

**ASSESSMENT OF THE CONTRACEPTIVE RESEARCH
ACTIVITIES OF THE *EUNICE KENNEDY SHRIVER* NATIONAL
INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT**

Full Report

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PREFACE

The contraception program within The *Eunice Kennedy Shriver* National Institute of Child Health and Human 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 NICHD's contraception programs is more critical now than ever.

While the Panel's review of NICHD's contraception-related activities and accomplishments identified a number of distinct issues, an overarching concern is that NICHD's contraceptive development activities do not represent a 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, making multiple recommendations to reengage the pharmaceutical and medical device industries in contraception research and product development. Although these recommendations were considered and discussed, for myriad reasons, they were not successfully implemented. Furthermore, in 2011, the 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, NICHD has yet to lead the field nor develop a research paradigm or method of operating that will achieve optimal success.

The Panel acknowledges the expertise and accomplishments of NICHD staff working in contraception development and the diversity of the development portfolio. Nevertheless, there is a need for a more focused strategic and leadership role for NICHD in 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 research is dynamic, and NICHD's contraception research initiatives must evolve and adapt to the essential demands of a field desperately in need of leadership. Thus, the Panel urges NICHD to lead the field, lead scientifically, and lead in product development.

These general observations led to a series of specific recommendations to advance the overall mission and vision of NICHD in this important field.

INTRODUCTION

I. Background and History of NICHD's Contraceptive Program

Since its inception in 1962, NICHD has been a leader in promoting research in human development. As one of twelve distinct extramural scientific subdivisions, the Contraceptive Discovery and Development Branch (CDDDB) supports research and training programs in contraceptive discovery and development. These activities are also supported by the Fertility and Infertility Branch (FIB) and the Population Dynamics Branch (PDB). Major research areas in the CDDDB have addressed the mechanisms of action and effects of contraceptive and reproductive hormones, drugs, and devices, as well as optimal formulations and dosages of contraceptive agents and spermicidal microbicides. This branch supports several coordinated research initiatives and networks, including the:

- Contraceptive Development Research Center Program (CDRCP), which is funded through a specialized NIH cooperative research center award mechanism (U54) for research into promising new leads for fertility regulation;
- Male Contraceptive Development Program (MCDP), a cooperative research program with contracts to other CDDDB initiatives to expand research into the development of male contraception;
- Medicinal Chemistry Facility (MCF), which uses high throughput screening, modeling, structural biology, synthesis, and biological testing to support research on the discovery, optimization, and development of female and male contraceptive agents;
- Chemical Synthesis Facility, which synthesizes and investigates the properties of chemical entities and their intermediates as potential male and female contraceptive agents;
- Peptide Synthesis Facility, which synthesizes peptides unavailable from commercial sources for a variety of research uses, including animal model and other preclinical research, clinical research, and studies of pharmacokinetics and metabolism (this program has now been terminated);
- Biological Testing Facility, which evaluates new drugs, formulations, and delivery systems for compounds of interest to contraceptive and reproductive health research; and
- Contraceptive Clinical Trials Network (CCTN), which performs multi-phase clinical trials on potential female and male contraceptives.

Through these centralized facilities and other supported efforts, NICHD's contraceptive programs have led the nation in determining the safety, efficacy, and optimal delivery and usage of female and male contraceptives. Over the years, NICHD research has been a key player in informing concerns about widely-used contraceptive methods, including oral contraceptive pills, intrauterine devices, and vasectomy. Ongoing work into the discovery and development of new and improved contraceptive methods, including a long-acting male contraceptive, holds great promise for the future.

II. The Importance of Contraceptive Research

The importance of contraceptive research cannot be overstated, as data indicate that nearly all American women use some form of contraception during their lifetimes. According to the National Survey of Family Growth (NSFG) for 2011-2013, approximately 62% of women aged 15-44 were actively using some form of contraception – a rate consistent with the previous five years. The oral contraceptive pill remains most popular (16% of all women currently using contraception use this method), followed by female sterilization (15.5%), male condoms (9.4%), and long-acting reversible contraceptives (LARCs; 7.2%). Use of any method differed markedly by age and race/ethnicity. For example, a larger percentage of women above age 25 ($\approx 68.7\%$) than women aged 15-24 (47.4%) were currently using contraception; likewise, a greater proportion of non-Hispanic white women (65.3%) than Hispanic (57.3%) and non-Hispanic black (57.9%) women used contraception. These rates did not vary by educational attainment, hovering between 67 and 69% across the board. However, use of each type of contraception significantly varied by age, race/ethnicity, and education for all methods except the male condom. In terms of age, female sterilization is highest among women aged 35-44 (31%); pill use highest among women aged 15-24 (22.4%); and LARC use highest among women aged 25-34 (11.1%). Non-Hispanic white women exhibited the lowest rates of female sterilization (14%) and highest rates of pill use (19%), while non-Hispanic black women had the lowest rates of LARC use (5%). Female sterilization declined and pill use increased with greater educational attainment. These data speak to the importance of having a mix of contraceptive methods that provide an array of choices to meet the needs of individuals in different settings and at various stages of their reproductive lifecycles.

As important as the current contraceptive choices are to women, the uptake and continuation rates of these methods are quite variable and are far from optimal. Almost half of all pregnancies in America are unintended, and among unintended pregnancies, almost half end in abortion. These rates are still unacceptably high and have tremendous impact on women, their families, and society in general. Among the many factors influencing suboptimal contraceptive use and continuation are accessibility, cost, safety, side effects, and efficacy in specific populations (e.g., obese women). Thus,

there is a need for the development of new generations of contraceptives that address these issues. In addition, new contraceptive modalities would increase choice and add to the contraceptive mix needed to meet the needs of individuals throughout their reproductive lifespans.

III. A Vision for NICHD

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 NICHD would take in the next decade.

Contraception was highlighted as a priority area due to the domestic and global need for innovative approaches to family planning. In particular, the report highlighted the significant individual, family, societal, and environmental effects of rapid population growth and persistently high rates of unintended and unwanted pregnancy, despite the ever-increasing availability of contraception. A critical review of research efforts toward the development, clinical testing, and behavioral dimensions of existing and novel contraceptive methods appeared warranted in order to ensure 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 the current status of contraceptive research and development at the NICHD, identifying areas for improvement and innovation, and making specific recommendations for increasing the likelihood of future success.

IV. The Panel's Approach

The process began with a conference call on June 9, 2014 with Drs. Alan Guttmacher and Catherine Spong, during which the full Panel was given its charge. Based on the overall goals of the project, the Panel decided to split the work into two phases. Phase One, conducted from June 9, 2014 to September 17, 2014, focused on (1) NICHD programs' accomplishments in the areas of contraceptive development, contraceptive use, and research workforce development; (2) the impact of NICHD's programs in these areas; and (3) non-NICHD activities related to contraception research and development (see Appendix A for the composition of these subcommittees). The Accomplishments Subcommittee, led by Dr. Carolyn Halpern, focused on summarizing accomplishments over the past two decades and held three teleconferences. The Impact Subcommittee, led by Dr. Daniel Johnston, focused on the measurable impact of NICHD's work and

held five teleconferences. Relevant non-NICHD activities referred to activities related to contraceptive development outside of NICHD (both within and outside of NIH). This subcommittee (Non-NICHD Activities Subcommittee) was led by Dr. Patricia Morris and held three teleconferences. Each subcommittee created a written draft of their findings that was circulated to the full Panel prior to an in-person meeting at NICHD on September 17, 2014 (Appendix B). One or both Panel co-chairs (Gilliam, Kopf) attended all subcommittee meetings to ensure consistency across meetings. NICHD staff members also attended all subcommittee calls to provide administrative support and institutional knowledge. In addition, the Panel co-chairs conducted 12 key informant interviews with leaders in the field chosen by Panel members (a list of the names of the key informant interviewees, as well as the types of questions asked, is in Appendix C).

During the September 17, 2014 meeting, the Panel met with Drs. Guttmacher and Spong. In addition, the Panel heard from the Directors of the CDDB, FIB, and PDB; held their own deliberations; presented results from the key informant interviews; and discussed their findings.

