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Issues - STDs [Sexually Transmitted Diseases] - Topical Microbicides Program [1]

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NIH

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

APR 10 1998

RECEIVED
1998 APR 13 A 9:27
NIH EXECUTIVE SECRETARIAT

The Honorable Connie Morella
U.S. House of Representatives
Washington, D.C. 20515

Dear Representative Morella:

Thank you for the letter that you and 29 colleagues sent to me expressing your support for research on topical microbicides and requesting an accounting of our current investment in this area. I am pleased to respond to your inquiry about the Department's efforts in advancing this important area of research. I apologize for the delay in my response.

The Department has supported vaccine, drug, diagnostic, and contraceptive research and development for many decades, and we share your commitment to the development of a woman-controlled method for STD/HIV prevention. It is, and will remain, a top priority for the Department. We have initiated a Public Health Service-wide initiative to facilitate this progress. The National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) are working in a collaborative and coordinated fashion on research and evaluation. Program staff from both agencies are involved in active consultation with the Food and Drug Administration (FDA) to develop science-based guidelines for product evaluation. Furthermore, representatives from all three agencies have had a leadership role in the International Working Group on Microbicides. The Working Group has developed and supported an international network of scientific and clinical investigators who are working with private sector sponsors to develop and evaluate these products.

We also recognize the critical role of industry in this effort. The Government's role in facilitating product development has been identified by the Vice President as one of our highest priorities. Mindful of this commitment, the Department has worked assiduously to foster and facilitate product development efforts. The NIH and CDC support research grants and contracts, including Small Business Innovative Research awards, to over a dozen small businesses as well as hold ongoing consultations with major pharmaceutical companies interested in topical microbicide development.

At the NIH, five Institutes or Centers support research on or related to topical microbicides: the National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), National Institute

on Drug Abuse (NIDA), National Institute of Mental Health (NIMH), and Fogarty International Center (FIC). In addition, two offices within the NIH Office of the Director, the Office of AIDS Research (OAR) and the Office of Research on Women's Health (ORWH), provide supplemental funds to augment research grants funded by the Institutes. In FY 1997, OAR and ORWH provided supplemental funds to NIAID, NICHD, and NIMH grants and contracts. At the CDC, three Centers support research on topical microbicides. These are the National Center for HIV, STD and TB Prevention (NCHSTP), the National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP), and the National Center for Infectious Diseases (NCID).

The Department's topical microbicides initiative has five major research goals. These goals are to: 1) define the molecular basis and chronology of the early steps in the infectious process; 2) define vaginal and cervical ecology and the natural defense mechanisms of the female reproductive tract; 3) facilitate pre-clinical development of topical microbicides; 4) facilitate clinical evaluation of topical microbicides for safety and efficacy; and 5) define product characteristics and use-patterns that facilitate acceptance of and compliance with topical microbicides. The research portfolio is built upon a basic biomedical and basic behavioral research foundation. These basic research efforts are key to the development and evaluation of safe, effective products. The portfolio for topical microbicides product development includes pre-clinical, clinical, and behavioral research components.

The four specific questions on topical microbicides contained in your letter are addressed below and in the attached tables.

What is the Department of Health and Human Services' current investment portfolio on microbicide research?

We made a commitment of $100 million dollars over four years to the topical microbicides research effort. The budget figures for FY 1997 are summarized in the attached Table 1. In FY 1998, the NIH AIDS budget estimate and the CDC budget estimate include funding increases for research on topical microbicides.

How much of the microbicide resources are devoted specifically to microbicide product development and testing versus to initiatives serving multiple purposes?

As shown in Table 2, approximately three-fourths of the FY 1997 resources were allocated for product development, clinical evaluation, and behavioral research and one-fourth for basic biomedical/behavioral research with multiple purposes.

If some research is serving multiple purposes, what are those projects and how much of the $100 million does this represent?

Studies funded in FY 1997 that are categorized as basic research with multiple purpose are shown in aggregate in Table 2. Table 3 provides a comprehensive list of these projects (by grant title and number) and identifies the relationship between the project and the microbicide research effort as well as the prorated amount of funding attributed to microbicide research. Please note that the dollar amount listed for each project reflects the percent effort attributed to microbicide research.

Is research related to non-chemical contraceptive barrier methods being counted toward the microbicide investment goal of $100 million? If yes, what are those projects and how much of the $100 million does this represent?

Research on the development of non-chemical contraceptive barrier methods is not included in these budget figures.

The Department shares your commitment to improving the health of women and to the research and development of topical microbicides. I look forward to continuing to work with you on this important problem. I will respond to each of your co-signatories in the same manner.

Sincerely,

Donna E. Shalala

3 Attachments

Identical letters sent to:

Rep. Nancy Johnson
Rep. Sue Kelly
Rep. Louise Slaughter
Rep. Eddie Bernice Johnson
Rep. Eleanor Holmes Norton
Rep. Nancy Pelosi
Rep. Carolyn Maloney
Rep. Lynn Woolsey
Rep. Sheila Jackson-Lee
Rep. Juanita Millender-McDonald
Rep. Carolyn McCarthy
Rep. Patsy Mink
Rep. Lynn Rivers
Rep. Zoe Lofgren
Rep. Ellen Tauscher
Rep. Darlene Hooley
Rep. Carrie Meek
Rep. Elizabeth Furse
Rep. Carolyn Kilpatrick
Rep. Diana DeGette
Rep. Karen Thurman
Rep. Cynthia McKinney
Rep. Donna Christian-Green
Rep. Pat Danner
Rep. Eva Clayton
Rep. Marcy Kaptur
Rep. Nydia Valazquez
Rep. Debbie Stabenow
Rep. Nita Lowey

Table 1
Department of Health and Human Services
Investment in Microbicide Research
FY 1997 (actuals)

NIH	Grants	Contracts	Total $
NIAID	45	15	13,124,804
NICHD	20	11	6,344,099
OAR	NIAID grant*	NIAID contract*	845,329
OAR	1 - NIMH grant	0	112,670
ORWH	NIAID grant*	0	100,000
FIC	3	0	100,000
NIDA	2	0	106,821
Total NIH	**71***	**26**	**20,733,723**
Total CDC	**7**	**3**	**3,969,283**
Total DHHS	**78***	**29**	**24,703,006**

*The supplements to NIAID grants and contracts have not been counted in the totals.

Table 2
Percentage of Microbicide Resources Dedicated
Specifically to Microbicide Product Development/Clinical Evaluation
Compared to
Basic Research with Multiple Purposes
FY 1997 (actuals)

Agency/ Institute	Product Development/ Clinical Evaluation		Basic Research with Multiple Purposes	
NIH	**Dollars**	**% of Total**	**Dollars**	**% of Total**
NIAID	9,215,773	70	3,909,031	30
NICHD	4,840,133	76	1,503,966	24
OAR (NIAID)	845,329	100	0	0
OAR (NIMH)	112,670	100	0	0
ORWH (NIAID)	100,000	100	0	0
FIC	0	0	100,000	100
NIDA	0	0	106,821	100
Total NIH	**15,113,905**	**73**	**5,619,818**	**27**
Total CDC	**2,979,239**	**75**	**990,044**	**25**
Total DHHS	**18,093,144**	**73**	**6,609,862**	**27**

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Allergy and Infectious Diseases			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
R37-AI-22624 Natural History of HIV Infection	Basic research; Clinical/Epi* information	5	43,881
R37-AI-29164 Antiviral Resistance in AIDS	Basic research; drug resistance mech	10	51,190
AI-SUB 30731 Epidemiology/Pathogenesis of Asymptomatic Genital Herpes	Basic research; shedding of HSV - early steps in infection process	25	28,605
AI-SUB 30731 Asymptomatic HSV-OB/GYN	Basic research; shedding of HSV - early steps in infection process	25	45,834
AI-SUB 30731 Asymptomatic HSV-HIV	Basic research; shedding of HSV in HIV+ people	25	27,771
AI-SUB 31494 Behavior Epidemiology of Reoccurrent STI in Adolescents	Basic research; risk perception and PX* of STDs	50	118,363
AI-SUB 31496 A Human Challenge Study of *Neisseria gonorrheae*	Basic/clinical research; early steps in infectious process; clinical eval of topical microbicides	25	43,109
AI-SUB 31496 A Lay Health Advisor Program to Prevent STDs	Basic research; epi* of STDs in rural South; health seeking behaviors related to PX*	25	97,633
R01-AI-32330 SIV and HIV Pathogenesis during Ontogeny	Basic research; early steps in infectious process	25	83,587

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Allergy and Infectious Diseases			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
R01-AI-32686 Chlamydia and Douching in Ectopic Pregnancy	Basic research; shedding of Ct* into vagina; acceptability of vaginal products	50	152,288
R29-AI-33522 Cytolysins of *Haemophilus ducreyi*	Basic research; early steps in the infectious process	50	50,400
R01-AI-33810 HIV-1 Transmission *in vivo*	Basic research; early steps in the infectious process	30	81,188
R29-AI-34354 Molecular Analysis of Treponemal Motility Genes	Basic research; early steps in the infectious process	20	20,650
AI-SUB 34582 Immune Responses to Gonococcal Infection	Basic research; early steps in the infectious process	50	116,032
AI-SUB 34616 HLA and Chlamydia Disease Pathogenesis	Basic research; pathogenesis of chronic infection	25	35,762
AI-SUB 34616 Lesion-Derived T Lymphocytes in Early Syphilis	Basic research; pathogenesis/early steps in the infectious process	25	35,793
AI-SUB 34617 Clinical-Chlamydial/Statistical Core	Basic research; early steps in the infectious process	25	176,853
AI-SUB 34617 Peptide Synthesis Core	Basic research; early steps in the infectious process	50	2,913
AI-SUB 34617 Epitope-HLA Specificity of Anti-Chlamydial Human T Cells	Basic research; pathogenesis	50	7,984

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Allergy and Infectious Diseases			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
AI-SUB 34617 Chlamydial Antigen Presentation by Native Human Cells	Basic research; pathogenesis	50	8,947
AI-SUB 34617 Chlamydial Persistence in Human Genital Cells	Basic research, pathogenesis	50	8,373
AI-SUB 34617 Molecular Specificity of Humoral Immunity to Chlamydia	Basic research; pathogenesis	50	9,302
R01-AI-34826-S1 STD Control for AIDS Prevention	Basic research; clinical/epi* of STDs	15	3,460
R01-AI-34826 STD Control for AIDS Prevention	Basic research; feasibility—clinical trial	15	321,779
R01-AI-34826-S2 STD Control for AIDS Prevention	Basic research; behavioral factors relating to use of prevention methods	15	12,446
AI-SUB 34831 Adult Clinical Trials Unit	Basic research; HIV in genital tract of women	10	7,409
AI-SUB 35682 Clinical Trial	Basic research; feasibility—clinical trial	10	16,398
R01-AI-35694 Gonococcal POR, OPA, and Neutrophil Activation	Basic research; pathogenesis	25	44,548
R01-AI-36643 Virus Variation and Sexual Transmission of SIV	Basic research; early steps in the infectious process	30	63,761
R01-AI-36986-S1 Perceived Risk for Sexually Transmitted Diseases	Basic research; behavioral factors; risk perception	50	15,457

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Allergy and Infectious Diseases			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
R01-AI-36986 Perceived Risk for Sexually Transmitted Diseases	Basic research; behavioral factors; risk perception	50	313,653
R01-AI-37466 Epidemiology of HIV-1 and HIV-2 in the Cervix and Vagina	Basic research; early steps in the infectious process	25	94,709
R01-AI-38492 Pathogenesis and Prevention of SHIV Disease	Basic research; early steps in the infectious process	50	176,401
R01-AI-38501 Determinants of HIV/SIV Mucosal Transmission	Basic research; early steps in the infectious process	50	155,876
AI-SUB 38514 Bacterial Vaginosis: Pathogenesis and Impact on STDs	Basic research; early steps in the infectious process	50	70,070
AI-SUB 38515 Condom Promotion Interventions for STD Clinic Patients	Basic research; behavioral factors relating to use of prevention methods	50	80,867
AI-SUB 38515 Humoral and Cellular Immune Response in Gonococcal Disease	Basic research; pathogenesis	25	58,839
R01-AI-38518 Early Infection in Women Exposed Mucosally to HIV-1	Basic research; early steps in the infectious process	50	147,805
R01-AI-38545 GP120 VH3 Superantigen and HIV-1 Pathogenesis	Basic research; pathogenesis	25	43,713
R01-AI-38559 Early Events in SIV Infection	Basic research; early steps in the infectious process	50	227,567

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Allergy and Infectious Diseases			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
R01-AI-38565 Pathogenesis - Sexual Transmission of Primate Lentivirus	Basic research; early steps in the infectious process	50	218,913
R01-AI-38573 Early Events in Mucosal Transmission of SIV and SHIV	Basic research; early steps in the infectious process	50	244,342
R01-AI-38580 Mucosal Infection of Macaques with an Acutely Lethal SIV	Basic research; early steps in the infectious process	50	182,342
R01-AI-39996 HIV Shedding in Women - Factors Influencing Infectivity	Basic research; early steps in the infectious process	25	50,832
R01-AI-40350 Antiviral Therapy and HIV in the Genital Tract of Women	Basic research; impact of Rx* on shedding	25	111,386

