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Female-Controlled Barriers to Prevent HIV Infection July 6, 1993

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KRISTINE M. GEBBIE, R.N., M.N., F.A.A.N.
NATIONAL AIDS POLICY COORDINATOR
DEPARTMENT OF HEALTH & HUMAN SERVICES
Room 729H Humphrey Building
200 Independence Ave., S.W.
Washington, D.C. 20201

DAY TUESDAY DATE July 6, 1993

TIME 2:00 p.m. LOCATION Deputy Secretary's Conference Room

SUBJECT MEETING TO DISCUSS FEMALE-CONTROLLED BARRIERS TO PREVENT HIV INFECTION & OTHER STDs

PARTICIPANTS:

SEE NOTE INSIDE FROM DR. LAWRENCE AND BRIEFING MATERIALS FOR BACKGROUND INFORMATION AND PARTICIPANTS.

July 2, 1993

Kristine:

Attached are the briefing materials for the barrier meeting on July 6, 1993. I have briefed Dr. Manley on the materials as well and she is on board.

The stapled package, "Premarket testing.....", is referenced in the FDA briefing materials but IS NOT included in the briefing package. It was prepared by FDA in 1990 as guidance. It is still good background.

You also need to know that NIH/Fauci is likely to bring a complete briefing book on research to the meeting. I have transmitted the message to NIH that if a separate briefing book will in fact be used that we would appreciate receiving a copy earlier in the day. They said OK, and will provide one if they have it ready in time to courier here.

For you little black book, my home telephone is 301-926-2628. My portable phone number (which I don't have on all the time) is 202-494-3250. If a female answers it could be my daughter, Brenda, or my wife who has appropriately retained her familial last name, Mary Ann Danello.

I'll be her on Saturday for some time. Try to have a pleasant and relaxing weekend (or reasonable portion thereof). Don't hesitate to call me.....

Art

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

JUL 2 1993

TO: Chief of Staff
Through: ES_____

FROM: Deputy Assistant Secretary for Health

SUBJECT: Your Meeting to Discuss Female-Controlled Barriers to Prevent HIV Infection and Other Sexually Transmitted Diseases--BRIEFING

PURPOSE

To provide you with information for your meeting on female-controlled barriers to prevent HIV infection and other sexually transmitted diseases (STDs) scheduled to be held in the Deputy Secretary's Conference Room at 2:00 p.m. on July 6, 1993.

PARTICIPANTS

Outside the Department

Ms. Kristine Gebbie, National AIDS Coordinator
Dr. Helene Gayle, AIDS Coordinator, Office of Health, A.I.D.

Inside the Department

Ms. Patsy Fleming, Special Assistant to the Secretary
Ms. Nan Hunter, Deputy General Counsel/Legal Counsel
Mr. Glen Harelson, Policy Coordinator for Health/OS
Ms. Joni Cunningham, Policy Coordinator for Health/OS
Dr. David Kessler, Commissioner, FDA
Dr. Anthony Fauci, Director, OAR, and Director, NIAID, NIH
Dr. James Curran, Associate Director for HIV/AIDS, CDC
Ms. Carol Roddy, Senior Assistant to the SG-Designate
Dr. Arthur Lawrence, Acting Deputy Director, NAPO

See TAB A for list of other participants

BACKGROUND

With the increasing number of women becoming infected with HIV and other sexually transmitted diseases (STDs), there is an growing concern for the need to develop and market female-controlled barriers to prevent HIV infection and STDs. At the Berlin International Conference on AIDS, a significant portion of the meeting was devoted to issues of prevention, research and services for women. A particular highlight of several of the

presentations concerned the need for the development of effective prevention strategies that would be under the control of women. Such strategies could better enable women to make informed decisions to protect their health and to prevent disease. Ideally, such strategies would allow women to retain flexibility in their reproductive decisionmaking. This issue also was highlighted by several gay and lesbian organizations which met with the Secretary and other senior staff in April during Gay and Lesbian Pride Week.

ISSUES TO BE DISCUSSED

- What is the state of the art for controlling and preventing pregnancy, STDs, and HIV in women?

- What are our current activities and initiatives to advance our knowledge and understanding about prevention efforts under the control of women (e.g., microbicides, virucides, spermicides and devices)?

- How can a coordinated approach within HHS to address the issue of female-controlled barriers to prevent HIV infection and STDs can be undertaken?

At TAB A is a list of participants. At TAB B is an agenda for the meeting. At TABS C, D and E, respectively, are fact sheets from NIH, CDC and FDA that describe the issues surrounding female-controlled barriers, provide information on current activities in the Department, and discuss what we know about activities outside the Department and examine future prospects for the development of such barriers. At TAB F is a copy of the NIAID Plan on Topical Microbicides.

/s/ Audrey F Manley
Audrey F. Manley, M.D., M.P.H.

6 Attachments:
TAB A - List of Other Participants
TAB B - Agenda
TAB C - NIH Fact Sheet
TAB D - CDC Fact Sheet
TAB E - FDA Fact Sheet
TAB F - NIAID Plan on Topical Microbicides

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TAB A

Divider Title: _____

LIST OF OTHER PARTICIPANTS

Female-Controlled Barriers to Prevent HIV Infection
and Other Sexually Transmitted Diseases

Dr. Penny Hitchcock, Chief of the Sexually Transmitted Diseases Branch, Division of Microbiology and Infectious Diseases, NIAID, NIH
Dr. Wendy Baldwin, Deputy Director, NICHD, and Acting Deputy Director for Extramural Research, NIH
Dr. Nancy Alexander, Chief, Contraceptive Development Branch, Center for Population Research, NICHD, NIH
Dr. Sten Vermond, Chief, Vaccine Trials and Epidemiology Branch, Division of AIDS, NIAID, NIH
Dr. Judy Wasserheit, Director, Division of Sexually Transmitted Diseases and HIV Prevention, CPS, CDC
Dr. Randolph Wykoff, Director, Office of AIDS Coordination, FDA

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TAB B

Divider Title: _____

AGENDA

FEMALE-CONTROLLED BARRIERS TO HIV INFECTION AND STDs

JULY 6, 1993

I. Introduction on PHS Activities.....Dr. Fauci

II. Presentation by NIH on Topical Microbicides....Dr. Hitchcock
(10 minutes)

III. Presentation by CDC.....Dr. Curran
(10 minutes)

IV. Presentation by FDA.....Dr. Kessler
(5 minutes)

V. General Discussion

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TAB C

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FACT SHEET

NIH-Sponsored Research Activities on Female-Controlled Barriers to HIV Infection and Other STDs

Several of the Institutes, Centers, and Divisions of the NIH sponsor biomedical research focusing on blocking heterosexual transmission of HIV with chemical and physical barriers. The NIAID and NICHD are the major sponsors of research activities in this area.

- NIAID has developed an extensive research plan for the development and evaluation of topical microbicides for the prevention of HIV infection and STDs. This plan is attached at TAB F.

- NICHD funds research on the medical effects of intrauterine devices, condoms, spermicides, and other contraceptive drugs and devices available in the United States. In addition, NICHD evaluates the role of barrier contraceptives in preventing STDs and HIV infection and studies the impact of oral contraceptives on susceptibility and disease progression relative to the cervical and vaginal environment and on the immune system.

  - In 1989, a program was conducted to evaluate the suitability of using condoms and condoms plus spermicides in preventing HIV transmission. The results indicated that condoms available in the United States are of high quality and should provide a substantial degree of protection from HIV infection and other STDs.

  - Studies have supported the findings that spermicides plus condoms might offer additional protection against HIV infection. The possibility that spermicides decrease the risk of STDs is derived from both *in vitro* and *in vivo* studies. Laboratory experiments have shown that six spermicides tested inactivated nine STDs including HIV.

  - A statistical model has been developed to project the effect of condoms on the AIDS epidemic in America. The results provided assurance that condoms can be recommended as protection from HIV infection for individuals at low risk even in the absence of quantitative data about condom efficacy. Findings indicate that avoidance of high-risk sexual activity for individuals at risk is the only way to assure protection from the disease.

- A spermicide-releasing, disposable diaphragm with increased potential for high efficacy and acceptability is currently being developed. The development of this product may allow women to protect themselves against HIV transmission, particularly in situations where male condom use is not culturally acceptable. Current indications, however, suggest that the product may be too costly on a per use basis to make it appealing for widespread use.

- FIC sponsors several programs investigating the use of barrier contraceptives and associated behavioral strategies for prevention of HIV transmission to women from HIV-infected males. These studies are conducted in parts of South America, Asia, and Africa.