Following the September 17, 2014 meeting, the Panel entered into Phase Two of the process. Phase Two focused on developing Panel recommendations to take forward into the final report. The Early Development Subcommittee was led by Dr. Daniel Johnston and held seven teleconferences, including two with Grants and Contracts to understand those mechanisms. The subcommittee addressing Phases I-III of the contraceptive development process was led by Dr. William Bremner and held five teleconferences. The subcommittee addressing behavioral research was led by Dr. Carolyn Halpern and held five teleconferences. (The composition of each of these Phase Two subcommittees is shown in Appendix A.) One or both Panel co-chairs (Gilliam or Kopf) attended all subcommittee meetings to ensure consistency across meetings. Each of the three subcommittees prepared a report following their deliberations and a PowerPoint slide deck summarizing their findings in preparation for a face-to-face meeting at NICHD of a majority of the Panel on December 9, 2014 (Appendix D).

During the two in-person meetings of the Panel at NICHD (September 17 and December 9), the Panel met with the following staff members: Alan Guttmacher, MD; Catherine Spong, MD; Caroline Signore, MD, MPH; Louis DePaolo, PhD; Mona Rowe, MCP; Sarah Glavin, PhD; Trent MacKay, MD, MPH; Diana Blithe, PhD; Rebecca Clark, PhD; Alice Pagan Pereira; Lisa Kaeser, JD (Administrative); Christie Rogers, MA (Administrative). Eugene Hayunga, PhD, was interviewed by the Early Development Panel by phone; and Min Lee, PhD, and Trent McKay, MD, MPH, were interviewed in person by Dr. Johnston.

The Panel also wishes to extend its gratitude to both Christie 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.

PHASE ONE: ASSESSING THE LAST TWO DECADES OF NICHD'S CONTRACEPTIVE DEVELOPMENT PROGRAMS

I. Accomplishments of NICHD's Contraceptive Development Programs

A. Contraceptive Development

NICHD is the only institute focusing on the development of new and innovative contraceptive methods. There are several key contract entities – the Biological Testing Facility, the Chemical Synthesis Facility, the Peptide Synthesis Facility (no longer functioning), and the Medicinal Chemistry Facility – that conduct biological and chemical studies to support product development. The Contraceptive Clinical Trials Network (CCTN), in place since 1996, conducts Phase I-IV contraceptive trials for drugs and devices. Since its inception, the number of trial sites has increased: there are currently 19 sites for studies of female contraceptives, two for studies of male contraceptives, and one Drug Consultation Center (DCC). CCTN maintains a leadership position in microbicide and intravaginal ring-based contraception trials and is the only group to have run trials on male contraceptive agents. It has also led a number of clinical trials in the areas of spermicide development, emergency contraception, and other female contraceptives. Trials of ulipristal acetate have led to the development of products for emergency contraception (Ella; EllaOne) and uterine fibroid treatment (Esmya) currently on the market. The CCTN as a whole has done well, and this network will be critical to NICHD's leadership of the field.

B. Contraceptive Use

In terms of behavioral research, there are accomplishments stemming from both independently-funded research programs and NICHD partnerships; these activities often overlap and are complementary. NICHD support for national studies that can be leveraged by many users has clearly been an outstanding investment. The cross-sectional NSFG allows ongoing surveillance of contraceptive behavior and outcomes, as well as the opportunity to look at trends across time. Such ongoing data collection has provided a mechanism for scientists within and outside of NICHD to identify gaps in the current knowledge base. The National Longitudinal Survey of Youth (NLSY), while not intended to focus on fertility and contraception, offers important cross-generational information about contraceptive behavior and the factors affecting it. Similarly, the National Longitudinal Study of Adolescent to Adult Health (Add Health), which has received funding from multiple NIH institutes and federal agencies but has been housed at NICHD as its primary funder, provides another opportunity to look at individual

contraceptive behaviors over time. There are hundreds of publications and scientific presentations that use these datasets to investigate contraception and broader related areas such as fertility, family formation, family planning, and unintended pregnancy.

Independent research projects, both “primary contraception research” and studies that use national datasets supported by NICHD and other data collection efforts, have generated critical surveillance information across time and socio-demographic groups. These projects have documented the prevalence and patterns of contraceptive use, reasons for method selection and discontinuation, contraception access, method-mixing trends, and aspects of unmet need. In addition, NICHD-supported research has illuminated population-based disparities in knowledge (e.g., what contraception options exist, actual contraindications versus myths, etc.) and has helped to disentangle the roles of access and knowledge as contributors to the contraceptive mix. Important research has also focused on the roles of partners and relationship dynamics in contraceptive use and continuation. An essential aspect of current research has examined the fit (or lack of fit) between users’ characteristics (e.g., age, socio-economic status, lifestyle, stress/depression, violence victimization, cognitive capacity) and social and physical contexts (e.g., fertility norms, community infrastructure/access issues, culture, gender roles), on the one hand, and the attributes and requirements of various contraceptive methods, on the other. These research lines inform behaviorally-based interventions to promote effective contraception.

NICHD-supported research has also yielded important information about healthcare provider knowledge and practices. For example, provider identification of candidates for certain methods and counseling strategies related to method selection (e.g., start by discussing LARCS) have been assessed. Reproductive coercion, and consistency between health counseling approaches that are in use and behavioral science theory and evaluation data have also been studied.

This broad research base has helped to inform important recommendations from the American Congress of Obstetricians and Gynecologists (ACOG), including:

- Distribution of oral contraceptives over the counter;
- Guidelines for physicians to deal with issues of reproductive coercion; and
- The safety and suitability of long-acting reversible contraceptives (LARCs; intrauterine devices and the contraceptive implant) for adolescents.

C. Research Workforce Development

NICHD commits approximately \$1,000,000 per year toward training in programs where contraception research is the primary focus. In addition, however, other training mechanisms (e.g., T32s, funded at \$2,600,000 in FY 2013) offer broader training support to develop skilled researchers in the health and behavioral sciences who will conduct research related to contraception and fertility. The K and F mechanisms have been exceptionally successful in terms of identifying promising candidates and training investigators: 75% receive subsequent competitive funding. Similarly, in FY 2004-2013, 22% of the 90 distinct R, P, and U grants in the contraceptive portfolio went to new investigators. The NICHD-supported Contraceptive Development Research Center Program, which uses the U mechanism, also offers opportunities to support the researcher pipeline through hands-on activity. An additional notable accomplishment is that the number of contraception-related publications appears to have increased over time, despite a relatively flat grant portfolio.

II. Impact of NICHD's Contraceptive Development Programs

A. Contraceptive Development

In general, the impact of funding in areas directly and peripherally related to contraception is strong in basic biomedical preclinical exploratory research. For example, research in the area of reproductive biology routinely identifies gene products that play key roles in reproduction, and evaluating those identified gene products and their associated pathways is a valid strategy for identifying new and novel contraceptive targets. NICHD has allocated research funding to both female and male contraceptive methods and contraceptive development. Data were not available, however, to allow itemization of either the number of grants or total spending invested into exploratory and preclinical work, preclinical and predevelopment work, behavioral studies, or clinical development. Such analyses would allow a clear assessment of investment over the entire project/product pipeline and would elucidate gaps within the pipeline. Development of new metric tools to track such information in the future would contribute to a more robust analysis of NICHD contraception research programs.

The best available index to measure research impact is publications, and the number of publications per grant is impressive (approximately 10 per grant). Studies were most often published in well-respected journals such as *Biology of Reproduction*, *Contraception*, and the *Journal of Andrology*. The citation index for publications is excellent; however, a significant percentage (about 10%) had never been referenced, indicating a low impact in these cases. In terms of research area, there were few identifiable publications from the predevelopment phase (the IND supporting phase),

though it is unclear whether this is due to a lack of pre-development programs or simply a lack of publications about such efforts.

Many studies have been coordinated and completed in both women and men, yielding a series of excellent publications. One agent for women, ulipristal acetate (Ella) for emergency contraception, has been supported by the CDDB from NICHD-supported basic research and proof-of-concept studies all the way to FDA approval and marketing. Recently, the European Medicines Agency's Committee for Medicinal Products for Human Use recommended a change in classification to non-prescription status for another ulipristal acetate emergency contraceptive (ellaOne). Therefore, this NICHD-developed contraceptive product (CDB-2914) demonstrates that effective partnerships have been forged through CDDB's joint research and development efforts with institutions/NGOs (e.g., Population Council) and industry (e.g., HRA Pharma). Several other hormonal and nonhormonal agents are in various stages of development for women and for men. Overall, with the departure of some foundations (e.g., Rockefeller, Mellon) and big pharmaceutical companies from the area of contraceptive development, NICHD's impact on new generations of female contraceptives and the creation of ground-breaking male contraceptives will become more important in the future.