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Child Health and Human Development			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
D43-TW-00003-10 International AIDS Training Program	Behavioral survey; international AIDS training program	50	161,060
P01-HD-31921 Prospective Longitudinal Study of Adolescent Health	Behavioral survey; adolescent health study - contraceptive use	5	97,120
R01-HD-17337 Mucosal Immunity in the Female Genital Tract	Basic research; female genital immune defenses	50	96,863
R01-HD-31646 Contraceptive Effectiveness and Unintended Pregnancy	Behavioral survey; estimate efficacy of contraceptives used by U.S. women	20	31,753
R01-HD-32789 Acceptability of Barrier Methods for Disease Prevention	Behavioral survey; acceptability of barrier contraceptives for disease prevention	25	197,511
R01-HD-33168 Vaginal Immunity Role of Endogenous/Exogenous Agents	Basic research; vaginal immunity – role of internal and external factors	50	81,248
R01-HD-33171 Mucins Covering the Cervix and Vagina	Basic research; female reproductive tract defenses	50	146,290
R01-HD-33194 Female Immune Response to Coitus	Basic research; effect of coitus on female immune defenses	50	96,091

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Child Health and Human Development			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
R01-HD-33205 Factors Affecting Vaginal Immunology and HIV 1 Infection	Basic research; factors affecting susceptibility to HIV-1 infection	50	207,840
R01-HD-34890 Contraceptive Use Dynamics in the U.S.	Behavioral survey; contraceptive method switching	10	12,736
R01-HD-34897 Dynamics and Meaning of Adult Unintended Pregnancy	Behavioral survey; contraceptive practices of young unmarried women	10	50,242
R01-HD-35037 Initiating Contraception in An STD Clinic Setting	Behavioral survey; introduction of contraceptive methods to an STD population	20	43,165
R29-HD-29924 Transepithelial Transport in Cultured Uterine Cells	Basic research; model for cervical susceptibility	50	53,550
R29-HD-33210 Mucosal Immunity of the Genital Tract	Basic research; female immune defenses	50	28,896

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Child Health and Human Development			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
Y01-HD-00081 National Survey of Family Growth - Cycle 6	Behavioral survey; national survey of family growth - section on contraceptive choices	5	30,000
R01-HD-33215 Cervicovaginal Inflammation and Infection and HIV Load	Basic/clinical research; relating infection, inflammation and HIV load	50	149,419
R01-HD-33275 Contraceptive Use/Unintended Pregnancy	Behavioral research; contraceptive use and STD infection	5	20,182

National Institute of Drug Abuse			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
R01-DA-08005 Skills and Self-help to Reduce HIV and Drug Use in Women	Basic research; risk perception; acceptability of vaginal products	10	88,660
R01-DA-09520 HIV Prevention in African American Drug Dependent Women	Basic research; risk perception; acceptability of vaginal products	5	18,161

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

Fogarty International Center			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
D43-TW-00007-10 International Training Grant in Epidemiology	Training and research capacity building in support of NIAID and NICHD funded studies	5	40,000
T22-TW-00001-10 Special International Postdoctoral Program	Training and research capacity building in support of NIAID funded study of nonoxynol-9 and HIV infections among prostitutes	5	10,000
D43-TW-00003-10 International AIDS Training Program	Training and research capacity building in support of an NICHD funded study	5	50,000

Table 3
CENTERS FOR DISEASE CONTROL AND PREVENTION - FY 1997 (actuals)

MULTIPLE PURPOSE BASIC RESEARCH IN TOPICAL MICROBICIDES

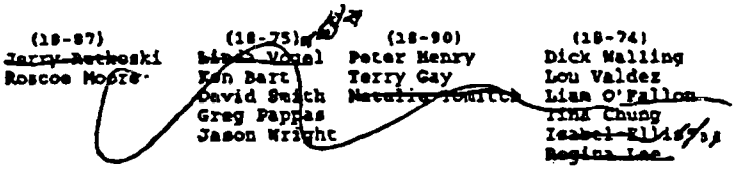
Centers for Disease Control and Prevention			
GRANT TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
Development of Assay to Detect and Quantify HIV in Cervicovaginal Secretions	Basic research; methods to detect HIV for use in clinical efficacy trials	75	643,544
Natural History of HIV Disease in Women	Basic research; relationship between bacterial STDs and HIV, measures of mucosal immunity in vagina	5	220,000
Immune Response to HIV Infection in the Female Genital Tract	Basic research; evaluate pathophysiology of HIV at mucosal surfaces and measures of mucosal immunity	50	126,500

*Epi = epidemiology
*PX = prevention
*Ct = Chlamydia trachomatis
*Rx = Treatment

Congress of the United States
House of Representatives
Washington, DC 20515

October 9, 1997

The Honorable Donna Shalala
Secretary
Department Of Health and Human Services
200 Independence Avenue, SW
Washington, D.C. 20201



Dear Secretary Shalala:

A year ago in Vancouver, you announced that the National Institutes of Health would spend $100 million over the next four years on research aimed at developing a safe and effective vaginal microbicide. As long-time advocates for the development of woman-controlled methods of STD prevention, we were extremely heartened by your announcement. We believe this research is critical to preserving the health of women around the world and to stopping the spread of HIV/AIDS.

Sixteen years into the AIDS crisis, the incidence of sexually transmitted diseases (STDs), including HIV/AIDS, continues to rise exponentially. As you know, women are currently the fastest-growing group with HIV/AIDS in the United States, and internationally, AIDS is already equally common in women and men. Women need prevention products they can use, if necessary, without their partners' knowledge or consent. Microbicides would allow women to protect themselves against HIV and other STDs without being forced to negotiate condom use with their partners.

The need for a woman-controlled method of STD and HIV prevention has only recently been recognized as a priority. It will take a number of years to complete the necessary research to bring a microbicide to market. Researchers working on the development of new products are pursuing some encouraging leads, and it is absolutely critical that resources be made available so that they can continue their efforts to develop, test, and make microbicidal products available to women.

We remain committed to ensuring that adequate funds are available for research aimed at developing microbicidal products. Industry estimates that it takes approximately $250 million to bring a new drug to market. However, large pharmaceutical companies have expressed little interest in pursuing microbicide research, so public sector collaboration is essential both for developing new product leads and for supporting the increasing number of small biotech companies that are entering the field of microbicide research. That is why the $100 million commitment you made is so important.

In the interest of better understanding the effectiveness of the public sector investment, we are writing to respectfully request an accounting of government's current investment in microbicide research.

- What is the Department of Health and Human Service's current investment portfolio on microbicide research (broken down by grant/contract or project in each participating institute or agency)?

- How much of the microbicide resources are devoted specifically to microbicide product development and testing versus to initiatives serving multiple purposes (e.g. research on heterosexual transmission, maintenance of clinical trial infrastructure)?

- If some research is serving multiple purposes (such as basic research or the development of animal models and clinical trial networks), what are those projects and how much of the $100 million does this represent?

- Is research related to non-chemical contraceptive barrier methods (i.e. diaphragms and new condoms) being counted toward the microbicide investment goal of $100 million? If yes, what are those projects and how much of the $100 million does this represent?

We thank you once again for taking a stand on the need for woman-controlled methods of HIV prevention. Microbicidal products will give women all over the world one more tool to protect themselves against the ravage of sexually transmitted diseases, including HIV/AIDS. Your commitment to fund microbicide research has the potential to save and improve millions of lives.

Sincerely,

Connie Morella, M.C.

Eddie Bernice Johnson, M.C.

Nancy Johnson, M.C.

Eleanor Holmes Norton, M.C.

Sue Kelly, M.C.

Nancy Pelosi, M.C.

Louise Slaughter, M.C.

Carolyn Maloney, M.C.

Lynn Woolsey, M.C.

Carrie Meek, M.C.

Sheila Jackson-Lee, M.C.

Elizabeth Furse, M.C.

Juanita Millender-McDonald, M.C.

Carolyn Kilpatrick, M.C.

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Diana DeGette, M.C.

Patsy Mink, M.C.

Karen Thurman, M.C.

Lynn Rivers, M.C.

Cynthia McKinney, M.C.

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Marcy Kaptur, M.C.

Debbie Stabenow, M.C.

Lydia Velazquez, M.C.

Nita Lowey, M.C.

10-15-97-0053

ALLIANCE FOR MICROBICIDE DEVELOPMENT
6930 Carroll Avenue, Suite 830 - Takoma Park, MD 20912
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fax

TO: person (1) Alexandra Levine (2) Daniel Montoya (3) Phyllis Greenberger institution FDA
(1) 323-865-0060
tel # _____ **fax #** (2) 202-456-2438
(3) auto

FROM: Libby Harrison **DATE:** 11/9, **1998**

RE: (1) Response to FDA (letter from Maura Murphy of 11/6/98
(2) "Community" Policy Document

PAGES: _____**(including cover sheet)**

☐ **urgent** ☐ **please respond ASAP** ☑ **for information** ☐ **for comment** ☐ **as discussed**

MESSAGE

(1) Harrison to Murphy (1 pg. memo)
(2) "Community" Policy Document (
(3) Final Version of Conference Call Minutes, circulated by FDA (Brandeisant 11/6/98) (4 pgs.)

ALLIANCE FOR MICROBICIDE DEVELOPMENT

A PROJECT OF THE TIDES CENTER

6930 Carroll Avenue, Suite 830
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MEMORANDUM

TO: **Dianne Murphy, MD – Office Director, ODEIV/CDER/FDA**
FROM: **Polly F. Harrison, PhD – Director**
RE: **Follow-up to PACHA Conference Call and Your Memo of 11/9: List of Issues Identified by the Topical Microbicide Working Group (TMWG)**
BY FAX: **301-827-2520**

Thank you so much for this list. It is enormously helpful and just what we'd hoped for. Our plan is to reproduce it in tabular form, using exactly your language, and send it to the researchers who participate in the Alliance as well as to colleagues at NIH and CDC. It will be covered by a full quotation of your paragraph 2, so all will be clear on what we are talking about. We will ask those individuals to:

- Describe briefly any activity they are engaged in or are planning that might provide illumination concerning any of the listed topics, with information on follow-up references, contacts, and an idea of when usable information might start to be available
- Advise us about any research they know of, with references and/or contacts, that might provide illumination concerning the listed topics
- Add any "missing" areas they see as especially significant.

Inevitably, response will be uneven but we'll press hard for a fast turnaround since, with the winter holidays, distractions grow. We should get enough from this approach to start a compilation of what we know, what we might know soon, and what needs directed attention. I'm particularly interested in identifying the major gaps, since it will take time to get those filled efficiently through research, workshops, papers, or whatever medium will get the quality of information needed for sound assessment.

If you all have ideas about how to make this exploration maximally useful to you, please send them along. If we get this right for starters, it could make a real difference, so we want to do it the best way possible.

With best regards and appreciation. Polly

c: FDA:
Janet Woodcock
Debbie Birnkrant
Sheryl Lard
Susan Cobb

PACHA:
Alexandra Levine
Daniel Montoya

TEN (10) PUBLIC-SECTOR POLICY MODIFICATIONS REQUIRED TO ACCELERATE THE DEVELOPMENT OF TOPICAL MICROBICIDES FOR THE PREVENTION OF SEXUALLY TRANSMITTED INFECTIONS, INCLUDING HIV/AIDS

prepared by the concerned research and development and advocacy communities

November 1998

PREMISE #1: GREATER PUBLIC-SECTOR INVESTMENT IS ESSENTIAL IF MICROBICIDE DEVELOPMENT IS TO ADVANCE EXPEDITIOUSLY

More public-sector investment is essential if microbicide research and development are to advance at the speed merited by the burdens of HIV/STD. The currently reported DHHS budget for all microbicide-related expenditures is roughly $25 million a year. Of that total, NIH expenditures on microbicide research account for $21 million--0.16% of the total NIH budget and 1% of its AIDS-related budget--against the almost $10 billion annual costs of STDs to the US economy. In considering the adequacy of this level, it is useful to remember that it costs roughly $50 million to take a single, existing compound through all phases of testing to final FDA approval.

PROPOSED ACTION: ***Increase investment in microbicide research to $75 million per year and authorize multi-year funding to facilitate long-range planning and accommodate multi-year trials***

PREMISE #2: TO MAKE A DIFFERENCE, MICROBICIDE FUNDING MUST BE BETTER COORDINATED AND MORE STRATEGICALLY DEPLOYED

Despite efforts to encourage coordination (e.g., through the Interagency Working Group on Topical Microbicides), progress has been hampered by the lack of an overall strategy to guide action. It is not sufficient that agencies and groups keep each other informed about their actions; investment must be planned, coordinated, and strategic.

PROPOSED ACTION: ***Produce a DHHS-wide, coordinated strategy for public-sector investment in microbicide-related research and development, emphasizing the actions indicated below***

PREMISE #3: CURRENT HUMAN RESOURCES WITHIN DHHS AGENCIES RESPONSIBLE FOR MICROBICIDE R&D ARE INADEQUATE

The ability of public-sector actors to facilitate microbicide R&D is extremely compromised by the lack of staff dedicated to this issue at key agencies, including NIH, CDC, and FDA. Key tasks are not being pursued for lack of time.