- OAR and NICHD recently sponsored a conference on "Research on the Role of Condoms in Reproductive Health" to determine ways to use recent condom research data to design better intervention programs.

Prevention/Intervention

The AIDS epidemic has presented significant challenges to both the biomedical and social and behavioral science research communities. Prevention of HIV infection involves behavioral changes in areas of life where such change may be difficult to effect.

- NICHD research on behavior/prevention examines the choices individuals make regarding their sexual behavior and protection against adverse outcomes of those behaviors. This research includes:

  - studies designed to understand the effect of HIV/AIDS and other STDs on choices regarding sexual and reproductive behavior utilizing the Health Belief Model, the Subjective Expected Utility Model, and other theoretical frameworks.

  - projects on reducing the risk of sexually transmitted HIV infection; preventing HIV-infection in sexually active adolescents; teaching youth social skills; evaluating AIDS prevention efforts; assessing social context for adolescent high-risk sexual behavior; understanding decision making processes in youths regarding AIDS risk behavior; and understanding the development of attitudes and knowledge about AIDS.

  - programs to improve negotiation skills so that women are empowered to use condoms and other barrier methods.

- NICHD planned research activities include:

  - development of a dedicated facility(ies) for testing new barrier contraceptives to assess both new physical and chemical agents for their efficacy and acceptability;

  - programs to develop safe, effective, and inexpensive chemical and physical barrier methods of contraception that will allow women to protect themselves against HIV infection;

  - an observational clinical trial comparing male vs. female condoms to evaluate their efficacy in the prevention of gonorrhea, chlamydia, and HIV infection;

  - screening and synthesis of new spermicidal products with microbicidal properties; and

  - studies to determine knowledge, attitudes, and practices related to the proper use of condoms and spermicides/microbicides with increased acceptability and efficacy in order to provide an information base for the development of intervention strategies.

- NIMH sponsors prevention programs designed to change high-risk behavior and maintain low-risk behavior among various populations through:

  - several AIDS research centers that focus on behavior change and prevention programs; and

  - a multisite, multipopulation prevention clinical trial.

- NIDA supports research to develop effective, cost-efficient comprehensive programs to reduce the use of illicit drugs and related high-risk behaviors thereby reducing the risk of HIV infection among drug abusing women.

  Planned research initiatives include:

  - clinical studies focused on psychotherapy, behavior therapy, and other psychosocial interventions;

  - treatment evaluations aimed at strategies to improve entry and retention in treatment and improve compliance with treatment regimens; and

  - health services studies directed at understanding the impact of organization, structure, financing, management, and staffing patterns on the availability, accessibility, and utilization of therapeutic and preventive interventions.

- NIAAA sponsors research on alcohol use/abuse and unsafe sexual practices with the goal of understanding the decision making processes and developing social-psychological prevention and interventions strategies to reduce the risk of alcohol-related HIV exposure.

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TAB D

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CDC FACT SHEET
CHEMICAL AND MECHANICAL BARRIER METHODS
TO PREVENT STDs INCLUDING HIV IN WOMEN

Prevention of sexually transmitted diseases (STDs), including HIV, is important for women for several reasons. STDs are more easily transmitted to women and are more difficult to diagnose. Economic and cultural constraints often result in women at highest risk of STDs having little power to influence when, where, how, and with whom intercourse occurs. Common bacterial STDs are usually asymptomatic and are detected only by screening. For nearly all STDs, long-term complications in women are far more common and much more serious than those in men. Broad use of STD prevention methods by women will result not only in prevention of long-term sequelae of STDs (such as infertility, potentially fatal ectopic pregnancy, and cervical cancer), but also will directly and synergistically decrease HIV transmission because STDs enhance HIV transmission.

Currently, chemical and mechanical barrier methods available to women are limited to male condoms, female condoms, other mechanical barriers (diaphragm/cervical cap), and spermicides.

- Consistent use of male condoms is a highly effective way to prevent STDs, including HIV infection, in women but relies on the cooperation of the male partner.
  - Several well-designed cohort studies have shown that consistent condom use reduced risk of HIV infection by 70-100% among seronegative partners of persons infected with HIV.
  - Data on effectiveness of condoms for preventing STDs other than HIV infection are less complete, especially among women. Several cohort studies of men showed condoms reduced risk of gonorrhea by 66-100% (Table 1). One cohort study in women showed condoms reduced risk of genital ulcers by 88%.

- A female condom has recently been approved by the FDA and will be marketed soon in the U.S. The product is a polyurethane sheath which fits inside the vagina, anchored by an inner and an outer flexible ring. The female condom may be inserted any time prior to intercourse.
  - Laboratory studies have shown this female condom to be an effective mechanical barrier to viruses including HIV.
  - A clinical study showed that the estimated contraceptive failure rate of the product was 26% in one year, but was lower for users who used the product correctly and consistently.
  - Factors which determine acceptability and compliance have not been studied adequately in the U.S.

- Little is known about the role of the diaphragm or cervical cap in preventing STDs, including HIV, in women. Cross-sectional and case-control studies have suggested a

protective effect for various STDs, but well-designed cohort studies are needed.

- Currently available spermicides offer women limited protection against gonorrhea and chlamydia, but their role in prevention of HIV infection and other viral STDs remains unclear.
  - Cohort studies showed vaginal spermicides reduced the risk of cervical gonorrhea by 24-89% and chlamydia by 22%.
  - A recent cohort study demonstrated that a vaginal sponge containing a large amount of spermicide did not protect women against HIV infection.
  - Because of the lack of other prevention methods controlled by women, many women in the U.S. are being advised to use spermicides to protect themselves from HIV infection when condom use is not possible, despite uncertainties about effectiveness.

- Because currently available spermicides are detergents which can damage the normal cells and bacteria which line and protect the vagina and cervix, questions have been raised about whether frequent use of spermicides may actually increase risk of HIV infection and other STDs.
  - One study found an increased risk of genital ulcers among women using a spermicidal sponge.
  - Several Family Health International studies suggest that spermicides used in high doses may result in irritation of the vagina and cervix.

OTHER ISSUES

- Very little is known about the complex interaction of individual, cultural, and societal factors which determine which, if any, method a women chooses to prevent STDs, including HIV. Even when new, safe, and effective methods become available, women and their partners must be willing to use them consistently and correctly.

- The cost of any method in the control of women has to be low enough that it is accessible to women anywhere in the world.

- Women who use other effective contraceptive methods may be less inclined to use barrier methods that would prevent HIV transmission.

- No information is available to assess the role of spermicides or other female-controlled methods in preventing transmission of STDs <u>from</u> women to their partners.

ACTIVITIES

- CDC [the Division of Sexually Transmitted Diseases and Human Immunodeficiency Virus Prevention (DSTD/HIVP) and the Division of Reproductive Health (DRH)] is conducting the

Prevention of HIV in Women and Infants Demonstration Project which focuses on developing, implementing and evaluating interventions to change high risk behavior and community norms regarding HIV risk reduction. One of the goals of the project is to determine factors which influence women's successful adoption and continued use of condoms.

- CDC [Division of HIV/AIDS (DHA)] is conducting studies to determine the prevalence of HIV-1 and HIV-2 infections and STDs in female prostitutes in Côte d'Ivoire and to evaluate diagnostic, therapeutic, and preventive interventions.

- CDC (DHA) is conducting a social science research project in Thailand to explore options and obstacles for the development of preventive measures through which women can be made aware of the risks of HIV within their marriages (from spousal contact with prostitutes) and can institute effective measures to protect themselves.

- CDC (DSTD/HIVP) co-funded an NIH conference on development of microbicides for STD/HIV prevention and establishment of priorities for a research agenda.

- CDC staff participated in a comprehensive workshop on development of microbicides and other barrier methods for STD/HIV prevention.

- CDC (DSTD/HIVP) formulated recommendations about female prevention methods in the prevention guidelines of the 1993 STD Treatment Guidelines.

- CDC staff are preparing an article for the CDC *Morbidity and Mortality Weekly Report* on barrier methods for prevention of STDs including HIV.

- CDC staff are preparing an article for the CDC *Morbidity and Mortality Weekly Report* on the female condom.

- CDC staff are assisting the FDA in their public education efforts.

- CDC staff provide ongoing consultation to FDA regarding possible labeling revisions for spermicides.

FUTURE NEEDS AND OPPORTUNITIES

Concurrent behavioral and biomedical research is needed and should be conducted collaboratively between CDC and NIH.