Data from the clinical trials provided by NICHD indicate that most trials have had at least one related publication. Outcomes of distinct trials coordinated through the CCTN could be combined for publication; therefore, it is not unreasonable to expect the number of publications from these activities to be low in comparison to those from non-clinical research activities. Yet, some clinical trials that concluded in the last two or three years still lack publications, which is of concern.

B. Contraceptive Use

Overall, the impact of NICHD's behavioral research is fairly strong in terms of funding and publication record. NICHD has funded a number of studies related to contraceptive use in the past decade, including roughly 15 R01s, 11 R21s, 10 R03s, and four K awards. However, it is unclear which of these proposals specifically pertain to contraception or contraceptive development, as proposals have included studies of HIV-related fertility behaviors, sexuality, sexual violence, and family communication. The portfolio has also attended to a number of specific populations, including racial and ethnic minorities, incarcerated women, women in violent relationships, and couples with HIV. Funding for international public health research related to contraception has been limited: few studies have dealt with global family planning, and those that do, with few exceptions, address it in the context of global HIV.

Some researchers funded by NICHD appear to have a strong publication track record, one index of impact. Articles have been published in high-impact journals like *Obstetrics and Gynecology*, *Contraception*, *Demography*, and *Perspectives in Sexual and Reproductive Health*. In addition, the NSFG serves as the basis of many of these publications. Nevertheless, when considering the studies specifically related to contraception and contraceptive behaviors, approximately one-third of these studies have not yet resulted in publications – a noticeable deficit.

In addition, NICHD funding has been an important contributor to public health outcomes. Studies supported by NICHD have been fundamental to our understanding of fertility and reproductive behaviors in the US. Specifically, the NSFG serves as an important foundation for many current research questions. NICHD has also funded analyses of these data through R01s. Terms like “unintended,” “mistimed,” and “unwanted” pregnancies have been defined through the NSFG.

The NSFG also tracks contraceptive behaviors over time and has influenced our understanding of contraceptive misuse. Other NICHD behavioral research has better informed our understanding of adolescent contraceptive behaviors. In particular, studies have illuminated contraceptive use patterns and early discontinuation rates of methods such as depot medroxyprogesterone acetate (DMPA). These studies are important, as they demonstrate that individual behavior is nuanced and likely to be missed in large cross-sectional studies.

There has been great success in the field of family planning. In particular, NICHD-funded research has had a strong impact on adolescent contraceptive behaviors and pregnancy rates. Teenage birth rates in the US are at an unprecedented low: the rate fell 57% between 1991 and 2013, and this decrease is seen for all races and Hispanic ethnic groups. These changes have been attributed to greater method use, decreases in sexual activity, and method mix. While one can argue that a confluence of factors has led to changes in method mix among adolescents (e.g., the advent of long acting reversible contraceptives, national attention toward teen pregnancy, the FDA black box warning for DMPA), NICHD-supported studies showing high discontinuation rates of methods have played an important role in the acknowledgement of and need for a greater method mix. Many additional governmental and non-governmental organizations (NGOs) have taken a significant interest in this issue, both domestically and globally, and have also made contributions.

With respect to male contraception, the data do not allow us to connect the male contraceptive development programs to public health gains at this time. This finding is to be expected given the limited number and development status of male contraceptives. On the other hand, NICHD has funded the NSFG, which has been used to document

male fertility and condom use behaviors. NSFG data has been very significant in describing later sexual debut for African American and Latino males, increased condom use, and safer sexual behaviors than in the past. In addition, NICHD has funded a number of studies on the male condom, particularly in relation to HIV/AIDs and fertility behaviors both domestically and globally.

Finally, NICHD has funded research with policy implications for improving access to contraception. These studies have covered direct pharmacy access and research along the US-Mexico border. While arguably there is no over-the-counter access to birth control, studies that have demonstrated the safety of pharmacy access and self-prescribing have had implications for access to emergency contraception.

C. Research Workforce Development

Overall, the number of funding opportunities available to trainees in the reproductive sciences (including contraception) through the training (T32), postdoctoral (F32), new investigator (Ks), and NICHD-supported programs with a women's or men's health focus is large. Numerous opportunities are available for MD, PhD, and non-terminal degree individuals. The postdoctoral and new investigator awards are extremely important in ensuring the future success of contraceptive research and development.

Although the number of training opportunities is seen as a plus, the training data are not strictly in the field of contraception, but also include the general discipline of reproductive biology and medicine. An additional gap is that the historical data are not of sufficient detail to assess the impact of training over the last 20 years. Instead, the data are in terms of overall trainee figures (representing multiple disciplines in the reproductive sciences), grant application counts, and funding percentages – which may indicate utilization, but not necessarily impact. Although the ability to attract subsequent funding (e.g., R01) by trainees looks, in some cases, to be positive (and would be considered a high impact endpoint), it is unclear whether the results are attributed to a small number of trainees with very high individual success rates or to the percentage of the trainee pool in general. Importantly, the data also do not indicate the percentage of trainees that remained in practice, either within basic research or within the biomedical sciences – a key measure of downstream scientific impact. More specific data collection mechanisms will need to be implemented to monitor and track trainee performance and retention in the area of contraceptive research and development. A more proactive, robust, and granular assessment of all training programs that relate to contraception would then be possible and would inform strategies and priorities moving forward.

III. Role of Non-NICHD Entities in Contraceptive Development

Overall, data show that NICHD is a major driver of contraceptive discoveries and research, both in basic/preclinical research and in clinical development. The 2011 NICHD Scientific Vision Workshop on Reproduction white paper highlighted the role of NICHD in supporting the development of new contraceptives, as well as the need for collaborations with other organizations to leverage assets and bring new products to the marketplace.

A key component in NICHD's contraceptive research and development strategy has been building alliances with major stakeholders, including industry, funders, donors, advocacy groups, scientists, reproductive healthcare and family planning professionals, organizations and research institutions, government agencies, and the public. There are additional partnerships that exist between non-NICHD organizations and institutions with both US and non-US governments to advance family planning and reproductive health services; introduce, improve, and expand use and efficacy of methods for contraception; increase user-appropriate contraceptive choices; and implement family planning services and product introduction.

The Non-NICHD Activities Subcommittee generated a table listing key non-NIH players, indicating their respective roles in the product discovery and development path continuum through new contraceptive product introduction (see attached spreadsheet in Appendix E; key players highlighted). Pharmaceutical companies, academic institutions, NGOs, clinical/contract research organizations (CROs), and domestic and international government agencies have played different roles in contraceptive development. Some relationships are competitive; other research and product development interactions and partnerships could be further expanded and better leveraged at different stages. Other non-NICHD donors and funders of contraceptive development include other NIH institutes as well as private foundations. It should be noted, however, that foundations largely support funding opportunities for later stage activities in the process (e.g., pre-development activities, activities for IND and FDA submissions, post-Phase III required regulatory and safety monitoring activities, product registration fees, and product introduction and distribution).

Strategic business leaders in the pharmaceutical industry have shied away from contraceptive development for many reasons. These reasons include lower-cost products already on the market; potential liability issues; profit/risk assessments; a perceived wide array of effective products already on the market, including those available over-the-counter in other countries that impact potential profits from developing markets; little industry desire to invest the finances required to bring

prospective contraceptive products through early research and development stages; and the associated costs of IND and clinical trials.

With the exit of large pharmaceutical companies from contraceptive research and development, NICHD has now become the major funder of early research and development activities that could lead to new and innovative contraceptive products for both females and males. As stated above, however, it will be essential for NICHD (and its grantees) to engage with many of these aforementioned organizations to eventually fulfill its mission to bring new and novel contraceptives to the marketplace.

PHASE TWO: PANEL RECOMMENDATIONS

I. Cross-Cutting Recommendations

The Panel developed a series of recommendations pertaining to NICHD contraceptive development programs as a whole. Some of these are further elaborated upon, as they pertain to an individual subcommittee's work. Where possible, the Panel offers ways in which these recommendations can be operationalized.