PROPOSED ACTION: ***Increase the number of staff dedicated to microbicide-related activities at key Federal agencies, fund existing Full-Time Equivalent (FTE) positions, and work to expand the available FTE's through thoughtful interagency planning***

PREMISE #4. FEDERAL CAPACITY FOR RAPID TESTING OF MICROBICIDAL COMPOUNDS NEEDS STRENGTHENING

Limits to Federal capacity to screen potentially promising compounds, particularly in vivo, is increasingly constraining microbicide R&D. Especially important are greater access to primates for preliminary efficacy testing and development of new animal models.

PROPOSED ACTION: ***Funnel more money through existing contract mechanisms designated specifically for microbicide testing; enhance intramural laboratory capacity; and/or develop a new contract mechanism specifically designed to facilitate preclinical development of microbicides, including product screening and formulation***

PREMISE #5. AN INCREASED PERCENTAGE OF MICROBICIDE FUNDING MUST BE TARGETED DIRECTLY TOWARD PRODUCT DEVELOPMENT

Almost all microbicide R&D is being carried out by small biopharmaceutical companies and academic research groups. Since large pharmaceutical companies have not been prepared to invest in microbicides, these groups depend heavily on public-sector funding. Yet, because such a small percentage of that funding is specifically directed toward product development, the majority of potential products are, in effect, trapped in the early stages of the pipeline.

PROPOSED ACTIONS:

- ***Expand funding for microbicide development through NIH's Small Business Innovation Research (SBIR) grants and Small Business Technology Transfer (STTR) program to $20 million yearly and explore potential for greater flexibility in program requirements***
- ***Establish a microbicide-specific review panel, including consumer representation, for proposal evaluation***

PREMISE #6. NIAID'S PROGRAM PROJECT GRANTS HAVE BECOME INCREASINGLY COMPETITIVE

Because the funding for Program Project Grants is limited, some worthy proposals are being rejected. An increase in the funding available through this program (RFA, April 1998) would allow more research teams to be funded and permit additional monies to be dedicated to existing projects that show particular promise.

PROPOSED ACTION: ***Expand the funding available through NIAID's Microbicide Project Grants***

PREMISE #7. RESEARCH IN MUCOSAL IMMUNOLOGY REPRESENTS A POTENTIALLY RICH INTERSECTION BETWEEN NIAID'S PRIORITIES IN HIV PROPHYLACTIC VACCINE DEVELOPMENT AND MICROBICIDE DEVELOPMENT

Greater cross-fertilization among scientists working in different parts of this field (e.g., antibodies, cell-mediated immunity, commensals, cytokines) might significantly enhance progress both in microbicides and vaccine development.

PROPOSED ACTION: ***Develop a plan for promoting such cross-fertilization, toward a systematic exploration of mucosal immunology and mechanisms of infection, beginning with a directed sequence of high-level scientific meetings***

PREMISE #8. ACCESS TO CLINICAL TRIAL SITES AND INFRASTRUCTURE WILL SOON BE A RATE-LIMITING STEP IN MICROBICIDE DEVELOPMENT

Only a limited number of sites worldwide now have the epidemiologic profile and infrastructure needed for large-scale efficacy trials of microbicides. Pressure for access to these sites will mount as more products emerge from early clinical testing. Most existing sites have been developed with public-sector investment through HIVNET, RO1's, or UNAIDS, and decisions about access to them have been made on a first-come, first-serve basis. As the array of candidate products grows, however, a systematic way to allocate access to this scarce public resource will be ever more critical. It will also be essential that candidate microbicides proceed through clinical testing in parallel, rather than singly and sequentially. Finally, trial sites will be required beyond those in the new Prevention Trials Network, which must meet a wide range of testing obligations (e.g., perinatal transmission, STD's and behavioral interventions, and hormonal and barrier contraceptives).

PROPOSED ACTIONS:

- ***Establish an external advisory group, with consumer representation, to guide selection of candidate products for preferential access to federally-funded clinical trial sites***
- ***Review the adequacy of the existing trial infrastructure for parallel testing of antimicrobial products***

PREMISE # 9. FDA EXPECTATIONS REGARDING MICROBICIDE TESTING AND APPROVAL HAVE BEEN UNCLEAR TO MUCH OF THE CONCERNED COMMUNITY

The newness, complexities, and urgency of microbicide R&D, and the fact that microbicides are being developed mostly by small, often inexperienced companies, will require innovative, coordinated, proactive, flexible responses from the FDA.

PROPOSED ACTIONS:

- ***Develop a user-friendly, well-disseminated guidance document on microbicide review and approval***
- ***Develop a comprehensive web page with a Q&A function***
- ***Hold regular, open meetings where companies can interact with the FDA***

PREMISE #10. FDA EFFORTS TO BE SUPPORTIVE WILL BE HAMPERED BY UNDER-STAFFING AND LACK OF UP-TO-DATE ADVICE FROM THE TECHNICAL COMMUNITY

The FDA has initiated actions potentially helpful to product sponsors. Still, as the number of candidate products grows, agency ability to provide timely guidance will be compromised by an inadequate number of qualified medical officers and by lack of a regular stream of communication from research, empirical field experience, and the sponsor community.

PROPOSED ACTIONS:

- ***Provide additional line item funds specifically for increasing the number of FDA medical officers whose primary responsibility is microbicide coordination and review***
- ***Hold regular informational meetings between FDA staff and the wider scientific community engaged in microbicide development***

NOTES: CONFERENCE CALL, 2:00-3:00 pm, 7 OCTOBER 1998

Representatives from the PRESIDENTIAL ADVISORY COUNCIL ON HIV/AIDS (PACHA), U.S. FOOD AND DRUG ADMINISTRATION (FDA), and ALLIANCE FOR MICROBICIDE DEVELOPMENT

Present for PACHA:
Jerry Cade
Scott Hitt
Alexandra Levine (Chair, PACHA Research Committee/Conference Call Leader)
Helen Miramontes
Bruce Weniger
ONAP Staff (Matthew Murguia, Kelly Stewart)
Present for FDA:
Debra Birnkrant, CDER
Susan Cobb, CDER
David Feigal, CBER
Sheryl Lard-Whiteford, CDER
Dianne Murphy, CDER
Janet Woodcock, CDER
Present for the Alliance:
Anne-Marie Corner
Polly Harrison

Dr. Levine explained the purpose of the call: to help guide the Council in following up on its 1996 recommendations regarding microbicide development and, in so doing, re-emphasize the urgency of adequately and appropriately stimulating the field. Given those objectives, given the complexities of microbicides as pharmaceutical products, and given that the great proportion of microbicide R&D is being carried out by small companies and university researchers with limited resources and sometimes little regulatory experience, the primary questions are:

1) Are FDA processes with respect to microbicides efficient enough and, if not,
2) How might they become more so?

Dr. Woodcock recognized microbicides as an important developmental area and expressed decided interest in seeing them advance. She noted that while these products may enter the FDA through different units, the recently established Topical Microbicides Working Group (TMWG) is intended to serve as a crosscutting committee that includes representation from all FDA units in CBER, CDER, and CDRH that could conceivably be involved in the review and approval of microbicides, to assure that policies and guidance concerning these products will be consistent. She added that the agency ombudsman offers an additional mechanism for sponsors unsure about the most appropriate point of entry into the regulatory system. **Dr. Murphy** further added that, nevertheless, if the process is not working, then something needs to be done toward rectifying what is dysfunctional.

DISCUSSION: The gist of the extensive dialogue that followed was that the issue may not necessarily be that these mechanisms are not working, but that they have not yet become sufficiently visible or understandable to a sufficient proportion of the outside world. This is especially the case with respect to the TMWG. In addition, FDA's involvement in microbicide-related workshops over the recent past, while useful, has been limited and seems not to have permeated the sponsor community adequately. There are possible explanations for this lack of impact: limited inclusion; lack of dissemination; arrival of new sponsors into the field; and inability to consistently cover all aspects of a complex, sometimes confusing product category that is in numerous aspects uncharted terrain, for sponsors and regulators alike.

CONCLUSION: The group agreed that a simple, very helpful first step would be for FDA to develop a brief (2 pages?), user-friendly "process map" or algorithm providing guidance for sponsors on points of regulatory entry, initial procedures, and the structure and functioning of the TMWG. This would be disseminated on the FDA web site(s) and through the various Alliance communication mechanisms.[1]

ACTION ITEMS:

FDA/CDER: **Develop process guidance document and put on FDA website(s)**
Alliance: **Disseminate document and announce web location widely**

Anne-Marie Corner praised the effectiveness of the FDA's pre-IND website and Q&A component in easing and accelerating agency-sponsor interaction. This is mutually beneficial since sponsors must often wait a long time to get individual meetings with FDA officers, whose numbers do not correspond to the breadth of their responsibilities. She then moved the conversation to the larger dilemmas associated with the later phases of product development, that is, human trials, where a number of highly significant issues remain unresolved. Irresolution about these issues, while natural enough in an evolving field, hampers development of clear, consistent, proactive guidelines for evaluation, approval, and marketing of vaginal microbicides, guidelines that are harmonized across the concerned FDA units. This deficit, in turn, raises risks for sponsors in the form of possible error, lost time, and excessive and unanticipated costs, especially hard on small companies and reported to be discouraging to the involvement of larger companies.

Polly Harrison noted that the Alliance had made a 550-page compendium of all possibly relevant FDA guidelines, whose table of contents had been reviewed by some CDER and CBER staff but whose full contents need thoughtful review for internal contradictions and sheer bulk. **Dr. Murphy** noted that the 1996 FDA "Points To Consider..." and "Recommendations..." emitted by the International Working Group on Vaginal Microbicides (IWGM) are a reasonable point of departure for dialogue with the TMWG.[2]

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[1]CDER has a simple web site for pre-IND processes and is trying to develop a separate web page for the TMWG.

[2]Office of Drug Evaluation II/Division of Reproductive and Urologic Drug Products, and Office of Drug Evaluation IV/Division of Anti-infective Drug Products and Division of Antiviral Drug Products. *Points to Consider in the Nonclinical Pharmacology/Toxicology Development of Topical Drugs Intended to Prevent the Transmission of Sexually Transmitted Diseases (STD) and/or for the Development of Drugs Intended to Act as Vaginal Contraceptives.* Rockville, MD: Food and Drug Administration, October 1996. - International Working Group on Vaginal Microbicides. *Recommendations for the Development of Vaginal Microbicides.* Geneva: UNAIDS, 1996. [Not discussed directly during the call was the possibility that some elements in these documents may have been overtaken by accumulating empirical understanding and might now be in the category of "unresolved issues."]

DISCUSSION: The ensuing discussion alluded to groups working to address unresolved issues, e.g., the IWGM, in which Dr. Feigal participates, and the HIVNET Microbicide, Contraceptive, and STD Working Group (MCSWG), which has no FDA participation.[3] Some unresolved areas were mentioned—use of colposcopy, sample size(s) needed to assess anti-STD effectiveness, questions related to formulation and vaginal volume—but there are clearly more.

The group agreed on two mutually useful steps: 1) FDA will supply the research community with a list of questions it regards as needing resolution and 2) the research community will supply a comparable list to FDA. **Dr. Murphy** said that her group had already prepared a list of questions about trial design they would like to have resolved and would be glad to provide that; **Dr. Harrison** reported that a subgroup of the Alliance had begun work on an annotated list of unresolved issues as a basis for work in the coming months and would be pleased to share that with the FDA as soon as it is finished. Harmonized, the two lists could provide directions for the future, in terms of 1) developing a synthesis document on what is currently known about the major clinical trials dilemmas and 2) shaping questions that could be resolved empirically and/or pursued with the help of appropriate expertise.

ACTION ITEMS:

ALLIANCE: Alliance staff will work with colleagues to complete its list, with the October 20 IWGM meeting *[at which Dr. Feigal will be present]* a good opportunity to move that along smartly.

FDA/CDER: Dr. Murphy will provide the FDA list to Dr. Harrison, who will disseminate it appropriately.

DISCUSSION: The next part of the conversation dealt with ways to somehow increase and systematize the flow of communication between the FDA and the research and sponsor communities about what is being learned, empirically and theoretically, from clinical trials of microbicides, as well as from other, related research that could nourish decisions about regulatory guidance. To date, the flow from the research community is seen as uneven and sporadic. While the discussants agreed that microbicides are a "moving target" requiring flexibility, they also agreed on the need for more focused effort to keep FDA staff concerned with microbicide development informed more regularly as understandings emerge, so that guidance can be based on systematic review of the best current knowledge.

The following action items were proposed to 1) regularize information exchange between FDA and the R&D community and 2) keep the FDA up to date on the state of the science of microbicide development, with particular emphasis on issues around human trials. *[While different participants in the conference call proposed the following action items, they are not attributed since everyone seemed to agree that they were all good ideas that should be pursued. Emphasis was placed on the value of assuring adequate lead time so as to maximize participation in all activities.]*

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[3] Formerly known as the Microbicide, Barrier, and STD Working Group (MBSWG).

ACTION ITEMS

- **Produce** a compendium on the state of what is presently known about the most critical questions related to human trials of microbicides. The suggestion was made that the Alliance might organize the production of such a document, which would, at least on first thought, involve collaborative effort with the IWGM, FHI, CONRAD, and the MCSWG.