- Behavioral Research Priorities
  - Descriptive analyses
    - explore determinants of barrier use among women and their partners
    - determine acceptability of various barrier methods

- define determinants of user compliance with barrier methods

- Develop, implement, and evaluate intervention strategies, including changing the perceived norms and "meanings" of barrier use within sexual relationships and determining how to move women successfully through the stages of behavior change to adopt and maintain consistent prevention behaviors

- Biomedical Research
  - Clinical trials of existing and newly developed microbicidal agents to evaluate safety and efficacy with respect to all STDs including HIV are needed.
    - Evaluate dose-response relationships between microbicides and inflammation, and characterize the inflammation to determine if it is likely to increase HIV transmission
    - Evaluate post-coital application of microbicides
    - Explore feasibility and efficacy of combined methods

  - Cohort studies of efficacy of the diaphragm or cervical cap to prevent STD/HIV are needed

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TAB E

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FDA FACT SHEET

Female Barrier Devices Against AIDS and STDs

- The Food and Drug Administration (FDA), through the Center for Devices and Radiological Health, has regulatory responsibility for assuring the safety and effectiveness of barrier contraceptives. In an effort to facilitate the development of a woman-controlled barrier device against AIDS, FDA published a guideline in April 1990 ("Premarket Guidelines for Female Barrier Contraceptive Devices Also Intended to Prevent Sexually Transmitted Diseases") for manufacturers in testing such devices. FDA developed the guideline in conjunction with the FDA Obstetrics-Gynecology Panel, NIH, and CDC. The guideline includes a mechanism for an expedited protocol for approving these types of devices.

- Recognizing the difficulty in studying STD prevention in clinical trials, the guideline allows pregnancy to be used as a surrogate study endpoint if pre-clinical studies demonstrate that the device is an effective barrier to STD size particles. The guideline also eliminates the need for a randomized clinical study comparing the new device to an old device.

- On May 7, 1993, FDA approved the REALITY Female Condom (Wisconsin Pharmacal), the first barrier contraceptive for women that also offers limited protection against sexually transmitted diseases. The REALITY Female Condom was the first barrier device approved using the guidelines.

- The agency gave the product and expedited review because it saw an urgent need for a means whereby women could protect themselves without depending on the cooperation of their partners. FDA had reservations concerning the approval of the female condom. These reservations include: the small number of women in the clinical studies; the short duration of use (6 months); and the pregnancy rate among users (13% at 6 months and an estimated 12-month pregnancy rate of 26%). The National Institutes of Health and FDA are working together to conduct future studies on the REALITY Female Condom, particularly investigating its effectiveness against STDs and pregnancy compared to the male latex condom.

- The agency continues to encourage manufacturers to develop new products and is committed to work with the manufacturers during all phases of product development.

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TAB F

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TOPICAL MICROBICIDES

Definition:

- products for intravaginal use that are microbicidal (virucidal and/or bactericidal); used by women to prevent sexually transmitted infections

Collaborative Aspects:

- within NIAID - DMID, DAIDS, DIR
- within NIH - NIAID, NICHD, NCI, ORWH
- within PHS - NIH, FDA, CDC
- within International Community - USAID, WHO/GPA, MRC/UK
- NGOS - Rockefeller Foundation, Population Council
- Industry

Meeting History:

- Summer 1992 - Population Council
- March, 1993 - CONRAD Program
- May, 1993 - NIH/PHS

Meeting Plans:

- planned: Winter 1993 - Industry and PHS
- planned: November, 1993 - GPA/WHO and MRC/UK

Rationale for female-controlled barrier methods:

- gender bias of infections
- non-consensual sex
- condom-use negotiations often unsuccessful
- high risk behaviors of partners

Prevention Aspects:

- Primary: STD and HIV infection
- Secondary: STD decreasing HIV transmission risk
- Tertiary: STD sequelae

Desirable characteristics:

- "invisible": colorless, odorless, tasteless
- stable
- easy to store
- fast acting, for appropriate duration
- ideally effective pre- and post-coitus
- inexpensive "pennies per dose"
- safe for use at least 1-2 times daily
- formulated with or without spermicidal activity

Spermicidal or not?:

- <u>microbicidal only</u> - currently no barrier methods exist which protect against infection but permit conception

- microbicidal only - some contraceptive methods arguably increase risk of sexually transmitted infections
- microbicidal AND spermicidal - may be necessary to penetrate infected host cells to prevent cell-associated transmission of viral STDs, including HIV
- microbicidal AND spermicidal - penetration of host cells (killing of host cells) may cause inflammation including epithelial erosions and ulcers which may increase risk of transmission

Feasibility:

- vaccines versus microbicides - preventing infection not easy with either approach but theoretically easier with topical microbicides

Microbicidal spectrum:

- bactericidal activity - prokaryotic cell-surface significantly different than eukaryotic cell-surface; these differences may provide a window of opportunity to kill bacteria without damaging host tissue
- virucidal activity - HIV, HSV are enveloped by host-cell membrane and cell-associated, therefore specificity of action may be difficult

Research Agenda:

- three parallel tracks - all critical and complementary
- basic science
- product evaluation
- clinical trial

Basic Science Research Agenda:

- early steps in the infectious process
- specificity - virucides versus bactericides
- toxicity and inflammation
- acceptability - behavioral research

Product Evaluation:

- *in vitro* - define spectrum and kinetics of microbicidal activity; define spermicidal activity;
- *in vivo* - preclinical testing - safety only;
- Phase I studies

Clinical trial - Microbicidal Efficacy of N-9 Spermicides:

- evaluate safety in Phase I/II studies
- Phase III - efficacy

Questions - can N-9 be safely used; how often and under what conditions are inflammation and ulcers induced; if safe concentrations and frequency of use can be defined, is the product effective in preventing sexually transmitted infections; if microbicidal, what is the spectrum of activity; is it still spermicidal, if not is it safe?

NIAID PLAN

Topical Microbicides: Prevention of STDs Including HIV Infection

BACKGROUND - HIV AND STDs:

The HIV pandemic has focused attention on STDs both because HIV infection is a fatal STD and because other STDs are implicated as risk factors for transmission of HIV. Current global estimates indicate that 14 million people are infected with HIV, the cause of AIDS. The majority of these infections were acquired through sexual intercourse. Unless effective prevention measures to stop sexual transmission of HIV are implemented, the number of AIDS cases will continue to grow.

Separate and apart from the HIV epidemic, STDs cause significant morbidity and mortality and contribute greatly to increasing health care costs. In the United States in 1992, an estimated 10 million cases of STDs occurred, 64 percent of which were in people less then 24 years old, and three million were in teenagers. In 1992, costs associated with these infections approached $6 billion.

Furthermore, STDs disproportionately affect the female, the fetus, and the newborn. Gonococcal and chlamydia infections cause pelvic inflammatory disease, infertility, and ectopic pregnancy. Several common STDs adversely affect pregnancy and result in spontaneous abortion, stillbirth, chorioamnionitis, premature rupture of membranes, preterm delivery, and postpartum endometritis. Neonatal infections include gonococcal conjunctivitis, which may lead to blindness, chlamydia pneumonia, which may lead to chronic respiratory disease, and herpes encephalitis. Moreover, genital infections due to human papillomavirus are causally associated with cervical cancer, one of the most common cancers in women throughout the world.

STD/HIV SYNERGY

It is now clear that the risk of becoming infected or infecting others with HIV is substantially increased if one has an STD such as chancroid, genital herpes, syphilis, trichomoniasis, gonorrhea, or chlamydia infection. Over 75 studies on the role of STDs in HIV transmission have been conducted. In 15, *both* ulcerative and non-ulcerative STDs increased risk of HIV

transmission approximately 3 to 5 fold, independent of the effect of sexual behavior. Although the risk of transmission of HIV in the genital ulcer diseases appears to be higher than the discharge diseases, the high prevalence of discharge diseases results in a much higher attributable risk in the United States.

Furthermore, preliminary data from over 80 reports on the impact of HIV infection on STDs suggest that, at a community level, HIV infection may increase the prevalence of some STDs (e.g. genital ulcers). If co-infection with HIV prolongs or augments the infectiousness of individuals with STDs, and if the same STDs facilitate transmission of HIV, these infections may greatly amplify one another. This "epidemiological synergy" may underpin the explosive growth of the HIV pandemic in some populations.

Despite recent global efforts in health education aimed at preventing sexual transmission of HIV, STDs remain hyperendemic in many developing countries and in the inner-city populations of industrialized countries. Throughout the world, the majority of these infections are clustered in the resource-limited settings of urban and peri-urban areas where increasing numbers of adolescents and young adults, poverty, unemployment, lack of education, inferior status of women, and social disintegration fuel the epidemic spread of STDs and set the stage for the spread of HIV infection.