A. Improve Internal and External Communication

Communication is one of the most critical areas for improvement regarding all aspects of NICHD's work. In early drug development, there are multiple areas where improved communication between the CDDB, other branches involved with contraceptive development (i.e., FIB, PDB) and other entities (e.g., industry, investigators) may improve the function and likelihood of achieving the CDDB's mission. *The Panel strongly recommends that a critical selection criterion for the next CDDB Chief be the ability to be an effective convener and communicator, as communication across branches of NICHD, NIH, the scientific community, and industry is crucial.* Specific recommendations regarding communication are detailed below.

The Panel recommends regular strategic meetings among the leadership of the three branches (CDDB, FIB, and PDB) and senior NICHD leadership. These conversations should focus on pipeline development and management, how the branches can work together to improve the quality of contraceptive programs entering the pipeline, and the appropriate and efficient progress of those projects through the pipeline. Alignment with the 10-year plan of NICHD (see the NICHD Visioning document) should be a guiding principle. In addition, regular meetings between the staff of the three branches should be held to implement the leadership strategy, discuss new trends and opportunities, and troubleshoot problems/issues as they arise.

Each branch has a specific and important contribution to make to the early development process. For example, input of the PDB could be particularly valuable in developing Target Product Profiles (TPP) for potential types of contraceptives to be developed for men and women (e.g., non-hormonal and hormonal contraception; gels, intrauterine devices, and other delivery systems for contraception; and/or multi-purpose technologies such as contraceptive/HIV prevention or contraceptive/non-infection based health benefit). The PDB could also have valuable input when products move toward clinical testing, such as in regard to acceptability aspects and questionnaires that could be used in conjunction with the clinical trials. While effective target identification

programs need to be identified and supported by the CDDB, targets will also arise from research within the FIB portfolio. In this regard, the FIB can serve as a potential target conduit for the CDDB. Proper and timely communication between the CDDB and FIB will be critical to ensure that the best and most promising targets are identified and presented to the CDDB for further consideration and potential development.

In addition, the *Panel recommends improved communication with non-commercial entities*. Advisory input could be effected by an annual assembly of a committee of experts/consultants from industry (e.g., medical, marketing, business), foundations, NGOs, and academia that would work with the leadership of the CDDB and CCTN Scientific Advisory Board to provide advice/recommendations to the CDDB and NICHD leadership. These meetings would provide a more global perspective of need and best products, identify industry contacts, and develop strategies about how to better approach industry.

The Panel recommends improved communication in the form of broadcasting/publicizing the NICHD mission with peer review panel members and the scientific community. The stated mission of the CDDB is, “To reduce unintended pregnancy by developing safe, easy-to-use, long-lasting, acceptable, effective contraceptive products/methods for women and men.” Yet this mission is not well known to most participants of peer review panels; thus, the statement should be provided to these panel members. The mission is also not well known or understood by many in the field of reproductive biology. To educate these groups and the field at large, the CDDB should identify effective outreach mechanisms to “spread the word” of its mission. This communication can be accomplished via web-based information outlets, publications, presentations at reproductive biology/medicine meetings, and sponsored symposia. Target Product Profiles (TPPs) should be written and used as examples. Communication with other government research entities such as NIEHS, NCATS, and NIAID are encouraged to make sure the CDDB’s mission is known and to increase the likelihood of identifying new and novel contraceptive targets.

In addition, NICHD has an important role as a global communicator and translator of scientific information for consumption by lay people and the public at large. In reviewing the accomplishments and impact of the behavioral branch there appear to be missed opportunities to ensure that the impact of NICHD’s work is appreciated and understood by others. NICHD should consider issuing RFPs for dissemination of findings, including specific language to guide investigators in describing dissemination plans for diverse audiences.

B. Restructure the Peer Review Process

During the Panel's deliberation, staff and key informants raised concerns about the expertise of peer review panels in regard to contraceptive development and contraceptive behavior. Concerns were raised that current practices, such as adding ad-hoc members to standing study sections, are inadequate for optimal review of contraception-related proposals. Typically, these individuals are not already members of standing study sections and are assigned specific grants relative to their particular (often narrow) area of expertise, restricting their familiarity with study section proceedings and influencing the review. As the number of researchers in family planning increases, there is opportunity to address these deficiencies. Thus, *the Panel recommends modifying the peer review process for work directed toward the development of new contraceptives*. In particular, consider developing a Contraception and Family Planning Subcommittee (or similar title) composed of individuals highly knowledgeable in the relevant basic, clinical, and population sciences, as well as in product development. This study section could address the breadth of research activities related to contraception.

C. Foster Closer and More Productive Interactions with Industry

The Panel recommends that NICHD identify more effective ways to engage and interact with private industry. The ultimate success of NICHD in contraceptive development will rely on re-engaging industry in all aspects of the drug development process, since NICHD lacks the large-scale manufacturing, marketing, and distribution capabilities of industry and industry will only commit these resources to products that they deem valuable to their therapeutic pipelines. Therefore, engagement of industry in the early drug development process will help to ensure their continued engagement in later development phases and marketing of the drug. Thus, *the Panel recommends that NICHD explore how to more effectively facilitate the use of Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) pathways for investigators and entrepreneurs, in turn helping to facilitate FDA approval and marketing of contraceptive compounds and devices*.

D. Foster Training in Reproduction Relevant to Contraceptive Development

The Panel is very supportive of the T, F, and particularly K series of grants that can be used for young MDs and PhDs who are developing their skills as biomedical, behavioral, and population scientists. RFAs may be appropriate to encourage young clinical and basic investigators at the start of their independent careers to focus on family planning research and contraceptive development, as well as to foster the further training and involvement of their mentors. *The Panel recommends that the cap on*

salary awards on NICHD-supported K awards be increased to at least \$100,000 annually, preferably to \$125,000. The current award levels have generally stayed at \$75,000 since these programs were initiated approximately 20 years ago, despite increases in salary levels required to recruit physician investigators, increased costs of living, and dramatic increases in educational debt, which is now incurred by nearly all young investigators. The Panel also encourages NICHD to seek opportunities to partner with other organizations dedicated to training and workforce development, such as the Society of Family Planning.

The Panel recommends an increase in the number of K24 grants for mid-career basic and clinical scientists whose research targets contraceptive development and related behavioral issues. *The Panel also recommends that the eligibility criteria for K24 mid-level career development grants be loosened 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.* This modification would enable more applicants and emerging researchers at a time when NIH funding is constrained.

E. Improve Monitoring, Evaluation, and Tracking of Progress

The Panel recommends that NICHD do a better job monitoring its contraceptive development programs and tracking outcomes. This issue became apparent during instances in which the Panel requested from NICHD staff specific types of information related to contraceptive development activities. For example, to determine research productivity, the Panel had to tally publication from the NIH database. Overall, it is critical that NICHD develop progress metrics and monitoring and evaluation (M&E) criteria to be tracked by the investigators and 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, which will greatly facilitate and improve future portfolio reviews. Likewise, 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.

M&E are central to assessing the impact of research and training efforts and determining optimal use of limited funds. These efforts are especially challenging for behavioral contraception research because of the unavoidable intersection of contraceptive behavior with other behavioral domains and interpersonal interactions. Developing and implementing explicit guidelines for grant/contract recipients to document progress in publications, knowledge gains, training, and practice/policy impact related to contraception and family planning are needed for effective monitoring

and evaluation. Where appropriate, have training programs track former trainees' later family planning/contraception research.

F. Increase Diversity

Contraception is a unique, complex, and sensitive topic, as efforts are often focused on the childbearing of poor and minority populations. As the US becomes more diverse and globalized, these issues will become more complex, as will the population of contraceptive users. Diversity is one of the shifting dynamics that NICHD must embrace. The Panel recommends that NICHD focus on issues of scientific and workforce diversity as follows.

- *Increase the diversity of researchers who conduct contraceptive research.* To do so, NICHD should prioritize and expand funding of minority supplement grants to high school, college, and post-graduate students. This relatively modest investment has the potential to enhance the pipeline of young investigators of color. Perform greater outreach to Historically Black Colleges, Hispanic Serving Institutions, and diverse communities to increase awareness of these opportunities. Partner closely with the Office of Minority Health and NIH's Chief Officer for Scientific and Workforce Diversity.
- *Increase workforce diversity.* Focus on hiring a diverse staff, ensure staff undergo regular cultural competency training, and work closely with Human Resources to learn best practices regarding hiring. Actively seek to reduce unconscious bias in study sections by ensuring that members are of diverse backgrounds.
- *Create robust relationships and communications with community organizations representing diverse populations (e.g., racial, ethnic, religious, sexual orientation) to understand their 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.

