommendation #5: Improve Monitoring and Evaluation, and Tracking of Progress

The Panel recommends that the NICHD be more proactive in monitoring and evaluating its contraceptive R&D programs and tracking the outcomes. This issue became apparent during several instances in which the Panel requested from the NICHD staff specific types of information related to contraceptive R&D activities. Overall, it is critical that the NICHD develop progress metrics and monitoring and evaluation (M&E) criteria to be tracked by the investigators and the NICHD staff. Proactive tracking is the only way to objectively assess performance and determine which processes/activities are successful, need to be altered, or should be abandoned. Development of new progress assessment tools and more frequent monitoring of product development and status will help to determine the value of implemented recommendations and will greatly facilitate and improve future portfolio reviews. Likewise, the NICHD should do a better job of monitoring the behavioral research related to contraception, including the extent to which it feeds into contraceptive product development.

Recommendation #6: Increase Diversity

Contraception is a unique, complex and sensitive topic as efforts often are focused on the childbearing of poor and minority populations. As the United States becomes more diverse and globalized, these issues will become increasingly complex, as will the population of contraceptive users. This increasing complexity requires new strategies, and the Panel recommends that the NICHD focus on issues of scientific and workforce diversity as follows:

- Strive to increase the diversity of researchers who conduct contraceptive research. Greater diversity will require increased attention to the pipeline of researchers through better use of mechanisms such as minority supplements to high school, college, and post-graduate students; career development awards; and training programs that target underrepresented populations.
- Strive to increase workforce diversity at all levels of the contraceptive development process by focusing on hiring diverse staffs, ensuring regular cultural competency training, and working closely with Human Resources to learn best practices regarding hiring.
- Create robust relationships with community organizations representing diverse populations (e.g., racial, ethnic, religious, sexual orientation) to better understand concerns and needs related to contraception.
- Increase consideration of issues of diversity within research by ensuring that diverse groups are represented in research populations in clinical and behavioral studies. This population diversity should include geographic, socio-economic, educational, age, physical and cultural aspects.

Recommendation #7: Inclusion of Global Populations

In its deliberations the Panel appreciated that although the primary focus of the NICHD programs in contraceptive R&D has been to develop methods that would be accepted and used domestically, over population and unwanted pregnancy are global issues and therefore global populations must be considered when developing strategies and product pipelines. The Panel recommends increased communication and integration of strategies with other international agencies (e.g., USAID; WHO) and NGOs focused on global health and human development.

Recommendation #8: Pursue Innovative Devices

In its deliberations, the Panel focused largely on the contraceptive development process. However, given the rapid progress in the development of drug delivery technologies and platforms the Panel agreed that the NICHD could play an important role in developing devices/delivery systems that could constitute innovative contraceptive platforms. There are data demonstrating the increasing importance of implants and intrauterine devices in the current mix of contraceptive methods and the public health impact of long acting reversible contraception has proven significant, both domestically and globally. The Panel urges the NICHD to play an important role in bringing new devices to market and supporting post-marketing device and related behavioral research.

The Panel also identified recommendations that are specifically within the scope of the nonclinical/preclinical (**Early Development; Recommendations 9-11**), clinical (**Clinical Studies [Phase I-III], Recommendation 12**), and behavioral (**Social and Behavioral Research, Recommendation 13**) contraceptive R&D and evaluation activities of the NICHD.

SPECIFIC RECOMMENDATIONS FOR EARLY DEVELOPMENT

Recommendation #9: Improve the Early Development Pipeline

The Panel endorses an increased focus on target ID programs in order to improve the product development pipeline. It is the impression of the Panel that recent applications to CDDB were weak, thus precluding the development of a robust pipeline. The following recommendations are made to improve the pipeline:

- The CDDB needs to increase its emphasis on target ID and validation with focused RFAs that contain strict relevant criteria required to be met for both male and female targets.
- More actively monitor the grant portfolio of the FIB for new potential targets; this branch can potentially feed the CDDB pipeline and is a valued asset. As stated earlier, this goal will require enhanced communication and an integrated strategy between the branches.
- Any NICHD funded bioinformatics analyses of identified target strategies should include mining publicly available data and data repositories, as well as

- establishing and/or contributing to public databases as new data are produced.
- Develop an RFA with the goal of curating all potential contraceptive targets from the various large-scale national and international consortia designed to understand gene function (e.g., International Mouse Knockout Consortium).
 - Given that the disciplines applied to drug/product development activities are quite disparate from those used in basic research, multiple funding approaches need to be considered. For example,
 - Shorter funding periods (1-2 years) and smaller budgets (\$100K-\$200K) with very clear milestones and go/no go decision criteria to be met for renewal.
 - Funding through R21, R33, or SBIR (if eligible) grant mechanisms, administrative supplements or through a centralized IDIQ type contract mechanism.
 - It should be noted that contraceptive development activities funded through these types of mechanisms could be carried out independently of any basic research around the respective target (e.g., supported through an R01 mechanism) so that the investigator's basic research program is not penalized in subsequent funding cycles if their product development activities are not successful.
 - Commit to programs until they fail to meet go/no-go criteria.
 - Implement a modified scoring mechanism for drug development program reviews; this mechanism should take into account the required disciplines and associated criteria used in product development, including those recognized by industry and regulatory agencies, as well as those that will promote maximum acceptance and/or utilization among end users.