RATIONALE FOR DEVELOPMENT OF EFFECTIVE BARRIER METHODS TO PREVENT INFECTION:

A consensus has emerged that the prevention of sexually transmitted HIV infection as well as the prevention of the major sequelae of STDs in women and infants will depend on the development of safe, effective, female-controlled mechanical and chemical barrier methods that will block transmission.

The barrier methods that are currently available have limitations. Most require consent, if not active cooperation of the male partner, and therefore cannot be independently implemented at the discretion of the female partner. Although epidemiological studies have demonstrated that the use of condoms or spermicides can reduce the risk of acquiring some STDs, there are many situations in which personal, social, or cultural barriers interfere with a woman's ability to successfully negotiate and implement their use. Specifically, the need for a method which can be implemented by women is grounded in the high prevalence of: i) non-consensual sex; ii) sex without condom use; and iii) risky behaviors that occur without partner knowledge.

Therefore, just as oral contraceptives dramatically enhanced the ability of women to avoid unwanted pregnancy, effective female-controlled mechanical and chemical barriers are urgently needed to enhance the ability of women to avoid sexually transmitted infections. Ideally, topical microbicides could be developed

with or without contraceptive efficacy; these would be responsive to women i) who wish to become pregnant while avoiding disease; ii) who use contraceptive methods which either have no effect on or increase risk of STD transmission; or iii) who wish to prevent STDs during their non-reproductive years. Furthermore, chemical barriers that inactivate pathogens in vaginal/cervical secretions as well as in the ejaculate could reduce female-to-male as well as male-to-female transmission.

STATUS OF TOPICAL MICROBICIDE DEVELOPMENT:

Currently there are no approved intravaginal microbicidal barriers (virucidal and/or bactericidal) that can be used at the discretion of women without partner knowledge or consent. Of the chemical barrier contraceptives, three spermicides are commercially available throughout the world - nonoxynol-9 (N-9), benzalkonium chloride, and Menfegol. Only N-9 containing spermicides are available in the United States.

Concerning the efficacy of spermicides, a few points should be emphasized. Although studies have been done, differences in study design, small sample sizes, high frequencies of sexual activity, compliance problems, including measurement of compliance, and validity of self-reported data, limit our ability to draw firm conclusions or extrapolate the findings to different populations. There are clearly trends in these results: spermicides and the male condom, if used consistently correctly, reduce the risk of gonorrhea and chlamydia infection. The spermicides used with diaphragms, the sponge, and the cervical cap deserve further study before such a statement could be made.

Unfortunately, the testing of barrier methods in populations at risk for STD and HIV presents some serious ethical issues, especially if the device is incompatible with the male condom. However, for several reasons, the prevention of pregnancy is not an acceptable surrogate for prevention of infectious diseases. First, the window of susceptibility is much smaller with pregnancy than with infection (three to five days each month versus thirty days). Second, STD pathogens are quite variable with respect to infectivity. For example hepatitis B and human papillomavirus are quite infectious; herpes simplex virus is not, nor is HIV. Third, STD pathogens vary enormously in size. One protozoan is larger than spermatozoa (7um head and 15um tail), but most are many times smaller. The protozoan that causes trichomoniasis is the size of a white blood cell (10-20um), whereas hepatitis B, the smallest sexually transmitted agent, is 42 nm. HIV is 100 -120 nm, depending upon the presence of the envelope. Fourth, since the eukaryotic cell membrane (i.e. the sperm cell membrane) is quite different from the bacterial cell membrane or the viral capsid in non-enveloped viruses (i.e., HPV). Therefore, it is not possible to predict microbicidal efficacy based on spermicidal efficacy. Fifth, if a given

compound has spermicidal activity it is unlikely to be specific for sperm. Cell membranes of vaginal and cervical cells could also be damaged and toxicity and inflammation could mitigate the protective effects of the microbicide by decreasing infectious dose.

The NIAID's research effort related to the development of topical microbicides is supported by efforts in the intramural and two extramural divisions. In the Institute's basic research portfolio for STDs and HIV, research on the early steps in the infectious process of sexually transmitted pathogens, as well as the microbial ecology of the vagina, form a solid foundation on which to expand a focused effort in topical microbicide development. In addition, through an interagency agreement, NIAID sponsors work on the microbicidal activity of N-9 containing spermicides at the CONRAD Program. Through the NIAID's Drug Discovery Program, compounds that are virucidal but do not penetrate eukaryotic cells have been identified. Data banks are being evaluated to identify all of these compounds for further screening and testing. Behavioral research related to compliance with other barrier methods for disease prevention is ongoing and will be expanded to include an agenda that addresses the specific issues related to chemical barrier use.

ROLE OF THE NIAID IN DEVELOPMENT:

Because of the strength of the NIAID's intramural and extramural research portfolio in the broad area of infectious diseases research, as well as the specific areas of STDs and HIV, we have developed a comprehensive, coordinated, focused research plan for the development of Topical Microbicides. This plan is based on a multidisciplinary research effort and co-sponsorship of many governmental and non-governmental agencies, as well as the commercial sector.

We anticipate the NIAID will pursue in a research agenda comprised of three parallel tracks - each one critical, complementary and ready for immediate implementation: 1) basic research; 2) product development and evaluation; and 3) clinical evaluation. The basic science agenda is based on expanding current efforts in delineating i) the early steps in the infectious process; ii) the molecular specificity of inactivation; iii) toxic and inflammatory changes and effect on infectious dose; iv) the characteristics of the normal vaginal and cervical environment and the role of physiological conditions and normal flora in prevention of infection; and v) factors influencing acceptability and compliance. Product development and evaluation will include i) development and standardization of *in vitro* assays to define spectrum and kinetics of microbicidal activity as well as spermicidal activity; and ii) *in vivo* preclinical safety testing and Phase I studies. Clinical evaluation will involve Phase II/III utilizing existing and new clinical trials infrastructure.

In addition to ongoing behavioral research to increase condom use, the NIAID has taken the lead in securing NIH Evaluation Funds to conduct an evaluability assessment of NIH-supported research on condom use. This is a trans-NIH initiative the purpose of which is to enhance NIH program initiatives on condom-use to prevent infectious disease and pregnancy.

Table 1. Studies investigating the efficacy of condoms in preventing STDs

Sex of population studied, study design, author and year published	Population and location	Outcome measure	Relative risk (95% C.I.)
MEN			
Cross-sectional			
Pemberton et al., 1972[57]	STD clinic clients, Belfast	Urethral gonorrhea	0.51 (0.33–0.80)
McCormack et al., 1973[58]	College volunteers, Massachusetts	Urethral Ureaplasma urealyticum	0.33 (0.16–0.68)
Barlow, 1977[59]	STD clinic clients, London	Urethral gonorrhea	0.25 (0.11–0.59)
Cohort			
Hart, 1974[60]	Australian soldiers, Vietnam	Self-reported STDs	0.00
Hooper et al., 1978[21]	Naval crewmen, Philippines	Urethral gonorrhea	0.00
Darrow, 1989[42]	STD clinic clients, California	Urethral gonorrhea	0.34 (0.10–1.13)
WOMEN			
Cross-sectional			
Oberle et al., 1989[63]	Controls from a case-control study of cervical cancer, Costa Rica	Herpes 2 seropositivity	0.60 (0.40–0.80)
Case-control			
Austin et al., 1984[64]	STD clinic clients, Alabama	Cervical gonorrhea	0.87 (0.64–1.19)
Syrjanen et al., 1984[65]	Ob/Gyn clinic clients, Finland	Cervical human papillomavirus	1.35 (0.72–2.78)
Rosenberg et al., 1992[66]	STD clinic clients, Colorado	Cervical gonorrhea	0.66 (0.52–0.84)
		Vaginal trichomoniasis	0.70 (0.55–0.89)
		Cervical chlamydia	0.97 (0.60–1.57)
		Bacterial vaginosis	1.11 (0.86–1.45)
Kelaghan et al, 1982[68]	Hospital patients, U.S.	PID	0.60 (0.40–0.90)
Cramer et al., 1987[69]	Women seeking infertility services, U.S.	Tubal infertility	0.70 (0.50–1.10)
Cohort			
Cameron et al., 1991[67]	Commercial sex workers, STD clinic clients, Kenya	Genital ulcers (adjusted for HIV infection)	0.18 (0.10–0.88)

Note: In this and subsequent tables, numbers in superscript refer to the reference list. *Source:* Table updated from D.A. Grimes and W. Cates, Jr., 1990 (see reference 1).