G. Include Global Populations

During its deliberations, the Panel appreciated that although the primary focus of NICHD programs in contraceptive development was to develop methods that would be accepted and used domestically, overpopulation and unwanted pregnancy are global issues. Global populations must be kept in mind when developing strategies and product pipelines. Global health is an area where communication and integration of strategies with other international agencies (e.g., USAID, WHO) and NGOs focused on human development may be particularly fruitful.

H. Pursue Innovative Devices

While the majority of recommendations relate specifically to the contraceptive development process, the Panel notes that many activities are also relevant to device development. Given the rapid progress in the development of drug delivery technologies and platforms, the Panel agreed that NICHD could play an important role in developing devices/delivery systems that 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 NICHD to play an important role in bringing new devices to market and supporting post-marketing device and related behavioral research.

In addition to recommendations developed by the full Panel, additional recommendations have evolved from the work of three subcommittees tasked with developing specific recommendations related to the Early Development, Clinical Studies (Phase I-III) and Training, and Behavioral Research activities of NICHD in the area of contraceptive development. Where possible, the Panel proposes ways in which these recommendations can be operationalized.

II. Early Development

These recommendations by the Early Development Subcommittee are made following a review of the drug discovery and development processes currently used in the NICHD Contraceptive Discovery and Development Branch (CDDDB) and other branches that impact NICHD's contraceptive development programs (i.e., FIB, PDB), from Target Identification (target ID) through Investigational New Drug (IND) approval. Several key areas have been identified where changes in approaches and processes may significantly enhance the effectiveness of the CDDDB in delivering novel and needed contraceptives to the marketplace. Information supplied to this subcommittee during their deliberations came from multiple sources, including NICHD staff; leadership of the

CDDB, FIB, and PDB; key informant interviews; and professional experiences of the subcommittee members.

A. Improve Internal and External Communication to Benefit Early Development Activities

*The Panel recommends improved communication between the CDDB, FIB, and PDB as well as with potential applicants prior to application submission. Support for contraception research and development is provided through the CDDB, FIB, and PDB, and all three branches need to be engaged in this mission. Together, these branches have the potential to form an effective consortium to assist applicants in preparing proposals to develop novel contraceptives. This assistance could come in the form of scientific discovery and understanding, target identification and validation, drug development, regulatory compliance, and social acceptance/implementation. Few applicants are likely to have a full understanding of all of these aspects of drug development and, without this knowledge, are at a disadvantage in putting together a proposal that meets the needs of the mission of NICHD in contraceptive development. What might appear to be an efficacious contraceptive development approach to an expert specializing in one branch may have features that are recognized as suboptimal by an expert in a different branch. Proposals for targets submitted to either the FIB or the CDDB, which may appear promising from the standpoints of both biological efficacy and drug development, might lack key demographic or social characteristics that will have a positive impact on acceptance among patient populations. *To minimize the risk of these potential pitfalls, the Panel recommends the development and implementation of a new and structured system of communication among the three branches such that PIs may submit applications to any of them, simultaneously conveying expertise from all three branches to the PIs and improving the overall scientific approach.**

Two potential models could be considered for implementation. First, an initial consultation service could be offered to investigators who may be looking to expand the scope of their current basic research program toward product development prior to application submission or who are seeking to identify new targets for drug discovery. This service could provide important insight from the PDB about the future likelihood that any newly proposed approach will be acceptable to users once developed. Implementation of this plan has the potential to optimally inform new research proposals via communication between investigators and NICHD, in addition to promoting enhanced communication among the three relevant branches within NICHD.

Second, applications that score well following relevant peer review and are thus strong candidates to be put forward by any one branch could be vetted by the other two branches. The goal would be to 1) point out to the primary funding branch additional considerations that the investigator might wish to incorporate into his/her project design

to better facilitate efficient future discovery/implementation/acceptance of the proposed approach; or 2) identify potential pitfalls in the application not generally recognized by investigators, panel reviewers, or even program officers in the primary funding branch that may be highly relevant to the potential success (or lack thereof) of any newly proposed approach, as perceived by experts in either of the other two branches.

Next, *the Panel recommends improved communication with potential industry partners.* Ultimately, any contraceptive development program has to be of interest to a commercial partner. Currently, there are no adequate mechanisms to understand the strategic, financial, and procurement interests of potential partners. Commercial input on potential programs of interest should be sought at least annually by the CDDB and lead by the CDDB Chief. Information from these meetings should be considered when creating RFAs, made known to review panels, and become a key part of the review process for any program prior to initiating IND-enabling studies, IND writing, and/or IND submission processes. Importantly, communications with potential commercial partners should not solely be about what commercial entities desire for licensing; NICHD must also educate potential partners about the technologies and potential products/methodologies available.

B. Target Selection and Validation

Selection of appropriate targets for pharmacologic modulation is the cornerstone of developing a strong contraception pipeline. Proper selection of targets is based on identifying those with a mechanism of action amenable to pharmacologic modulation, strong validation, proper delivery, and the likelihood of having a limited side-effect profile acceptable for contraceptives. *The Panel recommends that targets have a readily “druggable” mechanism of action.* Some mechanisms of action are historically more amenable to pharmacologic modulation and are preferred. However, before a drug program is initiated, all targets should be reviewed in the context of their full characterization (e.g., mechanism of action, validation, quality of compound binding region, related isoforms, similarity to other members of the target class).

There are a number of strategies for improving target selection. First, *the Panel recommends that target mechanisms of action that are traditionally amenable to pharmacologic modulation be given preference.* Examples of potential non-hormonal mechanisms of action that are amenable to pharmacologic modulation with minimal side effects include enzymes, receptors, transporters, and ion channels.

The Panel does recognize the role of endocrine modulation as it has been demonstrated for both men and women and is an acceptable mechanism, as long as

identified potential obstacles are monitored and addressed during development (e.g., libido, bone loss, mood).

In contrast, *the Panel recommends that target mechanisms of action that are not historically amenable to pharmacologic modulation be given low priority.* Examples of mechanisms of action not amenable to pharmacologic modulation with minimal side effects include protein:protein, protein:RNA and protein:DNA disruption.

Target validation is crucial for drug development programs. *The Panel recommends that targets be validated in a manner that strongly suggests that pharmacologic modulation would lead to a contraceptive effect; programs lacking target validation should not be pursued by NICHD.* The Panel's view of target validation strategies are detailed below.

A common method of target validation is targeted gene deletion ("knockouts"). This method is often employed in basic research as a mechanism to identify biological processes where the target has function. While this technology has been revolutionary to the scientific field, it has two important limitations for validating drug targets. First, it typically represents a total loss of the respective gene product (e.g., protein, target) rather than a total inhibition of a druggable function critical for fertility. The physical/structural requirement of the protein is often important to the action of other cellular functions, making it difficult to understand whether an infertile phenotype is due to a lack of activity or the absence of the protein. Second, a successful targeted gene deletion represents 100% inhibition of the target; this extent of inhibition cannot be expected from any therapeutic. While information from heterozygote knockout models can be valuable, the Panel recommends investigating improved methods of validation, such as, but not limited to, *in vivo* genetic knockdowns or specific mutation of genes encoding targets to recapitulate the target inhibition that might be seen with a drug.

The Panel recommends evaluating mechanisms for target validation that provide models of reduced function as opposed to complete loss of function, such as the development of animal models with mutated gene products that reduce that activity of the target protein by 60-80% or a targeted reduction of protein levels between 50 and 100% (e.g., 70-80% loss of target level). The first model is more appropriate for enzymatic targets, while the latter is preferred for non-enzymatic targets. Both models would give a more realistic indication of whether moderate pharmacologic inhibition will be more successful than a full knockout animal model. The subcommittee suggests that an investigation of these methods be carried out and that a pilot program of two or three targeted knockdowns to investigate the technology for contraceptive validation be initiated. See the websites below for more information.