- **Replicate** (within 6 months, and regularly thereafter at some interval not unduly burdensome on workloads) the workshop held at the NIAID-sponsored meeting in Atlanta in May 1998. Such a meeting would be broadly publicized so as to be maximally inclusive of microbicide product sponsors and would be held in Washington, DC, so as to facilitate maximum participation by the TMWG. It was suggested that the Alliance would take responsibility for arranging such a meeting and the request was made that the proceedings of such a meeting be recorded and distributed to all participants and to those interested members of the sponsor community unable to participate.

- **Invite.** As appropriate, extend invitations to TMWG staff to attend scientific meetings pertinent to microbicide R&D and assure their inclusion in distribution of minutes and proceedings.

- **Open** the annual CDER Advisory Committee(s) meeting(s) for updates on issues critical to microbicide development.

- **Pursue** the notion of NIH-sponsored meetings on the most critical scientific issues, at a rate of 1-2 annually, as such meetings make substantive sense.

FINAL WORDS: The last minutes of the conference call were dedicated to a summary of the Action Items agreed upon and to Dr. Levine's query about FDA staffing for response to the urgency that is increasingly perceived with regard to microbicide research and development. This topic was reserved for private discussion by the PACHA conferees and the meeting ended with further agreement: that the call had been most useful all around, in terms of getting people together and laying out out some concrete and reasonable steps for productive action.

NIH

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

APR 10 1998

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1998 APR 13 A 9:27
NIH EXECUTIVE SECRETARIAT

The Honorable Connie Morella
U.S. House of Representatives
Washington, D.C. 20515

Dear Representative Morella:

Thank you for the letter that you and 29 colleagues sent to me expressing your support for research on topical microbicides and requesting an accounting of our current investment in this area. I am pleased to respond to your inquiry about the Department's efforts in advancing this important area of research. I apologize for the delay in my response.

The Department has supported vaccine, drug, diagnostic, and contraceptive research and development for many decades, and we share your commitment to the development of a woman-controlled method for STD/HIV prevention. It is, and will remain, a top priority for the Department. We have initiated a Public Health Service-wide initiative to facilitate this progress. The National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) are working in a collaborative and coordinated fashion on research and evaluation. Program staff from both agencies are involved in active consultation with the Food and Drug Administration (FDA) to develop science-based guidelines for product evaluation. Furthermore, representatives from all three agencies have had a leadership role in the International Working Group on Microbicides. The Working Group has developed and supported an international network of scientific and clinical investigators who are working with private sector sponsors to develop and evaluate these products.

We also recognize the critical role of industry in this effort. The Government's role in facilitating product development has been identified by the Vice President as one of our highest priorities. Mindful of this commitment, the Department has worked assiduously to foster and facilitate product development efforts. The NIH and CDC support research grants and contracts, including Small Business Innovative Research awards, to over a dozen small businesses as well as hold ongoing consultations with major pharmaceutical companies interested in topical microbicide development.

At the NIH, five Institutes or Centers support research on or related to topical microbicides: the National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), National Institute

on Drug Abuse (NIDA), National Institute of Mental Health (NIMH), and Fogarty International Center (FIC). In addition, two offices within the NIH Office of the Director, the Office of AIDS Research (OAR) and the Office of Research on Women's Health (ORWH), provide supplemental funds to augment research grants funded by the Institutes. In FY 1997, OAR and ORWH provided supplemental funds to NIAID, NICHD, and NIMH grants and contracts. At the CDC, three Centers support research on topical microbicides. These are the National Center for HIV, STD and TB Prevention (NCHSTP), the National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP), and the National Center for Infectious Diseases (NCID).

The Department's topical microbicides initiative has five major research goals. These goals are to: 1) define the molecular basis and chronology of the early steps in the infectious process; 2) define vaginal and cervical ecology and the natural defense mechanisms of the female reproductive tract; 3) facilitate pre-clinical development of topical microbicides; 4) facilitate clinical evaluation of topical microbicides for safety and efficacy; and 5) define product characteristics and use-patterns that facilitate acceptance of and compliance with topical microbicides. The research portfolio is built upon a basic biomedical and basic behavioral research foundation. These basic research efforts are key to the development and evaluation of safe, effective products. The portfolio for topical microbicides product development includes pre-clinical, clinical, and behavioral research components.

The four specific questions on topical microbicides contained in your letter are addressed below and in the attached tables.

What is the Department of Health and Human Services' current investment portfolio on microbicide research?

We made a commitment of $100 million dollars over four years to the topical microbicides research effort. The budget figures for FY 1997 are summarized in the attached Table 1. In FY 1998, the NIH AIDS budget estimate and the CDC budget estimate include funding increases for research on topical microbicides.

How much of the microbicide resources are devoted specifically to microbicide product development and testing versus to initiatives serving multiple purposes?

As shown in Table 2, approximately three-fourths of the FY 1997 resources were allocated for product development, clinical evaluation, and behavioral research and one-fourth for basic biomedical/behavioral research with multiple purposes.

If some research is serving multiple purposes, what are those projects and how much of the $100 million does this represent?

Studies funded in FY 1997 that are categorized as basic research with multiple purpose are shown in aggregate in Table 2. Table 3 provides a comprehensive list of these projects (by grant title and number) and identifies the relationship between the project and the microbicide research effort as well as the prorated amount of funding attributed to microbicide research. Please note that the dollar amount listed for each project reflects the percent effort attributed to microbicide research.

Is research related to non-chemical contraceptive barrier methods being counted toward the microbicide investment goal of $100 million? If yes, what are those projects and how much of the $100 million does this represent?

Research on the development of non-chemical contraceptive barrier methods is not included in these budget figures.

The Department shares your commitment to improving the health of women and to the research and development of topical microbicides. I look forward to continuing to work with you on this important problem. I will respond to each of your co-signatories in the same manner.

Sincerely,

Donna E. Shalala

3 Attachments

Identical letters sent to:

Rep. Nancy Johnson
Rep. Sue Kelly
Rep. Louise Slaughter
Rep. Eddie Bernice Johnson
Rep. Eleanor Holmes Norton
Rep. Nancy Pelosi
Rep. Carolyn Maloney
Rep. Lynn Woolsey
Rep. Sheila Jackson-Lee
Rep. Juanita Millender-McDonald
Rep. Carolyn McCarthy
Rep. Patsy Mink
Rep. Lynn Rivers
Rep. Zoe Lofgren
Rep. Ellen Tauscher
Rep. Darlene Hooley
Rep. Carrie Meek
Rep. Elizabeth Furse
Rep. Carolyn Kilpatrick
Rep. Diana DeGette
Rep. Karen Thurman
Rep. Cynthia McKinney
Rep. Donna Christian-Green
Rep. Pat Danner
Rep. Eva Clayton
Rep. Marcy Kaptur
Rep. Nydia Valazquez
Rep. Debbie Stabenow
Rep. Nita Lowey

Table 1
Department of Health and Human Services
Investment in Microbicide Research
FY 1997 (actuals)

NIH	Grants	Contracts	Total $
NIAID	45	15	13,124,804
NICHD	20	11	6,344,099
OAR	NIAID grant*	NIAID contract*	845,329
OAR	1 - NIMH grant	0	112,670
ORWH	NIAID grant*	0	100,000
FIC	3	0	100,000
NIDA	2	0	106,821
Total NIH	**71***	**26**	**20,733,723**
Total CDC	**7**	**3**	**3,969,283**
Total DHHS	**78***	**29**	**24,703,006**

*The supplements to NIAID grants and contracts have not been counted in the totals.

Table 2
Percentage of Microbicide Resources Dedicated
Specifically to Microbicide Product Development/Clinical Evaluation
Compared to
Basic Research with Multiple Purposes
FY 1997 (actuals)

Agency/ Institute	Product Development/ Clinical Evaluation		Basic Research with Multiple Purposes	
NIH	**Dollars**	**% of Total**	**Dollars**	**% of Total**
NIAID	9,215,773	70	3,909,031	30
NICHD	4,840,133	76	1,503,966	24
OAR (NIAID)	845,329	100	0	0
OAR (NIMH)	112,670	100	0	0
ORWH (NIAID)	100,000	100	0	0
FIC	0	0	100,000	100
NIDA	0	0	106,821	100
Total NIH	**15,113,905**	**73**	**5,619,818**	**27**
Total CDC	**2,979,239**	**75**	**990,044**	**25**
Total DHHS	**18,093,144**	**73**	**6,609,862**	**27**

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Allergy and Infectious Diseases			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
R37-AI-22624 Natural History of HIV Infection	Basic research; Clinical/Epi* information	5	43,881
R37-AI-29164 Antiviral Resistance in AIDS	Basic research; drug resistance mech	10	51,190
AI-SUB 30731 Epidemiology/Pathogenesis of Asymptomatic Genital Herpes	Basic research; shedding of HSV - early steps in infection process	25	28,605
AI-SUB 30731 Asymptomatic HSV-OB/GYN	Basic research; shedding of HSV - early steps in infection process	25	45,834
AI-SUB 30731 Asymptomatic HSV-HIV	Basic research; shedding of HSV in HIV+ people	25	27,771
AI-SUB 31494 Behavior Epidemiology of Reoccurrent STI in Adolescents	Basic research; risk perception and PX* of STDs	50	118,363
AI-SUB 31496 A Human Challenge Study of *Neisseria gonorrheae*	Basic/clinical research; early steps in infectious process; clinical eval of topical microbicides	25	43,109
AI-SUB 31496 A Lay Health Advisor Program to Prevent STDs	Basic research; epi* of STDs in rural South; health seeking behaviors related to PX*	25	97,633
R01-AI-32330 SIV and HIV Pathogenesis during Ontogeny	Basic research; early steps in infectious process	25	83,587

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Allergy and Infectious Diseases			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
R01-AI-32686 Chlamydia and Douching in Ectopic Pregnancy	Basic research; shedding of Ct* into vagina; acceptability of vaginal products	50	152,288
R29-AI-33522 Cytolysins of *Haemophilus ducreyi*	Basic research; early steps in the infectious process	50	50,400
R01-AI-33810 HIV-1 Transmission *in vivo*	Basic research; early steps in the infectious process	30	81,188
R29-AI-34354 Molecular Analysis of Treponemal Motility Genes	Basic research; early steps in the infectious process	20	20,650
AI-SUB 34582 Immune Responses to Gonococcal Infection	Basic research; early steps in the infectious process	50	116,032
AI-SUB 34616 HLA and Chlamydia Disease Pathogenesis	Basic research; pathogenesis of chronic infection	25	35,762
AI-SUB 34616 Lesion-Derived T Lymphocytes in Early Syphilis	Basic research; pathogenesis/early steps in the infectious process	25	35,793
AI-SUB 34617 Clinical-Chlamydial/Statistical Core	Basic research; early steps in the infectious process	25	176,853
AI-SUB 34617 Peptide Synthesis Core	Basic research; early steps in the infectious process	50	2,913
AI-SUB 34617 Epitope-HLA Specificity of Anti-Chlamydial Human T Cells	Basic research; pathogenesis	50	7,984

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Allergy and Infectious Diseases			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
AI-SUB 34617 Chlamydial Antigen Presentation by Native Human Cells	Basic research; pathogenesis	50	8,947
AI-SUB 34617 Chlamydial Persistence in Human Genital Cells	Basic research, pathogenesis	50	8,373
AI-SUB 34617 Molecular Specificity of Humoral Immunity to Chlamydia	Basic research; pathogenesis	50	9,302
R01-AI-34826-S1 STD Control for AIDS Prevention	Basic research; clinical/epi* of STDs	15	3,460
R01-AI-34826 STD Control for AIDS Prevention	Basic research; feasibility—clinical trial	15	321,779
R01-AI-34826-S2 STD Control for AIDS Prevention	Basic research; behavioral factors relating to use of prevention methods	15	12,446
AI-SUB 34831 Adult Clinical Trials Unit	Basic research; HIV in genital tract of women	10	7,409
AI-SUB 35682 Clinical Trial	Basic research; feasibility—clinical trial	10	16,398
R01-AI-35694 Gonococcal POR, OPA, and Neutrophil Activation	Basic research; pathogenesis	25	44,548
R01-AI-36643 Virus Variation and Sexual Transmission of SIV	Basic research; early steps in the infectious process	30	63,761
R01-AI-36986-S1 Perceived Risk for Sexually Transmitted Diseases	Basic research; behavioral factors; risk perception	50	15,457

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Allergy and Infectious Diseases			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
R01-AI-36986 Perceived Risk for Sexually Transmitted Diseases	Basic research; behavioral factors; risk perception	50	313,653
R01-AI-37466 Epidemiology of HIV-1 and HIV-2 in the Cervix and Vagina	Basic research; early steps in the infectious process	25	94,709
R01-AI-38492 Pathogenesis and Prevention of SHIV Disease	Basic research; early steps in the infectious process	50	176,401
R01-AI-38501 Determinants of HIV/SIV Mucosal Transmission	Basic research; early steps in the infectious process	50	155,876
AI-SUB 38514 Bacterial Vaginosis: Pathogenesis and Impact on STDs	Basic research; early steps in the infectious process	50	70,070
AI-SUB 38515 Condom Promotion Interventions for STD Clinic Patients	Basic research; behavioral factors relating to use of prevention methods	50	80,867
AI-SUB 38515 Humoral and Cellular Immune Response in Gonococcal Disease	Basic research; pathogenesis	25	58,839
R01-AI-38518 Early Infection in Women Exposed Mucosally to HIV-1	Basic research; early steps in the infectious process	50	147,805
R01-AI-38545 GP120 VH3 Superantigen and HIV-1 Pathogenesis	Basic research; pathogenesis	25	43,713
R01-AI-38559 Early Events in SIV Infection	Basic research; early steps in the infectious process	50	227,567