Table 2. Studies investigating the efficacy of condom use in preventing HIV infection in heterosexuals

Study design, author and year published	Population and location	Measure of use	Outcome measure	Measure of effect
Cross-sectional				
Mann et al., 1987[70]	Commercial sex workers, Zaire	≥50% vs. <50% >50% vs. none	HIV seropositivity	0.0 (p=.046) 0.0 (p=.090)
Padian, 1987[71]	Partners of HIV+ men, California	Not specified	HIV seropositivity	0.6 (0.30–1.30)*
Quinn et al., 1988[71]	STD clinic clients, Maryland	Always vs. never	HIV seropositivity	0.6 (0.00–4.10)*
Smiley et al., 1988[71]	Partners of hemophiliacs, U.S.	Routine vs. none	HIV seroconversion	0.5 (p=0.5)
Roumelioutou-Karayannis et al.,1988[72]	Partners of HIV+ men, Greece	Regular vs. none	HIV seropositivity	0.0 (p<0.00)
Musicco et al., 1991[72]	Partners of HIV+ men, Italy	Always vs. other	HIV seropositivity	0.2 (0.00–0.70)*
Guimaraes et al., 1991[72]	Partners of HIV+ men, Brazil	Use vs. nonuse	HIV seropositivity	0.3 (0.10–0.90)*
Cohort				
Fischl et al., 1987[73]	Partners of AIDS patients, Florida	Regular use	HIV seroconversion	0.1 (0.00–0.40)*
Ngugi et al., 1988[74]	Commercial sex workers, Kenya	Any vs. none	HIV seroconversion	0.3 (0.13–0.92)*
Laurian et al., 1989[75]	Partners of hemophiliacs, France	Always vs. other	HIV seroconversion	0.0 (p=0.15)
Kamenga et al., 1991[76]	Partners of HIV+ men, Zaire	Sporadic	HIV seroconversion	HIV incidence= 1.9 per woman-year
Allen et al., 1991[77]	Women attending pediatric/prenatal clinic, Rwanda	Sporadic	HIV seroconversion	Decreased from 4.6% per year to 3.4% per year after increase in in condom use
Musicco et al., 1991[72]	Partners of HIV+ men, Italy	Always vs. other	HIV seroconversion	0.3 (0.10–1.50)*
DeVincenzi et al., 1991[78]	Serodiscordant couples, Europe	Systematic	HIV seroconversion	0.0 (p=0.0009)
Moss et al., 1991[79]	Serodiscordant couples, Kenya	Not specified	HIV seroconversion	"Not associated" HIV incidence= 18% per year

*95% confidence interval.

Table 4. Studies investigating the efficacy of spermicides and barrier contraceptives in protecting women against STDs

Study design, author and year published	Site	Method	Outcome measure	Relative risk (95%
SPERMICIDES				
Cross-sectional				
Quinn and O'Reilly, 1985[110]	STD clinic, Tennessee	Not specified	Cervical gonorrhea	0.39 (0.31–0.50)
Descriptive community				
Cole et al., 1980[111]	STD clinic, Florida	Phenylmercuric acetate	Cervical gonorrhea	0.51 (0.32–0.80)
Case-control				
Austin et al., 1984[64]	STD clinic, Alabama	Not specified	Cervical gonorrhea	0.90 (0.47–1.73)
Jick et al., 1982[112]	Health maintenance organization, Seattle	Octoxynol or nonoxynol-9	Cervical gonorrhea	0.13 (0.04–0.40)
Kelaghan et al., 1982[66]	16 hospitals, U.S.	Not specified	PID	0.7 (0.4–1.4)
Cramer et al., 1987[68]	Infertility centers, U.S.	Not specified	Tubal infertility	1.0 (0.6–1.8)
Randomized clinical				
Cutler et al., 1977[116]	STD clinic, Pennsylvania	Nonoxynol-9	Cervical gonorrhea	0.11 (0.02–0.55)
Rendon et al., 1980[116]	Outpatient clinic, Mexico	Phenylmercuric acetate	Cervical gonorrhea	0.30 (0.08–1.14)
Louv et al., 1988[115]	STD clinic, Alabama	Nonoxynol-9	Cervical gonorrhea	0.76 (0.59–0.98)*
			Cervical chlamydia	0.78 (0.64–0.96)*
Barbone et al., 1990[117]	STD clinic, Alabama	Nonoxynol-9	Trichomoniasis	0.83 (0.61–1.1)
			Bacterial vaginosis	0.86 (0.69–1.1)
BARRIERS				
Cross-sectional				
Berger et al., 1975[123]	Family planning clinic, Louisiana	Condom or diaphragm, with foam	Cervical gonorrhea	0.53 (0.18–1.59)
Quinn and O'Reilly 1985[110]	STD clinic, Tennessee	Diaphragm or condom	Cervical gonorrhea	0.11 (0.08–0.17)
Magder et al., 1988[124]	STD clinic, Colorado	Diaphragm	Cervical gonorrhea	Protective (p<0.0
			Cervical chlamydia	0.00 (0.00–0.20)
Kjaer et al., 1990[130]	Greenland and Denmark (population-based)	Condom or diaphragm	Cervical human papillomavirus	1.00 (0.70–1.40)
			Herpes 2 seropositivity	0.90 (0.60–1.30)
Case-control				
Austin et al., 1984[64]	STD clinic, Alabama	Diaphragm	Cervical gonorrhea	0.45 (0.12–1.67)
Rosenberg et al., 1992[44]	STD clinic, Colorado	Diaphragm	Gonorrhea	0.35 (0.16–0.75)
			Trichomoniasis	0.29 (0.15–0.58)
			Chlamydia	0.28 (0.05–1.54)
			Bacterial vaginosis	0.99 (0.63–1.55)
		Sponge	Gonorrhea	0.29 (0.09–0.95)
			Trichomoniasis	0.26 (0.08–0.86)
			Chlamydia	0.87 (0.24–3.09)
			Bacterial vaginosis	0.99 (0.20–0.70)
Kelaghan et al., 1982[66]	16 hospitals, U.S.	Diaphragm	PID	0.40 (0.20–0.70)
Cramer et al., 1987[68]	Infertility centers, U.S.	Diaphragm	Tubal infertility	0.50 (0.30–0.70)
Randomized clinical				
Rosenberg et al., 1987[125]	Thailand (prostitutes)	Nonoxynol-9 sponge	Cervical gonorrhea	0.67 (0.42–1.07)
			Cervical chlamydia	0.31 (0.16–0.60)

*90% confidence interval. *Source:* Table updated from D.A. Grimes and W. Cates, Jr., 1990 (see reference 1).

Premarket Testing Guidelines for Female Barrier Contraceptive Devices Also Intended to Prevent Sexually Transmitted Diseases

April 4, 1990

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Preface

Over the past several years, the Food and Drug Administration (FDA) has followed with alarm the increase in prevalence of sexually transmitted diseases (STDs) in the United States, especially Acquired Immunodeficiency Syndrome (AIDS). Aside from sexual abstinence or a monogamous sexual relationship with an uninfected partner, most responsible clinicians believe that barrier contraception may be the only way to avoid STDs. FDA recognizes the difficulty in developing any contraceptive device, with the necessary clinical studies demonstrating safety and effectiveness, as conventionally defined. The guidelines laid out in this document are FDA's attempt, in the interest of public health, to provide manufacturers and researchers a streamlined study and evaluation approach for bringing important barrier contraceptive devices to market. Such devices must meet certain design criteria, and labeling for these devices must highlight the limitations of the safety and effectiveness data; but, overall, FDA believes that this approach will lead to an improved public health with respect to STDs.

John C. Villforth
Director
Center for Devices
and Radiological Health

I. PRECLINICAL STUDIES

Preclinical studies are intended to identify the appropriate chemical, physical, design, and toxicological characteristics of the device that can be determined in laboratory studies and animal testing. This data should be submitted in the application for investigational device exemptions (IDE) to conduct clinical trials. Such testing should demonstrate the barrier performance of the device, with respect to STD microorganisms.

A. Description of Device

The applicant should provide detailed drawings and descriptions of the device. PMA applicants will be expected to make prototype, pre-production, and production device samples available to FDA for evaluation. The physical characteristics of the device should be detailed. The rationale for the device design should be stated in the light of the relevant literature or based upon sound theoretical reasoning.

A full description of the device should also be given in the device labeling. (See Section V - Labeling.)

The following design characteristics should be fully described:

1. shape and dimensions, including surface areas;

2. presence of projections, if any;

3. inserter design, including physical characteristics, insertion procedures, and any anticipated difficulties, if applicable; (If the device does not have an inserter, describe how the device is inserted, including any anticipated difficulties.) and

4. removal procedures and any anticipated difficulties.