- <http://www.sirion-biotech.com/> (gene expression knockdown)
- <http://www.genoway.com/> (targeted functional knockdown)

C. Target Areas of Focus for Early Stage Drug Development Programs

The Panel discussed areas of focus for early stage contraceptive drug development programs and its recommendations are below, with the caveat that all drug development programs (compound screening and beyond) should be initiated based on need within the market and the expectation/likelihood of attracting a commercial partner before or during clinical development.

Regarding male contraceptive development, the Panel makes the following specific recommendations regarding target identification.

Male hormonal methods: The testis is the preferred site for intervention in the male as it is the site of sperm production. Hormonal methods affect the somatic Leydig and Sertoli cells directly as well as the hypothalamic-pituitary axis, and *the Panel recommends the continued development of male hormonal methods.*

Male non-hormonal methods: *The Panel recommends that non-hormonal targets within the seminiferous epithelium that inhibit sperm production or function be pursued with the suggested prioritization of target types as outlined above (e.g., enzymes, receptors, transporters, ion channels). Additionally, development of potential strategies to target spermatogonia and early spermatocytes would have an added advantage, since these germ cells are not sequestered behind the blood testis barrier, and recent scientific advances and technologies related to spermatogonia suggest that such targets have the potential for further drug development.*

Male reproductive tract: The epididymis is the site at which sperm acquire the capacity to be motile, but enthusiasm for targets in this organ is tempered due to the comparatively small number of specific and localized targets. There is a lack of validated epididymal targets required for motility that are druggable. *Although the Panel DOES NOT recommend epididymal targets at this time, if strong targets are identified in the epididymis, further consideration for future development would be warranted.*

Spermatozoa: Spermatozoa possess hundreds of unique proteins, many of which remain uncharacterized. These include novel isoforms of somatic enzymes and signaling mechanisms that, if modulated, might function as a contraceptive that could be used by either males or females. A characterization of the sperm proteome has been reported, but the protein composition of human sperm has yet to be fully annotated, and complete annotation is likely to yield new classes of novel targets. As many of these will be of testicular or epididymal origin, the elucidation of the human sperm proteome will also provide an important characterization of testicular or epididymal protein products that persist in and/or on mature spermatozoa. For example, sperm proteins required for function that are known to be produced in the testis would indicate a large temporal

window for an effector molecule to bind to its target. *The Panel recommends that spermatozoan targets be considered, with the caveat that any drug would need to exert an inhibitory effect on the majority of the millions of sperm in typical ejaculate, which itself presents a challenge.*

Regarding female contraceptive development, the Panel makes the following specific recommendations regarding target identification.

Female hormonal methods: *The Panel recommends further development of new or reformulated hormonal methods of female contraception to address unmet need for increased choices of women-controlled products and those of specific populations (e.g., adolescent and adult women with unprotected or infrequent sex, obese women). Additionally, there is a need to pair a female hormonal method with an anti-STI/HIV therapeutic to develop a multi-purpose contraceptive/anti-STI/HIV drug with an appropriate delivery system (e.g., vaginal ring, implant, gel, nanotechnologies).*

Female non-hormonal methods: The development of a non-hormonal contraceptive based on modulation of female gamete production or function is laudable but problematic. In contrast to male targets, there are very few ovary-specific targets (i.e., zona pellucida proteins, a transcription factor, regulators of meiosis). In addition, achieving drug entry into non-quiescent follicles at necessary levels is difficult, and the pool of resting follicles cannot be damaged for multiple reasons. *The Panel recommends that non-hormonal female targets be monitored, and if strong targets are identified in the ovary in the future, consideration for further development is warranted.*

Female reproductive tract: The female reproductive tract offers the potential for the application of new and improved existing drug delivery systems, including hormonal, non-hormonal, and multi-purpose contraception/infection prevention. Importantly, contraceptives delivered to the tract directly are under discrete user control by women and may have reduced off-target side effects in other tissues, due to lowered circulating levels (in the case of hormones) and concentrated local drug levels. *The Panel recommends additional development of female contraceptive modalities that are delivered to the reproductive tract, which would represent the ability to effectively block the function of either the female or male gamete within the female tract on demand.*

D. Improve the Early Development Pipeline

Increased focus on target ID and validation programs is needed to improve the quality of targets available for development. From what the Panel can gauge, the recent applications presented to peer review panels have been weak. Given the lack of strong drug development programs, it is not surprising that few, if any, proposals focused on target ID have been funded in the last 5 years. *The Panel recommends that the CDDB*

increase emphasis on target ID and validation with focused RFAs that contain strict relevant criteria required to be met for male and female targets. It may be beneficial for the FIB to review target ID and validation RFAs and provide input to the CDDB branch. These applications could encompass target ID/validation activities confirmed through several types of screens (e.g., genomic, proteomic, functional, reverse genomics, bioinformatics, knockouts, targeted knockdowns), or could represent an application that includes an evaluation of reported data from previous large-scale target ID programs (see below). The results of large-scale target ID programs could be reviewed by an advisory group of reproduction experts with drug development knowledge and, ideally, drug development experience. Highly ranked druggable candidates should then be moved to validation (discussed above as part of the RFA).

Estimates state that 3% of the mammalian genome is dedicated to the production of sperm. Large genomic and proteomic efforts to identify and evaluate testis-specific genes and sperm proteomes have been performed by academic, non-profit, and industry investigators, and enormous amounts of data have been made public; these data are infrequently queried as a source of novel targets. There are a large number of targets that have not been characterized in discovery phase for biological activity and function. *The Panel recommends that any NICHD-funded bioinformatic analysis of identified target strategies include mining the large amount of publicly available data and data repositories.* Examples of available public data include:

- <http://mrgd.org/index.cgi>;
- <http://public.wsu.edu/~griswold/director.html> (microarray tab); and
- www.ncbi.nlm.nih.gov/geo (accession no. GSE8978).

New targets for contraceptive development can come from anticipated sources (e.g., CDDB, FIB) and unanticipated sources (e.g., non-NIH funded research, repurposing of pharmaceuticals), including other areas of science (e.g., other NIH institutes such as NIEHS, NIAID, etc.) and big science consortia (e.g., International Mouse Knockout Consortium). All potential sources of new targets should be monitored by the CDDB on a continued basis to identify and vet potential targets. *The Panel recommends that an RFA be developed to curate all potential targets identified from these consortia.* This could be done through either an RFA or contract mechanism.

- <http://www.mousephenotype.org>
- <https://www.eummcr.org/>

Maximizing the effectiveness of the drug development process will require identifying and implementing funding and review mechanisms that allow for greater flexibility and control by the CDDB of the drug development programs. The Panel recognizes that

basic science and drug/product development are both critical to the drug/device research and development process but distinct disciplines. Unlike the basic sciences, drug development programs will benefit from shorter funding periods with clear milestones and go/no-go decisions for renewal. *The Panel recommends that funding of these types of drug development activities be supported by specific grant mechanisms (e.g., R21, R33, SBIRs), administrative supplements, or a centralized IDIQ-type contract mechanism (similar to that used for the Biological Testing Facility).* The structure of these funding mechanisms should be of shorter duration (e.g., 1-2 years), in the range of \$100,000 to \$200,000, milestone-driven with go/no go decisions, and renewable if milestones are met, with emphasis on and linkage to a series of go/no-go checkpoints. Review of these funding programs and assessment of whether milestones are met, resulting in go/no-go decisions, should be made by an independent standing review and advisory panel consisting of members with expertise in drug development in the reproductive health area, thus ensuring an objective assessment of progress.

The Panel recommends that the CDDB commit to programs until they fail to meet go/no-go criteria. The present process and funding mechanism can result in the loss of funding for programs that might be progressing well, since the programs are being reviewed by review panels that may not have the correct or any drug development expertise. A switch to alternative funding mechanisms with shorter duration that allow for clear go/no-go decisions will allow programs to continue or cease based on meeting milestones established in the proposed development campaign. The Panel is in agreement that it is not advisable to terminate programs where millions of dollars have been invested unless critical milestones are not met, and the current process utilized by the CDDB is not designed to fully optimize resources for success. As outlined above, assessment of these drug development activities should be monitored by an independent review panel consisting of members with expertise in drug development in the reproductive health area so that an objective assessment of milestones can be determined. The CDDB should consider review models that are used by other programs at NIH (e.g., TRND program or other programs at NCATS).