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Allergy and Infectious Diseases			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
R01-AI-38565 Pathogenesis - Sexual Transmission of Primate Lentivirus	Basic research; early steps in the infectious process	50	218,913
R01-AI-38573 Early Events in Mucosal Transmission of SIV and SHIV	Basic research; early steps in the infectious process	50	244,342
R01-AI-38580 Mucosal Infection of Macaques with an Acutely Lethal SIV	Basic research; early steps in the infectious process	50	182,342
R01-AI-39996 HIV Shedding in Women - Factors Influencing Infectivity	Basic research; early steps in the infectious process	25	50,832
R01-AI-40350 Antiviral Therapy and HIV in the Genital Tract of Women	Basic research; impact of Rx* on shedding	25	111,386

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Child Health and Human Development			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
D43-TW-00003-10 International AIDS Training Program	Behavioral survey; international AIDS training program	50	161,060
P01-HD-31921 Prospective Longitudinal Study of Adolescent Health	Behavioral survey; adolescent health study - contraceptive use	5	97,120
R01-HD-17337 Mucosal Immunity in the Female Genital Tract	Basic research; female genital immune defenses	50	96,863
R01-HD-31646 Contraceptive Effectiveness and Unintended Pregnancy	Behavioral survey; estimate efficacy of contraceptives used by U.S. women	20	31,753
R01-HD-32789 Acceptability of Barrier Methods for Disease Prevention	Behavioral survey; acceptability of barrier contraceptives for disease prevention	25	197,511
R01-HD-33168 Vaginal Immunity Role of Endogenous/Exogenous Agents	Basic research; vaginal immunity – role of internal and external factors	50	81,248
R01-HD-33171 Mucins Covering the Cervix and Vagina	Basic research; female reproductive tract defenses	50	146,290
R01-HD-33194 Female Immune Response to Coitus	Basic research; effect of coitus on female immune defenses	50	96,091

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Child Health and Human Development			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
R01-HD-33205 Factors Affecting Vaginal Immunology and HIV 1 Infection	Basic research; factors affecting susceptibility to HIV-1 infection	50	207,840
R01-HD-34890 Contraceptive Use Dynamics in the U.S.	Behavioral survey; contraceptive method switching	10	12,736
R01-HD-34897 Dynamics and Meaning of Adult Unintended Pregnancy	Behavioral survey; contraceptive practices of young unmarried women	10	50,242
R01-HD-35037 Initiating Contraception in An STD Clinic Setting	Behavioral survey; introduction of contraceptive methods to an STD population	20	43,165
R29-HD-29924 Transepithelial Transport in Cultured Uterine Cells	Basic research; model for cervical susceptibility	50	53,550
R29-HD-33210 Mucosal Immunity of the Genital Tract	Basic research; female immune defenses	50	28,896

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

National Institute of Child Health and Human Development			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
Y01-HD-00081 National Survey of Family Growth - Cycle 6	Behavioral survey; national survey of family growth - section on contraceptive choices	5	30,000
R01-HD-33215 Cervicovaginal Inflammation and Infection and HIV Load	Basic/clinical research; relating infection, inflammation and HIV load	50	149,419
R01-HD-33275 Contraceptive Use/Unintended Pregnancy	Behavioral research; contraceptive use and STD infection	5	20,182

National Institute of Drug Abuse			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
R01-DA-08005 Skills and Self-help to Reduce HIV and Drug Use in Women	Basic research; risk perception; acceptability of vaginal products	10	88,660
R01-DA-09520 HIV Prevention in African American Drug Dependent Women	Basic research; risk perception; acceptability of vaginal products	5	18,161

Table 3
NATIONAL INSTITUTES OF HEALTH - FY 1997 (actuals)

BASIC RESEARCH WITH MULTIPLE PURPOSES

Fogarty International Center			
GRANT NUMBER AND TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
D43-TW-00007-10 International Training Grant in Epidemiology	Training and research capacity building in support of NIAID and NICHD funded studies	5	40,000
T22-TW-00001-10 Special International Postdoctoral Program	Training and research capacity building in support of NIAID funded study of nonoxynol-9 and HIV infections among prostitutes	5	10,000
D43-TW-00003-10 International AIDS Training Program	Training and research capacity building in support of an NICHD funded study	5	50,000

Table 3
CENTERS FOR DISEASE CONTROL AND PREVENTION - FY 1997 (actuals)

MULTIPLE PURPOSE BASIC RESEARCH IN TOPICAL MICROBICIDES

Centers for Disease Control and Prevention			
GRANT TITLE	RELATIONSHIP TO MICROBICIDE EFFORT	TOP MIC PRORATION	AMOUNT (in dollars)
Development of Assay to Detect and Quantify HIV in Cervicovaginal Secretions	Basic research; methods to detect HIV for use in clinical efficacy trials	75	643,544
Natural History of HIV Disease in Women	Basic research; relationship between bacterial STDs and HIV, measures of mucosal immunity in vagina	5	220,000
Immune Response to HIV Infection in the Female Genital Tract	Basic research; evaluate pathophysiology of HIV at mucosal surfaces and measures of mucosal immunity	50	126,500

*Epi = epidemiology
*PX = prevention
*Ct = Chlamydia trachomatis
*Rx = Treatment

Congress of the United States
House of Representatives
Washington, DC 20515

October 9, 1997

The Honorable Donna Shalala
Secretary
Department Of Health and Human Services
200 Independence Avenue, SW
Washington, D.C. 20201

(18-87) Jerry Nethercutt Roscoe Bartlett
(18-75) Sidney Yates Ken Bart David Skaggs Greg Pappas Jason Wright
(18-90) Peter Henry Terry Gay
(18-74) Dick Walling Lou Valdez Lisa O'Fallon Tina Chung Isabel Ellis Regina Lee

Dear Secretary Shalala:

A year ago in Vancouver, you announced that the National Institutes of Health would spend $100 million over the next four years on research aimed at developing a safe and effective vaginal microbicide. As long-time advocates for the development of woman-controlled methods of STD prevention, we were extremely heartened by your announcement. We believe this research is critical to preserving the health of women around the world and to stopping the spread of HIV/AIDS.

Sixteen years into the AIDS crisis, the incidence of sexually transmitted diseases (STDs), including HIV/AIDS, continues to rise exponentially. As you know, women are currently the fastest-growing group with HIV/AIDS in the United States, and internationally, AIDS is already equally common in women and men. Women need prevention products they can use, if necessary, without their partners' knowledge or consent. Microbicides would allow women to protect themselves against HIV and other STDs without being forced to negotiate condom use with their partners.

The need for a woman-controlled method of STD and HIV prevention has only recently been recognized as a priority. It will take a number of years to complete the necessary research to bring a microbicide to market. Researchers working on the development of new products are pursuing some encouraging leads, and it is absolutely critical that resources be made available so that they can continue their efforts to develop, test, and make microbicidal products available to women.

We remain committed to ensuring that adequate funds are available for research aimed at developing microbicidal products. Industry estimates that it takes approximately $250 million to bring a new drug to market. However, large pharmaceutical companies have expressed little interest in pursuing microbicide research, so public sector collaboration is essential both for developing new product leads and for supporting the increasing number of small biotech companies that are entering the field of microbicide research. That is why the $100 million commitment you made is so important.

186924

In the interest of better understanding the effectiveness of the public sector investment, we are writing to respectfully request an accounting of government's current investment in microbicide research.

- What is the Department of Health and Human Service's current investment portfolio on microbicide research (broken down by grant/contract or project in each participating institute or agency)?

- How much of the microbicide resources are devoted specifically to microbicide product development and testing versus to initiatives serving multiple purposes (e.g. research on heterosexual transmission, maintenance of clinical trial infrastructure)?

- If some research is serving multiple purposes (such as basic research or the development of animal models and clinical trial networks), what are those projects and how much of the $100 million does this represent?

- Is research related to non-chemical contraceptive barrier methods (i.e. diaphragms and new condoms) being counted toward the microbicide investment goal of $100 million? If yes, what are those projects and how much of the $100 million does this represent?

We thank you once again for taking a stand on the need for woman-controlled methods of HIV prevention. Microbicidal products will give women all over the world one more tool to protect themselves against the ravage of sexually transmitted diseases, including HIV/AIDS. Your commitment to fund microbicide research has the potential to save and improve millions of lives.

Sincerely,

Connie Morella, M.C.

Eddie Bernice Johnson, M.C.

Nancy Johnson, M.C.

Eleanor Holmes Norton, M.C.

Sue Kelly, M.C.

Nancy Pelosi, M.C.

Louise Slaughter, M.C.

Carolyn Maloney, M.C.

Lynn Woolsey, M.C.

Carrie Meek, M.C.

Sheila Jackson-Lee, M.C.

Elizabeth Furse, M.C.

Juanita Millender-McDonald, M.C.

Carolyn Kilpatrick, M.C.

Carolyn McCarthy, M.C.

Diana DeGette, M.C.

Patsy Mink, M.C.

Karen Thurman, M.C.

Lynn Rivers, M.C.

Cynthia McKinney, M.C.

Zoe Lofgren, M.C.

Donna Christian-Green, M.C.

Ellen Tauscher, M.C.

Pat Danner, M.C.

Darlene Hooley, M.C.

Eva Clayton, M.C.

Marcy Kaptur, M.C.

Debbie Stabenow, M.C.

Rydia Velazquez, M.C.

Nita Lowey, M.C.

10-15-97-0053

ALLIANCE FOR MICROBICIDE DEVELOPMENT
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fax

TO: **person** (1) Alexandra Levine (2) Daniel Montoya (3) Phyllis Greenberger **institution** PACHA

tel # ______________ **fax #** (1) 323-865-0060 (2) 202-456-2438 (3) auto

FROM: Polly Harrison **DATE:** 11/9, 1998

RE: (1) Response to FDA (letter from Dianne Murphy of 11/6/98
(2) "Community" Policy Document

PAGES: _____(including cover sheet)

☐ urgent ☐ please respond ASAP ☑ for information ☐ for comment ☐ as discussed

MESSAGE

(1) Harrison to Murphy (1 pg. memo)
(2) "Community" Policy Document (
(3) Final Version of Conference Call Minutes, cleared by FDA (Burnkrant 11/6/98) (4 pgs.)

ALLIANCE FOR MICROBICIDE DEVELOPMENT

A PROJECT OF THE TIDES CENTER

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Takoma Park, MD 20912
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http://members.aol.com/ggkidder/alliance.html

MEMORANDUM

TO: **Dianne Murphy, MD – Office Director, ODEIV/CDER/FDA**
FROM: **Polly F. Harrison, PhD – Director**
RE: **Follow-up to PACHA Conference Call and Your Memo of 11/9: List of Issues Identified by the Topical Microbicide Working Group (TMWG)**
BY FAX: **301-827-2520**

Thank you so much for this list. It is enormously helpful and just what we'd hoped for. Our plan is to reproduce it in tabular form, using exactly your language, and send it to the researchers who participate in the Alliance as well as to colleagues at NIH and CDC. It will be covered by a full quotation of your paragraph 2, so all will be clear on what we are talking about. We will ask those individuals to:

- Describe briefly any activity they are engaged in or are planning that might provide illumination concerning any of the listed topics, with information on follow-up references, contacts, and an idea of when usable information might start to be available
- Advise us about any research they know of, with references and/or contacts, that might provide illumination concerning the listed topics
- Add any "missing" areas they see as especially significant.

Inevitably, response will be uneven but we'll press hard for a fast turnaround since, with the winter holidays, distractions grow. We should get enough from this approach to start a compilation of what we know, what we might know soon, and what needs directed attention. I'm particularly interested in identifying the major gaps, since it will take time to get those filled efficiently through research, workshops, papers, or whatever medium will get the quality of information needed for sound assessment.

If you all have ideas about how to make this exploration maximally useful to you, please send them along. If we get this right for starters, it could make a real difference, so we want to do it the best way possible.

With best regards and appreciation.

c: FDA:
Janet Woodcock
Debbie Birnkrant
Sheryl Lard
Susan Cobb

PACHA:
Alexandra Levine
Daniel Montoya

TEN (10) PUBLIC-SECTOR POLICY MODIFICATIONS REQUIRED TO ACCELERATE THE DEVELOPMENT OF TOPICAL MICROBICIDES FOR THE PREVENTION OF SEXUALLY TRANSMITTED INFECTIONS, INCLUDING HIV/AIDS

prepared by the concerned research and development and advocacy communities

November 1998

PREMISE #1: GREATER PUBLIC-SECTOR INVESTMENT IS ESSENTIAL IF MICROBICIDE DEVELOPMENT IS TO ADVANCE EXPEDITIOUSLY

More public-sector investment is essential if microbicide research and development are to advance at the speed merited by the burdens of HIV/STD. The currently reported DHHS budget for all microbicide-related expenditures is roughly $25 million a year. Of that total, NIH expenditures on microbicide research account for $21 million--0.16% of the total NIH budget and 1% of its AIDS-related budget--against the almost $10 billion annual costs of STDs to the US economy. In considering the adequacy of this level, it is useful to remember that it costs roughly $50 million to take a single, existing compound through all phases of testing to final FDA approval.