B. Physical Properties

Appropriate engineering tests should be performed and the results considered relative to the device's mechanical and chemical properties, as well as to its design characteristics:

1. details of mixing, forming, curing, including the materials and sources employed and their percentage composition;

2. uniformity of components in the completed devices and procedures for quality control;

3. uniformity and texture of the device surface, as determined by surface scanning electron microscopy (SEM) or other appropriate methods;

4. tensile strength, tear strength, elasticity, and other measures

of the flexural characteristics of the device and its component materials, as well as vulnerability to puncture; and

5. material standards, if applicable.

Device labeling should include important findings from the physical testing, e.g., susceptibility to tearing or puncture (by fingernails, inserter, etc.), storage conditions, etc. (See Section V - Labeling.)

C. Stability

Physical and chemical properties of the device should be studied for prolonged exposure to the intended biological environment. Physical and chemical properties of the device may be altered by prolonged exposure to lubricants, or by the effects of transit and storage. Studies should be designed to support the use of the device in its intended biological environment, with lubricants or other agents, if appropriate. Testing should support the shelf-life claimed for the device.

D. Toxicity

The biocompatibility of device materials should be evaluated by appropriate in vitro and in vivo toxicological studies. The Tripartite Biocompatibility for Medical Devices Guidance may be useful for selecting the appropriate types of tests.

E. Barrier Properties

It is essential that the device under study be an effective physical barrier to bacterial and viral STD agents. Barrier performance of the device can be demonstrated by using test particles (e.g., microspheres, radio-labeled tracers, viruses, etc.) less than or equal to 42 nm in diameter, the size of the smallest known STD micro-organism (i.e., the hepatitis-B virus).

FDA encourages the development of new test protocols to demonstrate barrier performance. Given below are necessary considerations of a testing approach.

Under test conditions that simulate actual use, compare the new barrier device to an established (reference) device, such as the latex (rubber) condom. Demonstrate that the barrier performance of the new device is as good or better than that of the reference device.

Justify any test conditions that differ from actual use conditions and which may affect the comparison of barrier performance. Conditions which may be important include temperature, pH, viscosity, the surface tension of the fluid and the wetting angle of the barrier, physical and chemical properties of the test solutes, as well as other testing

conditions, such as the magnitude of applied pressure (steady or transient), barrier membrane stress or deformation, etc.

Test methodology must be sufficiently sensitive to evaluate the permeability of the reference device, particularly with respect to the size of the test particle, as stated above, and sufficient numbers of devices of each type should be tested to provide a statistically significant comparison.

Before choosing any barrier test method, you should consult with FDA's Office of Device Evaluation (Raju G. Kammula, D.V.M., Ph.D., at 301-427-1180) on whether the selected test method is scientifically sound in order to support the premarket approval of the device.

II. CLINICAL STUDIES

Before beginning clinical studies, all preclinical studies should be completed. An application for an investigational device exemption (IDE), per 21 CFR 812, should be submitted to FDA. FDA's IDE Manual (HHS Publication FDA 86-4159) should be consulted for overall guidance in the preparation of an IDE application. Patient informed consent must contain all required elements, per 21 CFR Part 50.25, including information on discontinuing use of the device and the study follow-up procedures.

A. Feasibility Study (Phase I)

1. Objectives

Phase I studies are done to determine the feasibility, acceptability, fit, size, etc., and safety of the device. These studies should evaluate the following:

a. potential adverse effects, including (i) mucosal irritation and sensitization, (ii) microbial flora of the vagina, cervix, and device, (iii) vaginal and cervical cytology, (iv) trauma, (v) ulceration, (vi) urinary tract infection, (vii) bleeding, (viii) salpingitis, (ix) pain, and (x) discomfort;

b. device wear-time and device displacement and/or expulsions (The device must remain in place for the intended duration.); and

c. post-coital testing.

Documentation should include Papanicolau (PAP) smears and cervical photographs. PAP smears should be evaluated at a single clinical laboratory in order to maintain consistency.

2. Study Subject Selection and Exclusion Criteria

The study subject must be protected by using an effective, non-barrier, means of contraception (oral contraceptives, IUD, or tubal sterilization).

3. Investigator Selection Criteria

An investigator must be knowledgeable about all types of contraception in general and experienced in managing patients who use barrier contraceptive methods. The investigator must be willing to monitor closely each study subject and maintain reasonable follow-up.

4. Study Size and Duration

The study should include at least 50 female study subjects, with at least 10 coital episodes per subject, giving a total of 500 evaluable coital episodes.

5. Instructions for Use

At the Phase I study, it should also be demonstrated that the target population can follow printed instructions, especially if the device is to be marketed as an over-the-counter (OTC) product. That is, 1) how well does the target population properly use the device , and 2) how well does the target population understand other important messages, such as visually checking for defects, proper storage, etc. Particular effort should be made to demonstrate that patients with limited education and/or literacy can understand printed instructions for an OTC device or can understand a health care provider's instructions for a prescription device. Such studies should include well-constructed questionnaires, as well as clinical observations by health professional investigators. (See also Section II.B.5 - Instructions for Use.)

Consult with FDA's recent "GUIDANCE ON THE REVIEW OF INVESTIGATIONAL DEVICE EXEMPTIONS (IDE) APPLICATIONS FOR FEASIBILITY STUDIES".

B. Safety and Effectiveness Study (Phase II)

The Phase II study demonstrates safety, effectiveness and ease of use of the device. Because the requirement for a Phase III randomized controlled clinical trial was eliminated, increased emphasis is placed on the results of the Phase II study for all aspects of safety and effectiveness. This evaluation approach must compare the results of study of the new device to results from the study of an appropriate historical control group (e.g., cervical cap or diaphragm) with a comparable population profile accounting for relevant factors, such as age and socio-economic status. A manufacturer may obtain further information the acceptable use of an historical control group by contacting FDA's Office of Device Evaluation (Raju G. Kammula, D.V.M., Ph.D., at 301-427-1180).

1. Study Subject Selection Criteria

   a. Study subjects must be between 18 and 40 years old and should not have a history of infertility or conditions that lead to infertility. Study subjects must agree not to use additional forms of contraception and must be willing to accept the potential risk of pregnancy.

   b. Selection of study subjects should reflect the intended target population when the device is marketed. Types of patients that should be included:

      i. previously gravid;
      ii. nulligravid (must have an established normal menstrual pattern);
      iii. current or previous barrier contraceptive users; (Note that if the device under investigation is very similar to the one the subject is using or previously

Introduction

These guidelines address the preclinical and clinical testing of female barrier contraceptive devices also intended to prevent transmission of sexually transmitted diseases (STDs), including Acquired Immunodeficiency Syndrome (AIDS). The guidelines were developed on August 25, 1989, at an open public meeting of the Obstetrics-Gynecology Devices Panel (the Panel) as a collaborative effort of experts from the Food and Drug Administration (FDA), the National Institute of Child Health and Human Development (NICHD), the Centers for Disease Control (CDC), and the Panel, involving substantial interactive dialogue with the public audience, as well.

Because of the profound detrimental effect of Human Immunodeficiency Virus (HIV) and AIDS on the public health and the need for such devices in the marketplace, CDRH prepared these guidelines to expedite device study and evaluation. These guidelines do not apply to barrier contraceptive devices without demonstrated potential to prevent transmission of STDs.

It is important to note that the barrier performance of the device, with respect to bacteria and viruses, must be established through adequate laboratory studies. Test methodology selected for this purpose should specify appropriate test conditions and be sufficiently sensitive to test STD-sized particles of interest. For these guidelines to be applicable, the device must also have been demonstrated to stay in place during use. MANUFACTURERS ARE STRONGLY ENCOURAGED TO CONSULT WITH FDA'S OFFICE OF DEVICE EVALUATION REGARDING THE APPLICABILITY OF THESE GUIDELINES TO THEIR OWN SPECIFIC PRODUCT.

These guidelines are general because of the anticipated diversity of such devices. A manufacturer should develop study protocols specific to its device with the help of these guidelines. FDA's Premarket Approval Application (PMA) Manual (HHS Publication FDA 87-4214) should be consulted for overall guidance in the preparation of a PMA. During the PMA review process, FDA will evaluate the study protocol(s) for individual contraceptive devices on a case-by-case basis.

Because of the extreme difficulty in studying effects on STD rates in a clinical trial, the guidelines designate pregnancy as a surrogate study endpoint for demonstrating the device's effectiveness to prevent transmission of STDs. A key feature of these guidelines is the elimination of the requirement for a randomized controlled clinical trial to compare the performance of the new device to that of an established barrier contraceptive device in a concurrent control group. This is coupled with requirements for a strengthened feasibility study (Phase I) with emphasis on health risks and device displacement during use, followed by the non-randomized clinical trial (Phase II). The manufacturer must compare the results from this Phase II study to appropriate historical controls.