E. Restructure the Peer-Review Process

The Panel has evaluated recent RFAs that were issued and found them, overall, to be well written. As the CDDB has little input or control over the outcome of any initial review of applications and the decisions of the initial peer review, the RFA represents a key mechanism to guide the composition of the development pipeline to achieve its mission. *The Panel recommends that greater specificity in the writing of future RFAs be considered to increase the likelihood of receiving applications aligned with the CDDB mission that address the programmatic needs of NICHD's contraceptive portfolio.* This is critically important given the Panel's concerns about the balance between drug

development expertise and scientific expertise comprising the study sections that have reviewed these applications in the past (see below). For example, the RFA could specify a preference for targets with a specific mechanism of action (e.g., enzymatic, endocrine modulation, etc.). Identifying such priorities in the RFA will provide better guidance for both investigators and peer reviewers in prioritizing and selecting appropriate projects for contraceptive product development. The CDDB should consider review models that are used by other programs at NIH (e.g., TRND program or other programs at NCATS).

The current review process to meet the product development goals of the CDDB program is viewed by the Panel as suboptimal, since desirable projects may not receive appropriate prioritization by an ad-hoc panel without the benefit of insight into key aspects of drug development and implementation. Peer review panels/initial review groups need to have the proper leadership and composition in terms of expertise. In general, within review panels, there is currently a disconnect between different understandings of the mission of the CDDB, product development, the breadth of the reviewers' expertise needed for application review, what constitutes strong drug targets and drug development programs, and the importance of selecting the optimal drug development programs.

The special emphasis review panels often contain a high percentage of basic researchers who possess expertise in the areas of discovery and mechanisms of action, rather than in the area of product development. Many are inclined to score applications based on scientific merit, hypothesis, or novelty of the target/molecule(s) rather than on the basis of the qualities of that target/molecule(s) for subsequent drug development. An overweighted emphasis on scientific merit does not adequately assess the potential or likelihood of successful outcomes for the development of a new contraceptive product, given the many other considerations required to reach an informed decision regarding product development strategies.

The Panel recommends that the composition of peer review panels reviewing RFAs from the CDDB be more aligned with the mission of the CDDB and the goals of the RFA. In addition to a more heightened awareness in the selection of expertise for panel recruitment as indicated above, this may include more appropriate assignment of applications to members of the peer review panel. It may also require more specificity in the RFAs (as described above), which will dictate the assembly of more specific and qualified panels to review and score the proposals. For example, a peer review panel to evaluate target ID applications should be composed of (reproductive) scientists that understand the biology of the reproductive systems and the molecular mechanisms of target ID methods (e.g., transcriptomics, proteomics, functional assays). Target validation applications need to be reviewed by scientists and drug development experts that understand the validation methodology and the requirement for thorough validation.

Thus, drug development special emphasis review committees need to include sufficient numbers of members with drug development expertise. At a minimum, the Panel recommends that peer review panels evaluating drug development applications be chaired by persons with a thorough knowledge of reproductive science/medicine as well as drug development, preferably with reproductive health drug development experience. The CDDB should consider review models that are used by other programs at NIH (e.g., TRND program or other programs at NCATS).

The scoring mechanism currently used for CDDB applications is inadequate for product development purposes. *The Panel recommends that a modified scoring mechanism be implemented for drug development program reviews.* The review criteria do not consider the appropriate evaluative criteria normally considered by all other drug development organizations when making project go/no-go decisions. *The Panel recommends that additional scored criteria be included for these development programs.* The criteria would address the general criteria required by the IRG but could also address development specific issues. Some examples are offered below.

- Quality of the target: Is the target validated? Will pharmacologic alteration of the target yield the desired effect?
- “Druggability” of the target: Is it likely that modulation of the target can be achieved while meeting the side effect profile, patient profiles, etc. found in the Target Product Profile?
- If the Target Product Profile is achieved, can it be marketed?
 - Is there a market?
 - What are any manufacturing hurdles likely to entail?
 - What is the likelihood of identifying a commercial partner?

It is recognized that these different additional criteria do not necessarily hold the same weighting depending on the maturity of the development program, but should be a consideration in the Panel’s assessment.

F. Focus on IND-Enabling Studies, Compilation, and Submission

Studies are conducted via contract mechanisms with Ash-Stevens, Inc. (ASI) for chemical synthesis and the Biologic Testing Facility (BTF) for formulation development and IND-enabling safety studies. From the information provided to the Panel, these contracts are functioning well and communication and relationship management with the contractors is excellent. The CDDB noted that the process has improved dramatically since the BTF expanded to include expertise at developing CMC and GLP toxicology packages to be compiled into the IND, as well as capability for GMP clinical batch formulation of drugs for testing in the CCTN. In conversations with CDDB staff, it was

suggested that the Panel recommend that the maximal length of the IDIQ contract used to support these activities be extended from 5 years to 7 years, due to the lengthy and labor intensive contractor selection process. *The Panel recommends that the maximal length of the IDIQ base contract be extended from 5 to 7 years, as long as the CDDB has the ability to terminate the contract without penalty if circumstances warrant such action.* This flexibility can be built into contract after the first year of performance.

II. Clinical Studies (Phase I-III) and Training

NICHD's clinical contraceptive studies program helps fill a major void in biomedical research world-wide. The NICHD contraceptive development program, particularly the Contraceptive Clinical Trials Network (CCTN), has done a remarkable job of fostering clinical contraceptive research for both women and men, in many cases using methods and agents developed through NICHD-supported basic research. The CCTN was formed in 1996 with eight sites for studies in women and has completed many studies since its inception; it now consists of 19 sites for studies in women and 2 sites (added in 2004) for studies in men.

NICHD contracts with a group of facilities that are very unusual and perhaps unique for an NIH institute, including a Chemical Synthesis Facility, a Medicinal Chemistry Facility, and a Biological Testing Facility. These contract facilities support the non-clinical and preclinical activities in contraceptive development at NICHD and allow the CDDB to guide and facilitate the development of chemical agents from basic laboratories in academic institutions through to compound selection, optimization, preclinical, and toxicology studies. Agents can then move into trials in men and women using the clinical sites of the CCTN. A distinct advantage of the CCTN is that it provides a network of clinical investigators and sites that have specific expertise and clinical interest in family planning. While the CCTN and other NICHD supported research and training have unquestionably done an excellent job in addressing a major need in biomedical research, the Panel identified some issues that necessitate the recommendations below.

A. Improve Intra-Branch Communication to Enhance Phase I-III Drug Development

As with the activities associated with early non-clinical and preclinical development described above, *the Panel identified the need for greater communication between the CDDB, FIB, and PDB to improve Phases I-III of the contraceptive development process.* For example, there could be better use of behavioral research to assess the types of technologies that would be appealing to women and men (and to partners in each case). Similarly, the use of behavioral and mood assessments during the administration of experimental hormonal contraceptive regimens would be very valuable. Closer

coordination between the FIB and the CDDB might allow for more targeted basic science and the development of a richer pipeline of potential contraceptive targets, as well as more facile and rapid movement of potentially useful compounds from basic laboratories into the contracted facilities of the CCTN.

Communication between CDDB and external entities is similarly critical. This communication could be accomplished by convening and supporting meeting(s) of small and large pharmaceutical companies, venture capital firms, foundations, non-government organizations, and NIH-supported investigators to facilitate and encourage development of contraceptive agents and their movement toward the marketplace. Among others, agencies and organizations including USAID, CDC, Bill & Melinda Gates Foundation, Population Council, FHI360, and WHO should be involved, as they play important roles in funding, research, and implementation activities associated with contraceptive development and use.

B. Formulate an Actionable Plan to Foster Closer and More Productive Interactions with the Private Sector

The Panel recognizes that product liability and litigation concerns regarding contraceptive products limits interest in industry engagement in this particular therapeutic area. *The Panel recommends that NICHD re-explore the indemnification of products (i.e., through a product liability exemption), supported and developed through NICHD, including but not limited to contraceptives.* With respect to contraceptives, it may be argued that such products are being developed for the public good, akin to the development of vaccines. Creating a program modeled after Congress' National Vaccine Injury Compensation Act could signal federal commitment to family planning, as well as create a favorable climate for reentry of industry into the field of contraceptive development.

C. Reassess Recent Changes within the CCTN

The Panel recognizes the unique role that the CCTN plays in contraceptive development as well as its many challenges. The Panel held a number of conversations with staff and key informants, including long-standing members of the CCTN and newer members.