Recommendation #10: Strengthen Target Selection and Validation Processes

Selection of appropriate targets for pharmacologic modulation is the cornerstone of developing a strong contraceptive product pipeline. The Panel identified several weaknesses in the current strategies used to select and validate new contraceptive targets, and recommends the following:

- Pursue targets that have a highly promising druggable mechanism of action.
- Pursue targets validated with specific and convincing methodologies.
- Evaluate novel methods that allow validation of targets in a manner that strongly suggests that pharmacologic modulation would lead to a contraceptive effect. Such validation approaches should include models of reduced target function

(e.g., “hypomorphs” produced by knock down techniques) as opposed to complete loss of function (e.g., knock out models).

- These aforementioned criteria should be clearly stated in any relevant RFA/PA issued to solicit proposals in these areas.

Recommendation #11: Target Areas of Focus for Early Stage Drug Development Programs

The advances made in the basic sciences with respect to a general understanding of the reproductive system, combined with the advent of the “omics” and its associated technologies, have provided the field of contraception with new strategies and opportunities for the development of new and novel therapeutics. The rapidly expanding areas of drug delivery and device technologies also afford the development of novel contraceptive platforms that can be used in many ways. The Panel recommends development in the following areas:

- Male hormonal contraceptive methods.
- Male non-hormonal contraceptive targets.
 - Within the seminiferous epithelium that inhibit sperm production or function.
 - Although to date the epididymis lacks druggable targets, epididymal targets should be considered if a strong target is identified.
 - Sperm proteomics may provide a rich source of novel targets.
- New or reformulated hormonal methods of female contraception, especially for specific populations (e.g., adolescents; obese women; women who have sex infrequently) and for multiple purposes (e.g., contraception and HIV protection).
- Female non-hormonal contraceptive targets.
 - Although there are very few ovary-specific targets, new strong ovary-specific targets should be considered if identified in the future.
 - Development of reproductive tract-delivered contraceptive approaches that effectively block the function of either the female or male gamete within the female tract on demand (see next bullet point).
- New delivery and device technologies that can be applied to contraception for males and females.
- Development of novel multipurpose family planning products that provide health benefits in addition to contraception (e.g., protection against cancer, bone loss).

SPECIFIC RECOMMENDATIONS FOR CLINICAL STUDIES (PHASE I-III) AND TRAINING

*Recommendation #12: **Contraceptive Clinical Trials Network (CCTN)***

The Panel recognizes the unique and very important role that the CCTN plays in contraceptive development as well as its many challenges. Several recommendations are proposed to make the operation of the CCTN more efficient and effective:

- Re-evaluate the number of female CCTN sites to maximize efficiency and effectiveness, as there does not appear to be enough work for all 19 of the present sites.
- Leverage the CCTN for training and cultivating expertise in contraceptive development. Create more opportunities for face-to-face meetings and collaboration among the female sites, and between the female and male sites to enhance knowledge exchange in collaboration with NICHD staff.
- Establish and utilize a single centralized Institutional Review Board (IRB) that would serve all of the CCTN sites in order to streamline some of the administrative burden and enhance communication and coordination when working with numerous institutions.
- Engage industry to help develop best practices so that the CCTN sites are more attractive to industry for conducting clinical trials.

SPECIFIC RECOMMENDATIONS FOR SOCIAL AND BEHAVIORAL RESEARCH

*Recommendation #13: **Better Integrate Behavioral Research Throughout Contraception Development***

The Panel felt that the research carried out in the PDB is critical to the NICHD mission of reducing unintended pregnancy and therefore should be more closely integrated with the activities of the CDDB. Behavioral research should play a key role in the strategic development of the contraceptive pipeline both on the front end (i.e., informing product needs and types for different end user populations) and on the back end (i.e., user acceptability and practices in the field). There is an opportunity to tackle many outstanding questions about contraceptive behavior and a more integrative approach will yield answers to such questions. The Panel recommends increased consideration of

the behavioral and social dimensions of contraception throughout the development process. To better integrate behavioral research the Panel recommends the following:

- Research the systems and factors that affect contraception acceptance, use and discontinuation.
- Investigate the priorities of both men and women for contraceptives for both their own use and for use by their sexual partners.
- Support new and expanded areas of research that reflect holistic approaches incorporating the physical and social contexts in which individuals live.
- Support studies that investigate quality of life issues related to contraception (e.g., behavioral and mood effects of hormonal and other contraceptive methods being developed by the CDDB).
- Continue and increase attention to the needs and contraceptive use of diverse populations (e.g., adolescents, minorities) in diverse settings.
- Leverage the National Survey of Family Growth (NSFG), the National Longitudinal Study of Youth (NLSY) and the National Longitudinal Study of Adolescent to Adult Health (Add Health) datasets to inform all aspects of contraceptive behavior and use.
- Expand the diversity of study samples through CCTN-supported post-marketing and behavioral studies.
- Focus strongly on communication, translation of findings, and the science of implementing knowledge.

CONCLUSIONS

As stated in this report, the contraceptive R&D programs at the NICHD serve a critical research and training role in the field of family planning. Given the abandonment of this area by private industry, the NICHD now must step up to a leadership role in the development of new and innovative contraceptives. The Panel strongly recommends that the NICHD/NIH continue to support this therapeutic area. However, in order to establish and maintain such a leadership role, the NICHD must evolve and adapt its current approaches to meet the dynamic changes and challenges in this field. The Panel believes that the recommendations it has made, if implemented, will significantly improve the prospects of development and approval of novel contraceptive products that meet the needs of women and men globally.