In summary, the material(s) and design of the new barrier contraceptive device should be thoroughly studied prior to beginning any clinical studies. Results from the clinical studies must support the safety and effectiveness of the new barrier contraceptive device, i.e., its risks or undesirable side-effects and its effectiveness in preventing pregnancy and transmission of STDs, leading ultimately to a risk-benefit assessment.

used, this may influence the study results.)
iv. non-barrier contraceptive users; and
v. never users of contraception (must have an established normal menstrual pattern).

c. Study subjects must be sexually active with at least 2-3 coital episodes weekly.

d. Study subjects must have had at least two normal consecutive menstrual cycles under the following circumstances:

i. after discontinuing hormonal contraceptives; or
ii. recently postpartum or postabortion.

2. Study Subject Exclusion Criteria

a. Study subjects who are pregnant, have a suspected pregnancy, or desire to become pregnant while participating in the study should be excluded from the study.

b. Study subjects who are unable to conform to the follow-up schedule or study subjects who anticipate moving away from the area within the study duration should be excluded from the study.

c. Study subjects who cannot be fitted with the device, or who are unable to understand instructions for use, or who are unable to correctly apply the device should be excluded from the study.

d. Study subjects with the following medical conditions should be excluded from the study:

i. a history of infection or surgery that might compromise fertility;
ii. a medical condition contraindicating pregnancy, such as diabetes or heart disease;
iii. undiagnosed vaginal bleeding;
iv. untreated abnormal PAP smear; or
v. cervical cytology equivalent to Class III or worse.

Data on study subjects using the device and later found to have one of the above conditions must be analyzed and reported separately. Such cases may not count towards the required total number of study subjects. (See Section II.B.6 - Statistical Evaluation, below.)

3. Investigator Selection Criteria

a. There should be at least two investigators conducting the studies at a minimum of two separate sites.

b. Each investigator shall contribute an equal number of study subjects to comprise a statistically valid sample.

c. An investigator must be knowledgeable about all types of contraception in general and experienced in managing patients who use barrier contraceptive methods. The investigator must be willing to closely monitor each study subject and maintain reasonable follow-up. The status of each patient must be determined on a monthly basis and significant events must be entered into a monthly report.

d. The investigator should use a 3-month "holding" period for data collection, after the designated study duration, to ascertain pregnancies and other events of interest that may have actually occurred during the duration of observed use, but not discovered by the patient or reported to the investigator during that time.

4. Study Size and Duration

The number of subjects should be sufficient to end up with at least 200 study subjects, contributing to a standard 12-month lifetable analysis. Depending upon monthly interval analysis, CDRH, on a case-by-case basis, may permit submission of a PMA application with a 6-month (or less) lifetable analysis. (See Section IV - Post Market Surveillance.)

5. Instructions for Use

Because the effectiveness of barrier contraceptive devices is so dependent upon proper use, Phase II studies must demonstrate, as an extension of the results from the Phase I studies, how well patients can understand printed instructions for an OTC device, or, for prescription devices, how well patients will understand the printed instructions and a health care provider's instructions. That is, similar to the Phase I studies, 1) how well does the target population properly use the device, and 2) how well does the target population understand other important messages, such as visually checking for defects, proper storage, etc. Particular effort should be made to demonstrate that patients with limited education and/or literacy can understand printed instructions for an over-the-counter (OTC) device, or can understand a health care provider's instructions for a prescription device. Such studies should include well-constructed questionnaires, as well as clinical observations by health professional investigators.

As stated, FDA recommends that PMA applicants conduct consumer field evaluations to determine a lay person's ability to properly use the device unassisted, following instructions in the labeling. This information should be submitted to FDA in the PMA application. Key features of such an evaluation are given below:

a. Lay users selected for the study should be of limited education and literacy. (Patient selection criteria should

be submitted to FDA with the study protocol and results.)

b. The number of subjects selected for testing should be sufficient to support statistically valid conclusions.

c. A simple questionnaire, provided to study participants, may be used to determine if the user understood the purpose of the device, the conditions for its use, and any limitations or special precautions. (The PMA should contain a sample of the questionnaire, as well as a tabulation of all questionnaire responses.) The study write-up should also contain the results of observations made by nurse investigators.

6. Statistical Evaluation

Statistical analyses of safety and effectiveness should be done via the multiple decrement life table method or other appropriate analytic models, to permit simultaneous statistical treatment of important outcome events, such as pregnancy, expulsion or displacement, infection, abnormal PAP smears, discontinuation for pain/bleeding/other medical reasons, and discontinuation for personal reasons (desired pregnancy or dissatisfaction). Analysis should be conducted at one month intervals to examine the data for trends. Appropriate actions, warnings, or precautions should be taken if the monthly analysis so warrants. A standard 12-month life table analysis should be performed, but CDRH may accept a PMA with a 6-month (or less) life table analysis, depending upon the results of the monthly interval analysis. The confidence interval should be provided for the final cumulative pregnancy rate.

The start time for an individual subject's participation in the study, for the purposes of follow-up and life table analysis, is the date of first coitus after the woman has received a supply of contraceptive devices. The stop time depends upon decisions made on important outcome events, such as those given above. Each patient who has not terminated device use or who has not been lost to follow-up should have the required number of months of observed use of the device prior to completion of the analysis (unless discontinued for reasons given above). At least 200 study subjects should be analyzed, but more may be required, as appropriate, depending on the statistical power of the study. Both net and gross life table rates should be presented.

7. Data Collection

Provide demographic data on each study subject, including age, race, and socioeconomic status. If feasible, data should be collected on respondent satisfaction with prior contraceptive methods, particularly barrier methods.

Important outcome events, such as pregnancy or infection,

should be accompanied with both the date of reporting and estimated date of occurrence, and not just the ordinal month in which they occurred. This additional data will permit estimates of the time lapse between occurrence and reporting of events, and will also permit, if necessary, use of more elaborate statistical analyses such as Cox regression models.

The following specific data should be recorded and analyzed to evaluate safety and effectiveness:

a. date of pregnancy (Correlate to items #i and/or #j below.);

b. date of infection, type, and method of diagnosis;

c. trauma to vagina, cervix, or penis;

d. PAP smear conversions and intake history (The same laboratory should be used for all PAP smears.);

e. discomfort;

f. pain;

g. any other reported adverse effects;

h. ease of insertion and removal;

i. device rupture, tear, or puncture;

j. displacement/expulsion during use: how frequently and when;

k. subject compliance with study protocol and instructions for device use; data should be collected on subject understanding of other key messages in the labeling, such as under what circumstances one's personal health care provider should be contacted;

l. device discontinuation

   i. discontinuation date, medical reasons (specify, e.g., allergy, infection, trauma, odor, itching, etc.);
   ii. discontinuation date, dissatisfaction with device (specify, e.g., inconvenient, uncomfortable, partner can feel it, subject can feel it, etc.); and
   iii. discontinuation date, personal reasons unrelated to device (specify, e.g., desire to become pregnant, putting off sterilization, move from geographical area, etc.)

m. Level of acceptability - study subject

n. Level of acceptability - partner(s)

III. GOOD MANUFACTURING PRACTICES (GMPs)

A description of Good Manufacturing Practices (GMPs) and quality assurance (QA) procedures for the device should be submitted in the premarket approval application. FDA will evaluate these procedures and practices for the specific device design. Refer to FDA's PMA Manual.

IV. POST MARKET SURVEILLANCE

During its review of the PMA, FDA may identify unforeseen device-related adverse effects. In this instance, FDA, in consultation with its advisory Panel, may impose post market surveillance requirements to obtain further information.

V. LABELING

Labeling must contain a complete description of the device based upon the findings from the preclinical and clinical studies. Because of the limited nature of the Phase I and Phase II studies for these devices, FDA will require full disclosure of the safety and effectiveness of the new barrier contraceptive devices, in the product labeling, with respect to all aspects, known and unknown, of device safety, effectiveness, and instructions for use. A limited product claim will also be necessary. FDA also recommends that the device manufacturer provide a toll-free telephone number or an address in the labeling for consumers to direct questions about device use or problems.

Manufacturers are encouraged to consult with FDA's manual, "Labeling: Regulatory Requirements for Medical Devices", (HHS Publication FDA 89-4203). It is also important, as stated earlier, that general labeling guidance given in FDA's PMA and IDE manuals be followed, as appropriate.