The Panel recommends that NICHD re-evaluate the number of female CCTN sites to maximize efficiency and effectiveness. With the recent expansion of the number of female sites to 19, it is unclear whether these sites are being used to maximal effectiveness. Several of the people with whom the Panel has spoken, including investigators from both the original CCTN network and from newly-added sites, believe

that there are too many sites. The sites previously viewed the CCTN as a rare collegial collaborative opportunity; but with new expansion, they are more competitive and underfunded. In addition, several of the sites are not busy and believe that it would take considerable effort and local investment to be able to take on new studies. Information gathered from sites contradicts the view from NICHD that large numbers allow for rapid expansion, should a major trial emerge. Given the current pipeline, a more likely scenario is that only a few sites would be used and others would never gain the expertise to be a robust clinical trial site. One model to be considered across the CCTN is that which has been adopted by the two male sites (i.e., primary sites with the ability to subcontract to additional sites as needed).

The Panel also noted missed opportunities to increase capacity across the existing CCTN sites. Specifically, the CCTN serves as an excellent training ground for building expertise in contraceptive clinical trials. *The Panel recommends creating more opportunities for face-to-face meetings and collaboration among the female sites.* The Panel also suggests fostering better communication and interaction between the female and male CCTN sites. The sites could benefit from “lessons learned” by the individual sites, and there may be opportunities to leverage assets between the female and male sites. There should be support and encouragement for the inclusion of T, F, and K clinical scientist awardees in these site meetings.

The Panel recommends establishing and using a single centralized Institutional Review Board (IRB) that would serve all of the sites of the CCTN. Such a model has been used for clinical trials supported by NCI, NINDS, and the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT); this approach has also recently been proposed for all NIH-supported studies. For example, using the Western IRB (or some other centralized IRB) rather than the individual institutional IRBs would be more efficient and allow studies to be initiated much more quickly. It would also increase the likelihood that the CCTN could be used, when appropriate, for industry-sponsored trials, as industry has expressed concern that going through individual CCTN site IRBs makes the process extremely time intensive. This change could potentially facilitate and strengthen partnerships with industry.

III. Behavioral Research

The Panel noted the critical role of behavioral research in general, as well as its role in the drug development, dissemination, and implementation processes. Understanding the needs, desires, attitudes, and behaviors of the end user population can help determine which methods are most desirable, perhaps influencing the contraceptive pipeline. In addition, the Panel noted the increasing diversity of the United States population and the advent of issues such as the rising rate of obesity, as well as the

importance of addressing the global population. Thus, there is a need for research that focuses on these specific issues. The Panel's review of the approaches to behavioral contraceptive research currently used by the PDB revealed several key areas where changes in approaches and processes may significantly enhance the effectiveness of the PDB to contribute to the delivery of novel and needed contraceptives to the market.

A. Improve Internal and External Communication to Enhance Behavioral Research

The Panel recommends increased integration of behavioral considerations into contraceptive product development, including early development, clinical testing, marketing, and post-marketing of products. *Effective front and back-end communication across the three branches (i.e., CDDB, FIB, PDB) is key to successfully accomplishing this goal and to ensuring the development of a portfolio of diverse products suitable for different populations and contexts.* Improving communication and inclusiveness could take multiple forms. One possibility – a variation on industry models – is to conduct regular brainstorming and strategic planning meetings between the branches. For example, information regarding why methods are succeeding or failing in general practice should inform questions of early identification of targets and method types and, in turn, NICHD funding decisions for all phases of drug development. In order to maximize the effectiveness and contributions of behavioral research, there is a need to increase communication with those outside of NICHD. *The Panel recommends that NICHD capitalize on its capacity as a “convener” to initiate partnerships with organizations that have shared interests.* These stakeholders could be convened through workshops and planning meetings.

B. Strategically Address the Issue of Unintended and Undesired Pregnancy

Despite the array of available contraceptive methods, there are still high rates of contraceptive nonuse and misuse among women and couples who do not desire pregnancy. Thus, there is an opportunity to tackle many outstanding questions about contraceptive behavior through funding intended to address these problems (see Appendix D for specific topics). Fruitful areas of funding include multisystem interventions, priorities of men and women, physical and social context of contraception, and quality of life issues related to contraception. Further, the research supported by NICHD should reflect the US and global populations, attending to issues of diversity in age, body type, disease status, race/ethnicity, religion, cognitive stage, sexual orientation, and ability status. Each of these dimensions can affect the ways in which contraception functions at a biological level (e.g., safety, efficacy, side effects), the perception of the biological effects of a method, and the social dimensions of a method. Moreover, for many women, contraception is dyadic and affected by relationships with sexual partners or even parents, peer, or health care providers. Contraception is also

governed by systemic factors (e.g., policies, geography, economics, health care), which affect access, attitudes, delivery, and availability of contraception. There is an opportunity to consider this more comprehensive view of the social and behavioral aspects of contraception throughout contraceptive development and delivery.

C. Increase Attention to Behavioral and Post-Marketing Studies

In order to improve strategic focus on research into the perceptions and use of contraception, *the Panel recommends that NICHD continue support for the invaluable national studies that monitor contraception, behavior change, and reproductive health in the US population, as well as secondary analyses that use these data.* Examples of such studies include 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). However, the Panel also noted that the resources these studies offer could be even better leveraged by improving certain methodological and organizational procedures. For example, efforts could be made to capture standard metrics of contraceptive usage across studies, as well as to validate and harmonize user-centered measures. In addition, partnering with other NICHD branches, non-NICHD organizations, and publishers of relevant scientific journals may further expand and optimize use of these resources. Creating an online hub on the NICHD website to link these studies with similar NICHD-funded initiatives, offer funding for projects using their data, and provide training on accessing these resources might also be considered.

In addition, while the panel recognizes the importance of the CCTN for contraceptive development, a long discussion was held regarding its potential to contribute to post-marketing and behavioral trials. *The Panel ultimately concluded that the CCTN would contribute important information to the field through involvement in post-marketing research.*

D. Focus on Implementation Science and Dissemination

The Panel recommends focusing on implementation science to enhance the impact of NICHD research findings. Landmark studies such as the CHOICE Project demonstrate the public health impact that can be effected through better implementation of existing science in conjunction with new discoveries. NICHD can also play a larger role in mobilizing findings for use in practice. Relationships with NCATS can be used to facilitate clinician training and translation of findings to the clinical setting. NICHD could place a greater focus on research into the safety, quality, and understanding of contraceptive policies, as well as the structural barriers to contraceptive access and uptake.

Similarly, there is a need for NIH to better communicate its research and translate its findings to a wider community. NIH is a trusted source of information with tremendous opportunity to serve as a megaphone for scientific findings. As the preeminent producer of new knowledge and development of contraceptive methods, NICHD should support communication efforts related to contraceptive research. In addition, NICHD should increase its efforts to partner with organizations that have a specific public health focus, such as the Centers for Disease Control and Prevention, American Congress of Obstetricians and Gynecologists, Society of Adolescent Health and Medicine, United Nations, and American Academy of Pediatrics.

CONCLUSION

NICHD envisions a world in which every person is born healthy and wanted, women suffer no harmful effects from reproductive processes, and all children have the chance to achieve their full potential for healthy and productive lives. The ability to plan and prevent pregnancy are critical components of this vision. Over the past six months, the Panel has reviewed material provided by NICHD staff, met with staff members, interviewed key informants, and conducted independent research to assess the productivity and progress of NICHD's contraceptive programs. Overall, the Panel is very supportive of NICHD and its activities. The Panel recognizes the significant role that the NICHD plays in contraceptive development. With the limited contraceptive development activities of private industry, NICHD is more important than ever. Yet despite endorsing NICHD's role in contraceptive development, behavioral research, and training, the Panel also recognizes that the institute must adapt significantly if it is to succeed. There are many new players in the field of contraceptive research and family planning, as well as many opportunities for expansion and impact. NICHD must take the initiative to lead this field. This leadership will entail greater communication, convening of stakeholders, collaboration, monitoring, and evaluation. NICHD will need to focus on diversity, training, and strategic partnerships with industry. The Panel has provided many ideas for achieving these goals and believes that the recommendations detailed in this report, if implemented, will address several aspects of this important challenge. The Panel members are grateful for the opportunity to collaborate with NICHD and its committed staff in preparing this report.