PROPOSED ACTION: ***Increase investment in microbicide research to $75 million per year and authorize multi-year funding to facilitate long-range planning and accommodate multi-year trials***

PREMISE #2: TO MAKE A DIFFERENCE, MICROBICIDE FUNDING MUST BE BETTER COORDINATED AND MORE STRATEGICALLY DEPLOYED

Despite efforts to encourage coordination (e.g., through the Interagency Working Group on Topical Microbicides), progress has been hampered by the lack of an overall strategy to guide action. It is not sufficient that agencies and groups keep each other informed about their actions; investment must be planned, coordinated, and strategic.

PROPOSED ACTION: ***Produce a DHHS-wide, coordinated strategy for public-sector investment in microbicide-related research and development, emphasizing the actions indicated below***

PREMISE #3: CURRENT HUMAN RESOURCES WITHIN DHHS AGENCIES RESPONSIBLE FOR MICROBICIDE R&D ARE INADEQUATE

The ability of public-sector actors to facilitate microbicide R&D is extremely compromised by the lack of staff dedicated to this issue at key agencies, including NIH, CDC, and FDA. Key tasks are not being pursued for lack of time.

PROPOSED ACTION: ***Increase the number of staff dedicated to microbicide-related activities at key Federal agencies, fund existing Full-Time Equivalent (FTE) positions, and work to expand the available FTE's through thoughtful interagency planning***

PREMISE #4. FEDERAL CAPACITY FOR RAPID TESTING OF MICROBICIDAL COMPOUNDS NEEDS STRENGTHENING

Limits to Federal capacity to screen potentially promising compounds, particularly in vivo, is increasingly constraining microbicide R&D. Especially important are greater access to primates for preliminary efficacy testing and development of new animal models.

PROPOSED ACTION: ***Funnel more money through existing contract mechanisms designated specifically for microbicide testing; enhance intramural laboratory capacity; and/or develop a new contract mechanism specifically designed to facilitate preclinical development of microbicides, including product screening and formulation***

PREMISE #5. AN INCREASED PERCENTAGE OF MICROBICIDE FUNDING MUST BE TARGETED DIRECTLY TOWARD PRODUCT DEVELOPMENT

Almost all microbicide R&D is being carried out by small biopharmaceutical companies and academic research groups. Since large pharmaceutical companies have not been prepared to invest in microbicides, these groups depend heavily on public-sector funding. Yet, because such a small percentage of that funding is specifically directed toward product development, the majority of potential products are, in effect, trapped in the early stages of the pipeline.

PROPOSED ACTIONS:

- ***Expand funding for microbicide development through NIH's Small Business Innovation Research (SBIR) grants and Small Business Technology Transfer (STTR) program to $20 million yearly and explore potential for greater flexibility in program requirements***
- ***Establish a microbicide-specific review panel, including consumer representation, for proposal evaluation***

PREMISE #6. NIAID'S PROGRAM PROJECT GRANTS HAVE BECOME INCREASINGLY COMPETITIVE

Because the funding for Program Project Grants is limited, some worthy proposals are being rejected. An increase in the funding available through this program (RFA, April 1998) would allow more research teams to be funded and permit additional monies to be dedicated to existing projects that show particular promise.

PROPOSED ACTION: ***Expand the funding available through NIAID's Microbicide Project Grants***

PREMISE #7. RESEARCH IN MUCOSAL IMMUNOLOGY REPRESENTS A POTENTIALLY RICH INTERSECTION BETWEEN NIAID'S PRIORITIES IN HIV PROPHYLACTIC VACCINE DEVELOPMENT AND MICROBICIDE DEVELOPMENT

Greater cross-fertilization among scientists working in different parts of this field (e.g., antibodies, cell-mediated immunity, commensals, cytokines) might significantly enhance progress both in microbicides and vaccine development.

PROPOSED ACTION: ***Develop a plan for promoting such cross-fertilization, toward a systematic exploration of mucosal immunology and mechanisms of infection, beginning with a directed sequence of high-level scientific meetings***

PREMISE #8. ACCESS TO CLINICAL TRIAL SITES AND INFRASTRUCTURE WILL SOON BE A RATE-LIMITING STEP IN MICROBICIDE DEVELOPMENT

Only a limited number of sites worldwide now have the epidemiologic profile and infrastructure needed for large-scale efficacy trials of microbicides. Pressure for access to these sites will mount as more products emerge from early clinical testing. Most existing sites have been developed with public-sector investment through HIVNET, RO1's, or UNAIDS, and decisions about access to them have been made on a first-come, first-serve basis. As the array of candidate products grows, however, a systematic way to allocate access to this scarce public resource will be ever more critical. It will also be essential that candidate microbicides proceed through clinical testing in parallel, rather than singly and sequentially. Finally, trial sites will be required beyond those in the new Prevention Trials Network, which must meet a wide range of testing obligations (e.g., perinatal transmission, STD's and behavioral interventions, and hormonal and barrier contraceptives).

PROPOSED ACTIONS:

- ***Establish an external advisory group, with consumer representation, to guide selection of candidate products for preferential access to federally-funded clinical trial sites***
- ***Review the adequacy of the existing trial infrastructure for parallel testing of antimicrobial products***

PREMISE # 9. FDA EXPECTATIONS REGARDING MICROBICIDE TESTING AND APPROVAL HAVE BEEN UNCLEAR TO MUCH OF THE CONCERNED COMMUNITY

The newness, complexities, and urgency of microbicide R&D, and the fact that microbicides are being developed mostly by small, often inexperienced companies, will require innovative, coordinated, proactive, flexible responses from the FDA.

PROPOSED ACTIONS:

- ***Develop a user-friendly, well-disseminated guidance document on microbicide review and approval***
- ***Develop a comprehensive web page with a Q&A function***
- ***Hold regular, open meetings where companies can interact with the FDA***

PREMISE #10. FDA EFFORTS TO BE SUPPORTIVE WILL BE HAMPERED BY UNDER-STAFFING AND LACK OF UP-TO-DATE ADVICE FROM THE TECHNICAL COMMUNITY

The FDA has initiated actions potentially helpful to product sponsors. Still, as the number of candidate products grows, agency ability to provide timely guidance will be compromised by an inadequate number of qualified medical officers and by lack of a regular stream of communication from research, empirical field experience, and the sponsor community.

PROPOSED ACTIONS:

- ***Provide additional line item funds specifically for increasing the number of FDA medical officers whose primary responsibility is microbicide coordination and review***
- ***Hold regular informational meetings between FDA staff and the wider scientific community engaged in microbicide development***

NOTES: CONFERENCE CALL, 2:00-3:00 pm, 7 OCTOBER 1998

Representatives from the PRESIDENTIAL ADVISORY COUNCIL ON HIV/AIDS (PACHA), U.S. FOOD AND DRUG ADMINISTRATION (FDA), and ALLIANCE FOR MICROBICIDE DEVELOPMENT

Present for PACHA:
Jerry Cade
Scott Hitt
Alexandra Levine (Chair, PACHA Research Committee/Conference Call Leader)
Helen Miramontes
Bruce Weniger
ONAP Staff (Matthew Murguia, Kelly Stewart)
Present for FDA:
Debra Birnkrant, CDER
Susan Cobb, CDER
David Feigal, CBER
Sheryl Lard-Whiteford, CDER
Dianne Murphy, CDER
Janet Woodcock, CDER
Present for the Alliance:
Anne-Marie Corner
Polly Harrison

Dr. Levine explained the purpose of the call: to help guide the Council in following up on its 1996 recommendations regarding microbicide development and, in so doing, re-emphasize the urgency of adequately and appropriately stimulating the field. Given those objectives, given the complexities of microbicides as pharmaceutical products, and given that the great proportion of microbicide R&D is being carried out by small companies and university researchers with limited resources and sometimes little regulatory experience, the primary questions are:

1) Are FDA processes with respect to microbicides efficient enough and, if not,
2) How might they become more so?

Dr. Woodcock recognized microbicides as an important developmental area and expressed decided interest in seeing them advance. She noted that while these products may enter the FDA through different units, the recently established Topical Microbicides Working Group (TMWG) is intended to serve as a crosscutting committee that includes representation from all FDA units in CBER, CDER, and CDRH that could conceivably be involved in the review and approval of microbicides, to assure that policies and guidance concerning these products will be consistent. She added that the agency ombudsman offers an additional mechanism for sponsors unsure about the most appropriate point of entry into the regulatory system. **Dr. Murphy** further added that, nevertheless, if the process is not working, then something needs to be done toward rectifying what is dysfunctional.

DISCUSSION: The gist of the extensive dialogue that followed was that the issue may not necessarily be that these mechanisms are not working, but that they have not yet become sufficiently visible or understandable to a sufficient proportion of the outside world. This is especially the case with respect to the TMWG. In addition, FDA's involvement in microbicide-related workshops over the recent past, while useful, has been limited and seems not to have permeated the sponsor community adequately. There are possible explanations for this lack of impact: limited inclusion; lack of dissemination; arrival of new sponsors into the field; and inability to consistently cover all aspects of a complex, sometimes confusing product category that is in numerous aspects uncharted terrain, for sponsors and regulators alike.

CONCLUSION: The group agreed that a simple, very helpful first step would be for FDA to develop a brief (2 pages?), user-friendly "process map" or algorithm providing guidance for sponsors on points of regulatory entry, initial procedures, and the structure and functioning of the TMWG. This would be disseminated on the FDA web site(s) and through the various Alliance communication mechanisms.[1]

ACTION ITEMS:

FDA/CDER: **Develop process guidance document and put on FDA website(s)**
Alliance: **Disseminate document and announce web location widely**

Anne-Marie Corner praised the effectiveness of the FDA's pre-IND website and Q&A component in easing and accelerating agency-sponsor interaction. This is mutually beneficial since sponsors must often wait a long time to get individual meetings with FDA officers, whose numbers do not correspond to the breadth of their responsibilities. She then moved the conversation to the larger dilemmas associated with the later phases of product development, that is, human trials, where a number of highly significant issues remain unresolved. Irresolution about these issues, while natural enough in an evolving field, hampers development of clear, consistent, proactive guidelines for evaluation, approval, and marketing of vaginal microbicides, guidelines that are harmonized across the concerned FDA units. This deficit, in turn, raises risks for sponsors in the form of possible error, lost time, and excessive and unanticipated costs, especially hard on small companies and reported to be discouraging to the involvement of larger companies.

Polly Harrison noted that the Alliance had made a 550-page compendium of all possibly relevant FDA guidelines, whose table of contents had been reviewed by some CDER and CBER staff but whose full contents need thoughtful review for internal contradictions and sheer bulk. **Dr. Murphy** noted that the 1996 FDA "Points To Consider..." and "Recommendations..." emitted by the International Working Group on Vaginal Microbicides (IWGM) are a reasonable point of departure for dialogue with the TMWG.[2]

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[1]CDER has a simple web site for pre-IND processes and is trying to develop a separate web page for the TMWG.

[2]Office of Drug Evaluation II/Division of Reproductive and Urologic Drug Products, and Office of Drug Evaluation IV/Division of Anti-infective Drug Products and Division of Antiviral Drug Products. *Points to Consider in the Nonclinical Pharmacology/Toxicology Development of Topical Drugs Intended to Prevent the Transmission of Sexually Transmitted Diseases (STD) and/or for the Development of Drugs Intended to Act as Vaginal Contraceptives*. Rockville, MD: Food and Drug Administration, October 1996. - International Working Group on Vaginal Microbicides. *Recommendations for the Development of Vaginal Microbicides*. Geneva: UNAIDS, 1996. [Not discussed directly during the call was the possibility that some elements in these documents may have been overtaken by accumulating empirical understanding and might now be in the category of "unresolved issues."]

DISCUSSION: The ensuing discussion alluded to groups working to address unresolved issues, e.g., the IWGM, in which Dr. Feigal participates, and the HIVNET Microbicide, Contraceptive, and STD Working Group (MCSWG), which has no FDA participation.[3] Some unresolved areas were mentioned—use of colposcopy, sample size(s) needed to assess anti-STD effectiveness, questions related to formulation and vaginal volume—but there are clearly more.

The group agreed on two mutually useful steps: 1) FDA will supply the research community with a list of questions it regards as needing resolution and 2) the research community will supply a comparable list to FDA. Dr. Murphy said that her group had already prepared a list of questions about trial design they would like to have resolved and would be glad to provide that; Dr. Harrison reported that a subgroup of the Alliance had begun work on an annotated list of unresolved issues as a basis for work in the coming months and would be pleased to share that with the FDA as soon as it is finished. Harmonized, the two lists could provide directions for the future, in terms of 1) developing a synthesis document on what is currently known about the major clinical trials dilemmas and 2) shaping questions that could be resolved empirically and/or pursued with the help of appropriate expertise.