7/6/93
Helene Gayle

USAID-Funded Projects on Female Control Methods for HIV/STD Prevention

Through the Offices of Population and Health, USAID has or is currently supporting the following types of activities:

Female condoms

- Acceptablity of female condoms in high and low risk populations (Thailand, Kenya and Cameroon)
- Acceptability of the female condom in discordant couples (Zambia)
- Male attitudes towards female condoms (sites to be determined)
- Re-use of female condoms (sites to be determined)
- Efficacy of female condom against STDs (possible to include US site)

Microbicides

- Efficacy of condoms/spermicides against STDs (Columbia and Honduras)
- Acceptability of vaginal film (Kenya, Domincian Republic, Mexico)
- Spermicide acceptability in STD clinics (Zambia)
- Efficacy of N-9 lubricated condoms vs. silicone lubricated condoms against STDs (Honduras)
- Spermicide use and STDs (Thailand)
- Effects of frequent use of N-9 (Dominican Republic)
- Activity of spermicides against other STDs in macques
- Development and screening other microbicidal compounds

NEEDS & OPPORTUNITIES: CDC's FUTURE ROLE

* Behavioral research priorities

  Descriptive analyses
  - determinants of barrier use among women and their partners
  - acceptability of various barrier methods
  - determinants of user compliance with barrier methods

  Intervention development & evaluation
  - to change perceived norms and "meanings" of barrier use
  - to change behaviors involved with adoption and consistent use of barrier methods

* Clinical trials of existing and newly developed microbicidal agents for safety & efficacy with respect to all STDs, including HIV infection

  - definition of dose-response relationships between agents & inflammation
  - characterization of nature of inflammatory response
  - evaluation of post-coital use of microbicides
  - examination of feasibility & efficacy of combined methods (eg. diaphragm or cervical cap with microbicide)

7/6/93 - Wasserheit

DEVELOPMENT OF FEMALE-CONTROLLED BARRIER METHODS TO PREVENT HIV INFECTION & OTHER STDs

WHAT HAVE WE LEARNED?

* Method mix is essential to meet diverse contraceptive needs among women, and for each woman through her lifecycle & relationships

* Perceived safety and effectiveness are central in contraceptive selection; perceived side-effects are major determinants of discontinuation

* Counselling plays key role in acceptance and consistent use of contraception; counselling couples may be more successful than counselling women alone. (This may not be applicable for STD/HIV prevention)

* Pregnancy prevention & STD/HIV prevention messages compete, rather than complement

* Social "meanings" of condom use for STD/HIV prevention present huge barriers (particularly in primary relationships)

* High self-efficacy, ability to talk with partners about STD history, and HIV positivity have been positively associated with condom use; emotional closeness, living with partner, and having or wanting children with partner have been associated with non-use

* CD4 cells may be present in a gradation of concentrations that is highest in the endocervix (or zone of ectopy) and lowest in the vagina

* N-9 has good activity against bacterial STDs such as gonorrhea and chlamydia; there are inadequate data for viral STDs

* In high doses or with frequent use, N-9 may cause sufficient inflammation to offset activity against HIV/STDs

TO: Chief of Staff
Through: ES_____

FROM: Acting Assistant Secretary for Health

SUBJECT: Your Meeting to Discuss Female Controlled Barriers to Prevent HIV Infection and Other Sexually Transmitted Diseases--BRIEFING

PURPOSE

To provide you with information for your meeting with OS and PHS staff, scheduled to be held in the Deputy Secretary's Conference Room at 2:00 p.m. on July 6, 1993.

PARTICIPANTS

Outside the Department

Dr. Helene Gayle, AIDS Coordinator, A.I.D., Office of Health

Inside the Department

Ms. Kristine Gebbie, AIDS Policy Coordinator
Ms. Nan Hunter, Deputy General Counsel/Legal Counsel
Ms. Claudia Cooley, Executive Secretary
Ms. Patsy Fleming, Special Assistant to the Secretary
Mr. Glen Harelson, OS Policy Coordinator
Dr. David Kessler, Commissioner, FDA
Dr. Anthony Fauci, Director, OAR, and Director, NIAID, NIH
Dr. James Curran, Associate Director for HIV/AIDS, CDC
Dr. Florence Hazeltine, Director, Center for Population Research, NICHD, NIH
Dr. Penny Hitchcock, Chief of the Sexually Transmitted Diseases Branch, Division of Microbiology and Infectious Diseases, NIAID, NIH
Dr. Wendy Baldwin, Deputy Director, NICHD, and Acting Deputy Director for Extramural Research, NIH
Dr. Nancy Alexander, xxxx, NIH
Dr. Sten Vermond, Chief, Vaccine Trials and Epidemiology Branch, Division of AIDS, NIAID, NIH
Dr. Judy Wasserheit, Director, Division of Sexually Transmitted Diseases and HIV Prevention, CPS, CDC
Dr. Randolph Wykoff, Director, Office of AIDS Coordination, FDA
Dr. Jocelyn Elders, Surgeon General-Designate
Dr. Arthur Lawrence, Acting Deputy Director, NAPO

V. W

PHS CORRESPONDENCE

13627

REFERRAL DATE: 6-24 **DUE DATE:** 7-2

TO:

2 ☒ ASH Acting
☐ DEPUTY ASH
☐ SG
☐ DASH-MO
☐ DASH-SE
☐ DASH-C
☐ DASH-DPHP
☐ DASH-IGA / RHA
☐ DAS-IH
☐ DAS-MH
☐ DASH-PA
☐ DAS-PHP

☐ ADAMHA
☐ AHCPR
☐ ATSDR
☐ CDC
☐ FDA
☐ HRSA
☐ IHS
☐ NIH
1 ☒ NAPO
☐ NVP
☐ PCPFS

☐ OEEO
☐ OEP
☐ OGC / H
☐ OHL
☐ OHPE
☐ OM
☐ OSIR
☐ OWH

3 ☒ ES / PHS
4 ☒ OTHER D. Lee

ACTION:

☐ SECRETARY'S SIGNATURE
1 ☒ ASH SIGNATURE Acting
☐ DIRECT REPLY
☐ _____ SIGNATURE
☐ DRAFT FOR OS SIGNATURE (WHITE HOUSE REFERRAL)

☐ REVIEW / CLEARANCE
☐ NECESSARY ACTION
☒ FOR YOUR INFORMATION
2-4

SPECIAL

SPECIAL INSTRUCTIONS

EXPEDITE

PHS-5175
Rev. 4/92

PHS / ES
Rm. 710H

Phone: 690-6761

Routed by:

135

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

JUN 29 1993

NOTE TO DR. SETLOW

Through: Bob Rickard

SUBJECT: OS Briefing Material Request for Meeting with the Chief of Staff on Female Controlled Barriers to HIV Infection and Other STD's -- ACTION

The Secretary's Executive Secerttariat has requested briefing materials for a meeting that has been scheduled for July 6 at 2 PM to brief the Chief of Staff, Kevin Thurm, on the above subject (see attached note to Dr. Lee from Glen Harelson.)

After receiving this note from OS we were informed by Glen Harelson that it is uncertain whether Dr. Lee will be able to participate in this meeting due to a scheduling conflict. However, OS has asked that PHS take the lead in presenting the material to Mr. Thurm.

We would appreciate NAPO taking the lead in preparing the requested materials, coordinating with NIH, CDC and FDA as necessary. In view of the extremely tight turnaround time for submission of this material to OS, I would suggest that the briefing package contain:

- a short cover memo to the COS listing the date, time, and place of the meeting and the participants, and,

- fact sheets in bullet form describing: the issue; current activities in Federal and other research on female barriers; and any other related issues or concerns that would be pertinent to the discussion.

In order to meet the due date for submission of this material to OS, please forward the completed briefing package to this office **no later than noon on Friday, July 2, 1993.**

Barbara Brady
PHS Executive Secretariat

Attachment

cc: Dr. Lee
Dr. Manley

RECD 1pm
ESPHS 6-29-93

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Washington, D.C. 20201

JUN 29 1993

MEMORANDUM FOR PHIL LEE, M.D.

On Tuesday July 6, at 2:00 PM, in the Deputy Secretary's Conference Room, a briefing is scheduled for the Chief of Staff on Female-Controlled Barriers to HIV Infection and Other STD's. I ask that you please prepare a briefing memorandum for the Chief of Staff which provides an overview of the subject. Namely, current activities in the Department that address the issue, what we know about activities outside the Department and future prospects for the development of such barriers. Please provide a briefing memorandum for the COS to OS/ES by Friday July 2, 1993. PHS will have the lead in presenting the material to the COS.

Thank You.

Glen Harelson