ACTION ITEMS:

ALLIANCE: Alliance staff will work with colleagues to complete its list, with the October 20 IWGM meeting *[at which Dr. Feigal will be present]* a good opportunity to move that along smartly.

FDA/CDER: Dr. Murphy will provide the FDA list to Dr. Harrison, who will disseminate it appropriately.

DISCUSSION: The next part of the conversation dealt with ways to somehow increase and systematize the flow of communication between the FDA and the research and sponsor communities about what is being learned, empirically and theoretically, from clinical trials of microbicides, as well as from other, related research that could nourish decisions about regulatory guidance. To date, the flow from the research community is seen as uneven and sporadic. While the discussants agreed that microbicides are a "moving target" requiring flexibility, they also agreed on the need for more focused effort to keep FDA staff concerned with microbicide development informed more regularly as understandings emerge, so that guidance can be based on systematic review of the best current knowledge.

The following action items were proposed to 1) regularize information exchange between FDA and the R&D community and 2) keep the FDA up to date on the state of the science of microbicide development, with particular emphasis on issues around human trials. *[While different participants in the conference call proposed the following action items, they are not attributed since everyone seemed to agree that they were all good ideas that should be pursued. Emphasis was placed on the value of assuring adequate lead time so as to maximize participation in all activities.]*

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[3] Formerly known as the Microbicide, Barrier, and STD Working Group (MBSWG).

ACTION ITEMS

- **Produce** a compendium on the state of what is presently known about the most critical questions related to human trials of microbicides. The suggestion was made that the Alliance might organize the production of such a document, which would, at least on first thought, involve collaborative effort with the IWGM, FHI, CONRAD, and the MCSWG.

- **Replicate** (within 6 months, and regularly thereafter at some interval not unduly burdensome on workloads) the workshop held at the NIAID-sponsored meeting in Atlanta in May 1998. Such a meeting would be broadly publicized so as to be maximally inclusive of microbicide product sponsors and would be held in Washington, DC, so as to facilitate maximum participation by the TMWG. It was suggested that the Alliance would take responsibility for arranging such a meeting and the request was made that the proceedings of such a meeting be recorded and distributed to all participants and to those interested members of the sponsor community unable to participate.

- **Invite.** As appropriate, extend invitations to TMWG staff to attend scientific meetings pertinent to microbicide R&D and assure their inclusion in distribution of minutes and proceedings.

- Open the annual CDER Advisory Committee(s) meeting(s) for updates on issues critical to microbicide development.

- Pursue the notion of NIH-sponsored meetings on the most critical scientific issues, at a rate of 1-2 annually, as such meetings make substantive sense.

FINAL WORDS: The last minutes of the conference call were dedicated to a summary of the Action Items agreed upon and to Dr. Levine's query about FDA staffing for response to the urgency that is increasingly perceived with regard to microbicide research and development. This topic was reserved for private discussion by the PACHA conferees and the meeting ended with further agreement: that the call had been most useful all around, in terms of getting people together and laying out out some concrete and reasonable steps for productive action.

Penny Hitchcock

From: Penny Hitchcock
Sent: Friday, March 27, 1998 5:35 PM
To: NSAF
Cc: Lucy Renzi
Subject: Follow up to the Meeting

Greetings and warm personal regards, Members of the National STD Action Forum -

First, I really enjoyed working with all of you this week at the NSAF meeting. The ideas and approaches that were developed were very thought provoking; it feels like the beginning of an important new approach to combine our talents, perspectives and energy to prevent and control STDs. On a more personal note, it was the beginning of some very special friendships and collaborations for me and I am grateful and hopeful.

In the interest of strengthening our communications, we have set up a user group which enables us to send everyone in the forum an Email with one address. To send a new message type:

NSAF@mercury.niaid.nih.gov

My understanding is that this works by coming back into a server located in NIH and the message is then forwarded to all members of the group. It would be great if you could confirm receipt of this note and try sending one out de novo. There are two members who are not yet included - Edwin Sanders and Sheila Johnson - I think we will have their Email addresses by the first part of next week; Dr. Walker at Howard, who was not able to attend the forum, prefers to receive the Email over the FAX, so the Email messages are automatically faxed to him.

We are sending two documents to you on Monday by FedEx, the NIAID TOPICAL MICROBICIDES Briefing Booklet, UPDATE 1997 and an overview of our STD Research Program. Please feel free to follow up with questions, if you have any. I will also send out new requests for applications (grants), or proposals (contracts) and press releases using this system. Hopefully you will have up to date information about what is going on here.

Special thanks to Judy, Felicia and Helene et al. for getting this started. Please don't hesitate to contact me if I can be helpful in any way. Take care and have a great weekend. PJH

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The Sexually Transmitted Diseases Program

of the National Institute of Allergy and Infectious Diseases

Overview

The mission of the Sexually Transmitted Diseases (STD) program of the National Institute of Allergy and Infectious Diseases (NIAID) is to foster, develop, and administer a research program that will contribute to the reproductive health of people and specifically lead to prevention and control of STDs. The strategic plan for this research program reflects long-term public health goals:

- **prevention of infertility;**
- **prevention of adverse outcomes of pregnancy;**
- **prevention of reproductive tract neoplasia;**
- **prevention of other chronic STD sequelae; and**
- **prevention of human immunodeficiency virus (HIV) infection.**

The portfolio emphasizes research on the ten pathogens: *Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum, Hemophilus ducreyi, Trichomonas vaginalis*, herpes simplex viruses (HSV), human papillomaviruses (HPV), cytomegalovirus (CMV), hepatitis B virus (HBV), and human immunodeficiency virus (HIV). Although many Institutes sponsor STD research, the NIAID, the National Institute of Child Health and Human Development (NICHD), and the National Cancer Institute (NCI)support most of the STD research projects. Program staff work together to coordinate and in many cases co-sponsor relevant research.

The central theme of the NIAID's STD program is the synergism of combined biomedical, behavioral, clinical and epidemiological research efforts. Implementation of the plan has been strongly influenced by the realization that we must develop new tools, interventions and paradigms. Furthermore, the appropriateness and effectiveness of these tools and interventions are determined by the settings in which they are used. Some of the factors that have influenced our thinking include:

- **the common aspects and global nature of the problem;**
- **the importance of resource-limitation in the delivery of health care;**
- **the key role of behavioral factors in the spread of sexually transmitted infections;**
- **the effectiveness of combined primary, secondary and tertiary prevention approaches;**
- **the cost-effectiveness of community-based interventions;**
- **the potential role for rapid, inexpensive, ease-to-use biomedical interventions; and**
- **the potential impact of rapid, efficient product approval processes.**

Multidisciplinary Research Efforts in STDs

The NIAID supports a number of multidisciplinary research efforts, either in the form of program projects, cooperative agreements or contracts. These include:

- Sexually Transmitted Diseases Cooperative Research Centers (seven U19s)
- Research on Molecular Immunology of STDs Program Projects (three P01s)
- Topical Microbicides Program Projects (four P01s)
- Genital Herpes Program Project (one P01)
- Clinical Antiviral Studies Group (one N01)
- Molecular and Structural Approaches to Antiviral Drug Design (U01s)
- Collaborative Antiviral Testing Group (N01s in genital herpes and
- HIV Infection, U01s in HPV infection)
- Animal Model Studies on Hepatitis B Antivirals and Vaccines (one N01)
- Hepatitis C Research Cooperative Agreements (four U19s)
- STD Diagnostic Development Groups (three U01s)
- STD Diagnostic Evaluation Group (one U01)
- STD Clinical Trials Unit (one N01)
- Adolescents and STDs Cooperative Research Center (one U19 in 1998)
- STD Primate Prevention Unit (one N01 to be awarded in 1999)

Areas of Program Interest

Pelvic Inflammatory Disease (PID)-Prevention of Infertility

Approximately half of the investigator-initiated research portfolio in STDs focuses on the basic research of gonorrhea and chlamydial infection, the antecedent causes of most PID cases. Focused clinical research on PID is conducted within the STD Cooperative Research Centers; there are several clinical projects on PID, including studies of risk factors, characteristics of male partners, and host factors (such as HLA) that contribute to susceptibility or resistance to PID and chronic sequelae. NIH-funded research (U. Washington) demonstrated that screening and treating asymptomatic women for chlamydial infection could reduce PID by approximately 60 percent compared to women who received symptom-driven diagnosis and treatment. Within the three vaccine development program projects (Research on Molecular Immunology of STDs), more than 50 percent of the studies focus on gonorrhea, chlamydial infection or PID. Within the topical microbicides program projects, prevention of gonorrhea and chlamydial infection is the focus of preclinical research projects. Recently, the Institute conducted a workshop to assess directions for future efforts in clinical research in PID. The recommendations of this working group led to the establishment of the STD Clinical Trials Unit at the University of North Carolina. The STD CTU will conduct two clinical trials on PID.

Prevention of Adverse Outcomes of Pregnancy

Virtually all of the STDs, with the exception of chancroid, cause adverse outcomes of pregnancy. The severity and extent to which pregnancy may be adversely affected is well documented in diseases such as syphilis, but is poorly documented in diseases like chlamydial infection. In addition to the basic research efforts in each of the STDs, the program includes research on congenital syphilis, neonatal herpes, low birth weight and prematurity caused by trichomoniasis, bacterial vaginosis, and chlamydial infection. Research recently funded in the Genital Herpes Program Project demonstrated that chronic suppressive acyclovir therapy dramatically reduces shedding of genital herpes viruses, suggesting the potential for a public health intervention using this therapeutic approach. The program project as well as the clinical antiviral studies group conducts clinical studies in maternal infection and neonatal herpes. The NIH (NICHD and NIAID) is currently sponsoring a treatment trial for bacterial vaginosis and trichomoniasis to determine the impact of

treatment on pre-term labor and prematurity. In the Uganda community-based trial for STDs, pregnant women are being studied to assess the impact of STD treatment on pregnancy outcomes.

The NIAID recently sponsored a meeting, in collaboration with the CDC, to review the current state of knowledge on adverse outcomes of pregnancy and to assess the research needs and opportunities for the NIH and the CDC. In preparation is a monograph of the proceedings; publication is anticipated in 1998.

Human Papillomavirus Infection-Prevention of Reproductive Tract Neoplasia

HPV infection is, arguably, the most common sexually transmitted infection in the world. An estimated 40 million people are infected in the United States; the estimated attack rate is 25 percent in the first year of sexual activity (from a recent study conducted in college women with fewer than two life-time partners). The Institute's investigator-initiated HPV research program consists of basic science and clinical research, including several clinical studies of adolescent and young adult females. In one of the vaccine development program projects (Research on Molecular Immunology of STDs at Johns Hopkins University), scientists are studying the molecular nature of the immune response to HPV infection; their findings have led to a promising strategy for a therapeutic vaccine. In collaboration with US Department of Energy, the Institute recently established, the HPV DNA Sequence Data Base. Compendiums for 1994-1996 are available. Antiviral drug development efforts are supported through cooperative agreements and contracts.

STD Treatment and HIV Prevention

Discharge and ulcerative STDs increase the risk of HIV transmission from three- to five-fold for the discharge diseases and up to ten-fold for the ulcerative diseases. All but one of these STDs (genital herpes) is treatable with curative single-dose therapies. The primary obstacle in using secondary prevention of STDs to prevent HIV infection is the asymptomatic nature of most STDs. The Institute is currently funding two international studies aimed at assessing the feasibility and/or the effectiveness of community-based interventions to treat STDs. In the NIAID-sponsored Uganda study, mass treatment on a community basis is being compared to symptom-driven treatment; the study outcome measures include point prevalence of STDs and HIV incidence rates. The results of this study will build on those of another study sponsored by the European Union conducted in Mawanza, Tanzania. In the Mawanza study, investigators observed approximately 40 percent reduction of HIV incidence rates when symptomatic STDs were treated. The Uganda study will contribute two vital pieces of information to our understanding of this problem and the potential for STD prevention and control to impact on HIV infection rates. First, it will document the change in STD infections in response to treatment, microbiologically linking change in STD prevalence with change in HIV infection rates; and second, it will determine how much asymptomatic STDs contribute to increased risk of HIV transmission. In another other NIH-sponsored community-based study of chlamydial infection of the eye in Egypt and Tanzania, two community-based approaches to treatment are compared: single-dose therapy with azythromycin versus daily application of tetracycline eye ointment. The outcome measures are prevention of infection and ocular disease. In addition, investigators are evaluating patterns of re-emergence of infection. Both NIH studies should yield valuable information with respect to feasibility of community-based interventions and the number of HIV infections that might be prevented by treating STDs.

Recently the NIAID sponsored a workshop on the methodology of conducting community-based STD treatment trials. The NIAID also sponsored a symposium on STD treatment and HIV prevention at the International AIDS Conference; it included presentations on the molecular mechanisms of the interactions between the HIV and other sexually transmitted pathogens as well as the development of antimicrobial resistance as use of therapeutic interventions increase.

STD Diagnostic Test Development and Evaluation

In the absence of screening programs, secondary prevention of STDs is confounded by the indolent nature of these infections. For a number of reasons, the types of diagnostic tests available are not amenable for use as screening tests. These tests require invasive samples and are either expensive or technically complex, and they are slow to yield results. Given that the majority of these infections occur in the resource-limited settings of the developed and developing worlds, there is an urgent need for rapid, inexpensive, easy-to-use diagnostic tests that do not require an invasive sample. In collaboration with the US Agency for International Development (USAID), the Institute sponsored a meeting on the Development of STD Diagnostic Tests for Resource Limited Settings. Subsequently, the Institute co-founded the STD Diagnostic Initiative (SDI). The SDI is a multilateral task force the purpose of which is to facilitate the development, production and distribution of STD diagnostic tests appropriate for use in resource limited settings. In 1994, the Global Program on AIDS/World Health Organization assumed responsibilities of the SDI Secretariat.

In December 1994, the Institute awarded four cooperative agreements to support research development, manufacturing development and evaluation of diagnostic tests for gonococcal and chlamydial cervicitis and urethritis. In addition to these ongoing research efforts, the STD Program has actively used the Small Business Innovative Research (SBIR) Program to fund research and development of tests for yeast vaginitis, bacterial vaginosis, trichomoniasis and genital herpes.

Topical Microbicides

Through discussions at four international meetings, a consensus has developed that prevention and control of STDs and HIV infection will depend upon the development of female-controlled barrier methods, both chemical and physical, to prevent transmission. Topical microbicides are products, such as gels, foams, creams or films, that prevent sexually transmitted infections; these products are designed for intra-vaginal/rectal use and may or may not be spermicidal (i.e., contraceptive). In 1993, the Institute launched the Topical Microbicides Research Initiative that includes three parallel tracks: basic research, product development and clinical evaluation (including behavioral research on acceptance and compliance). To further scientific knowledge required for the development of new products, the Institute has funded four Topical Microbicides Program Projects; included are Children's Hospital of Cincinnati, University of California Los Angeles, University of Pittsburgh, Pennsylvania State University. In addition, the Institute has contracts for *in vitro* and *in vivo* screening of antiviral/antimicrobial compounds as well as for formulation development. Currently, clinical studies on five products, two over-the-counter and three experimental, are in progress or about to begin. An investigator-initiated grant, a Vaccine Treatment and Evaluation Unit, an STD Cooperative Research Center and the HIV Network for Prevention Trials (HIVNET) provide the infrastructure for this research. NICHD and NCI each have active programs in this area as well. NIH staff participate in a number of interagency activities that are designed to facilitate the development, evaluation and approval of existing and new products for use as topical microbicides. The International Working Group for Topical Microbicides has recently published guidelines for preclinical and clinical development of these products. The NIAID and the UNAIDS program co-sponsored a Topical Microbicides Symposium at the International AIDS conference. The second edition (1997) of the NIAID's Topical Microbicides briefing book is available.

STD Vaccine Development Research

Vaccines are strategically important for STD prevention and control; in particular for viral diseases for which there are no curative treatments and for bacterial diseases for which antibiotic resistance is common, as well as those diseases which are either asymptomatic or are associated with symptoms that are so indolent

that the patient neither seeks nor receives effective therapy. Most desirable are vaccines that prevent infection; however, vaccines may play a critical role in reducing transmission, ameliorating disease or interrupting disease progression. Unfortunately, except for Hepatitis B, no vaccines exist for STDs. STD vaccine development is extremely difficult and complex for reasons related primarily to: 1) the nature of the host-pathogen relationship, and 2) the consequences of co-infection with more than one sexually transmitted pathogen. As obligate pathogens of humans, the etiologic agents of these diseases have evolved to effectively avoid, subvert, or ignore the immunodominant host response. In addition to investigator-initiated vaccine development research, the Institute funds three program projects on Research on Molecular Immunology of STDs (ROMIS) at Johns Hopkins University, University of Washington and University of Wisconsin and a program project on herpes vaccine development at the University of Chicago (terminated 1995). A number of STD vaccines are either in clinical trails or are ready for clinical testing. A clinical trial for a genital herpes DNA vaccine is in progress. Plans to test three other HPV vaccines are in progress, two are prophylactic and the other is therapeutic. Plans for a phase I study of a gonorrhea vaccine are in progress; an IND will be filed in the summer of 1997. The NIAID funds grants to sequence the genomes of *N. gonorrhoeae, C. trachomatis, Ureaplasma urealyticum* and *T. pallidum*. Sequencing the genomes of these important STD pathogens is anticipated to provide new insights into pathogenesis and potentially identify new antigens for evaluation as vaccine candidates.

Adolescents and STDs

Numerous epidemiological studies document a high prevalence of STDs and sequelae in youth. In the US, sixty-three percent of all STD cases occur in persons younger than 25. Three million teenagers are affected with an STD annually. Two recent studies have provided data that indicate sexual activity among teenagers to be increasing. These data support concerns that these problems may get worse. Although available epidemiological data from developing countries are incomplete, it appears that this trend maybe global in scope. Behavioral factors contribute to the increased risk of contracting an STD. For instance, due to perceived invulnerability of youth, adolescents often reject precautions. Girls may rely solely on oral, not barrier, contraceptives. In many cases, the relationship between sexual partners is not mature enough to facilitate the discussion of STD risk. Behavioral factors also contribute to the prevalence of STD sequelae, especially upper tract infection or pelvic inflammatory disease in girls. Adolescents often deny symptoms and even if the disease is recognized, they are often too embarrassed and/or frightened to seek treatment. Many health care facilities are inaccessible to young people, either for logistical or financial reasons. If they are fortunate enough to be diagnosed and treated, like all of us, they frequently fail to comply with treatment, which complicates recovery. Anecdotally, we think a great deal of self-prescription of antibiotics occurs; these drugs are either purchased on the street or obtained from friends. Finally, and most importantly, non-consensual sexual intercourse is often the source of infection for young people. Biological factors greatly compound these behavioral risk factors. Features of adolescent cervical anatomy increase the likelihood of chlamydial infection, gonorrhea and, perhaps HIV infection. Hormone changes at puberty alter vaginal flora and natural mucus barriers to infection. These factors, in conjunction with immunological naiveté, mean that exposure often results in infection. In collaboration with the Rockefeller Foundation, the Santa Fe Institute and the Office of Research On Women's Health, the NIAID sponsored two workshops on Adolescents and STDs. A comprehensive monograph detailing the state of knowledge and recommendations for a research agenda will be published in 1998. The NIAID recently requested applications for a cooperative research center focused solely on STDs and adolescents. One award will be made in Summer, 1998.

Behavioral Research

Prevention and control strategies for infectious diseases focus on blocking transmission, identifying and treating patients, and interrupting progression of disease. Biomedical research has developed very important tools to support effective strategies: vaccines to prevent disease, diagnostics to detect infection, antibiotics and

antivirals to treat patients and prevent sequelae. However, behavioral research can also contribute to disease prevention and control by changing behaviors to prevent exposure; increasing acceptance of vaccines in both child and adult populations; promoting health behaviors leading to diagnosis of infection; and improving compliance with treatment regimens. A significant portion of the behavioral research portfolio is included in the STD Cooperative Research Centers. However, the Institute also supports numerous investigator-initiated research grants. This intervention-oriented research is focused on STDs in a variety of populations, including high-risk adolescents, active duty servicemen, minority women, populations in the rural South and sexual partner networks. In an effort to further develop the NIAID's behavioral research program, a program announcement was published in 1993; NIAID also conducted a Phase 1 evaluation of NIH-sponsored condom research and held a workshop on STD vaccine acceptance and compliance, 1994.

The Sexually Transmitted Diseases Cooperative Research Centers (STD CRCs)

The Sexually Transmitted Diseases Cooperative Research Centers (STD CRCs) are cooperative agreements designed to provide multidisciplinary approaches to STD research. The STD CRCs bridge basic biomedical, clinical, behavioral and epidemiological research, promote productive collaborations among academic researchers and facilitate the development of intervention-oriented research. Seven STD CRCs are currently funded; these include Boston University, Johns Hopkins University, Indiana University, University of Alabama at Birmingham, University of North Carolina, University of Pittsburgh/McGee's Women's Hospital, and University of Washington. More than thirty research projects are included in the CRCs; the studies conducted are directly linked to the five strategic aims. In collaboration with the Centers for Disease Control and Prevention (CDC), NIAID established a fellowship program in the CRCs designed to strengthen the link between the public health departments and the universities; we hope to renew this program in the currently funded CRCs. In summer of 1996 NIAID launched a summer research program for Howard University Medical Students within the STD CRCs; the program is in its third iteration. The NIAID will issue a request for applications to renew the STD CRCs, Summer 1998.

Hepatitis B and C

The Enteric and Hepatic Diseases Branch manages the hepatitis portfolios for the Division of Microbiology and Infectious Diseases. Although some of the hepatitis viruses have sexual transmission modes, these modes do not represent the primary route of infection. Hepatitis B is the only sexually transmitted disease for which vaccines exist. Two vaccines licensed in the U.S.A. are over 90% effective at preventing hepatitis B virus (HBV) infection including that acquired via sexual transmission. Implementation of vaccine use has been slow. Universal infant and adolescent vaccination are recommended and being implemented in this country. Vaccine development for hepatitis C is expected to be difficult because of multiple viral genotypes and the existence of quasispecies. Basic research to define protective immunity is in its infancy.

Development of effective therapeutics is a high priority since the licensed interferon preparations used to treat chronic hepatitis, which can result from both hepatitis B and C acute infections, are inadequate. Two preclinical efforts to develop and evaluate antiviral candidates for treatment of hepatitis B are managed and coordinated by the Virology Branch and the Enteric and Hepatic Diseases Branches. Patient populations are being accessed through four Hepatitis C Cooperative Research Centers and other grant and contract efforts. Clinical studies of therapies for both hepatitis B and C now are an option through the Collaborative Antiviral Study Group managed by the Virology Branch and are supported by the preclinical activities. Defining pathogenic mechanisms and host responses that influence recovery versus chronic infection is an important goal. Grantee investigators are working to develop some of the key tools needed for hepatitis C virus (HCV) research. These include development of infectious viral clones as well as tissue culture and small

animal model systems. A Program Announcement (97-053) entitled "Enteric and Hepatic Infections Diseases" summarizes these scientific needs and new opportunities.

Antiviral Drug Development

The Virology Branch supports several antiviral drug discovery and evaluation efforts in the area of viral STDs. Clinical activities include multicenter evaluations of therapies for neonates who have acquired herpes simplex infections at birth. In addition, a clinical trial of an experimental therapy for recurrent respiratory papillomavirus infections, also thought to be the result of maternal transmission at birth, is in the late planning stages. Other STD-related antiviral activities include preclinical drug discovery and animal model evaluations for papillomavirus and HSV infections.

Basic Research In The Biology Of Trichomonas vaginalis

The Parasitology and International Programs Branch (PIPB) of DMID is responsible for administering grants on the basic biology of *T. vaginalis*, the protozoan pathogen which is commonly found in the human genitourinary tract. Infection is prevalent worldwide and causes vaginitis in women and asymptomatic urethral infection in men.

STD Clinical Trials Unit

The STD Clinical Trials Unit is based at the University of North Carolina, Dr. Myron Cohen, Primary Investigator. The Unit will support clinical trials to test safety and efficacy of biomedical and behavioral interventions aimed at the prevention and control of sexually transmitted diseases. Diseases or pathogens of interest include, but are not limited to: chlamydial infection; gonorrhea; syphilis; chancroid; human papillomavirus (HPV) infection; genital herpes (herpes simplex virus 1 & 2 infections), human herpes virus 8 (Kaposi's sarcoma virus) and human immunodeficiency virus (HIV) infection as it is associated with other STDs (both in terms of increased transmission rates of HIV and alteration of the natural history of STDs). The syndromes of interest include, but are not limited to: pelvic inflammatory disease (and sequelae - infertility, ectopic pregnancy and chronic pelvic pain); adverse outcomes of pregnancy; and cervical cancer as well as other genital cancers associated with HPV infection..

These prevention and control strategies encompass primary, secondary and tertiary prevention. The interventions of interest include but are not limited to: topical microbicides, vaccines, diagnostics tests, screening tests, therapeutics and behavior change. Although the scope of interventions is broad, the number of microbicides, vaccines, diagnostic tests, behavioral interventions, that are appropriate for clinical trials is finite. That said, a prioritization process with respect to category of intervention and specific intervention will be implemented and those interventions of highest priority will be selected for study in the STD CTU.

Given currently available funds, it is anticipated that the trials will be Phase I and Phase II in scope. Infrequently, but when appropriate, Phase III (efficacy) and Phase IV (post-marketing application) trials may be conducted in the STD CTU.

STD Genome Sequencing

Genomic sequencing has provided important new information about bacterial and viral sexually transmitted pathogens. The sequences of five bacterial pathogens will soon be completed. *Mycoplasma genitalium,* and *Ureaplasma urelyticum* genome sequences are completed. Genomes for the causative organisms of gonorrhea, syphilis and chlamydial infection are in progress. A consensus has developed that establishment of a specialized nucleic acid database for STD pathogens would address this need. The STD DNA data base was

established in 1998. It has responsibility for analysis, curation, information management and generation of a Worldwide Web publication pertaining to the STD pathogens.