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Phase III Trials of Cellulose Sulfate Microbicide for HIV Prevention Closed

Arlington, VA – CONRAD, a reproductive health research organization, announced today that it has halted a Phase III clinical trial of cellulose sulfate – a topical microbicide gel being tested for HIV prevention in women – because preliminary results indicated that cellulose sulfate could lead to an increased risk of HIV infection in women who use the compound. The trial was being conducted in South Africa, Benin, Uganda, and India.

Simultaneously, Family Health International (FHI) has halted a second Phase III cellulose sulfate trial in Nigeria. Although the FHI trial did not detect an increased HIV risk associated with cellulose sulfate, the decision was made as a precautionary measure, given the preliminary results in the CONRAD trial. Cellulose sulfate (CS) was one of four microbicides currently in effectiveness trials for prevention of HIV and other sexually transmitted infections.

At this point, it is not clear why use of cellulose sulfate was associated with an increased risk of HIV infection in the CONRAD trial. The Independent Data Monitoring Committee (IDMC), an independent advisory group of experts overseeing the trial, will conduct a detailed review of the data to better understand the findings, and help determine any implications for other microbicide studies.

Dr. Lut Van Damme, principal investigator of the CONRAD trial, stated: “It was our hope that this product would have helped women in protecting themselves from HIV. While the findings are unexpected and disappointing, we will learn scientifically important information from this trial that will inform future HIV prevention research.”

The microbicide, also known as Ushercell, is a cotton-based compound developed by Polydex Pharmaceuticals, based in Toronto, Canada. Prior to beginning the Phase III efficacy trials, there were 11 earlier safety and contraceptive trials on cellulose sulfate involving more than 500 participants in Africa, India, and the U.S. -- none of which identified safety concerns. **(SEE ATTACHED CLINICAL TRIAL SUMMARY)**

Recruitment for the CONRAD Phase III study began in July 2005. The study was conducted in areas of the world where HIV risk is greatest, and where infection occurs primarily through heterosexual intercourse. Half of the participating women were given cellulose sulfate, and half a placebo gel, in a double-blinded randomized trial design. All

participants received intensive HIV prevention counseling at each monthly visit and all women were given high-quality condoms free of charge. Participants received regular testing and treatment for sexually transmitted infections. Pregnant women were not included in the study.

Participants were admitted into the study only after receiving detailed information about the purpose of the study and the possible health benefits and risks. During this process, their understanding of the study was assessed prior to their signing a consent form. Each trial site is linked to local organizations that provide care for women who become HIV-infected during the trial. As part of the trial preparation, CONRAD set aside funding for women who become HIV-positive during the trial to ensure adequate health care, including HIV antiretroviral treatment when needed.

Jeff Spieler, Chief of USAID's Research, Technology and Utilization Office of Population and Reproductive Health said, "I am surprised and disappointed by these findings given the pre-clinical effectiveness profile of CS, and its safety profile demonstrated in Phase I and Phase II trials. I believe strongly that the field learns a great deal from every study, even those with disappointing results. The effort and resources that have been expended in terms of site and infrastructure development, training of clinical and laboratory staff, and community involvement activities will help move the field forward and pave the way to future studies."

He continued, "I am also hopeful that one or more of the other microbicide candidates now in development will be shown to be safe and effective in helping to prevent HIV infection along with other behavioral interventions."

"Developing new tools to prevent HIV – particularly for women – is an urgent priority," said Dr. Henry Gabelnick, Executive Director of CONRAD. "We are committed to learning as much as possible from the trials of cellulose sulfate, and will use that knowledge to continue searching for compounds and collecting evidence to find a successful microbicide. Continued support for microbicide research is critical to our eventual success."

CONRAD is a cooperating agency of USAID committed to improving reproductive health by expanding the contraceptive choices of women and men and by helping to prevent the transmission of HIV/AIDS and other sexually transmitted diseases. CONRAD is administered through the Department of Obstetrics and Gynecology at Eastern Virginia Medical School (EVMS) in Norfolk, VA and headquartered in Arlington, VA.

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Cellulose Sulfate: Clinical Trial History (Safety and Efficacy)

Overview:

Prior to initiating two HIV prevention trials, CONRAD sponsored 11 clinical trials of cellulose sulfate (CS) involving 518 women and 48 men in the CS arms. These studies fall into four categories as follows:

- Safety studies in women – 5
- Safety studies in men – 2
- Other (safety of CS when used with a diaphragm and MRI imaging)- 2
- Contraceptive effectiveness studies - 2

Most of the trials were undertaken in the United States (7), one was done in Europe, and three in countries where the HIV prevention trials were expected to be carried out. The contraceptive effectiveness trials were carried out in the United States in mutually monogamous populations at low risk for STIs in which condom counseling was not required.

Type of trial		Cellulose sulfate (Site Location)	# on CS	Start Date	End Date
Safety	♀	•6-day, 1x/day (U.S.)	•24	•1999	•2000
		•7-day, 2x/day (Nigeria, Uganda, India)	•90	•2001	•2004
		•14-day, 2x/day (U.S., Dominican Republic)	•30	•2002	•2004
		•14 day, 4x/day (Cameroon)	•27	•2002	•2004
		•14 day, 1 & 2x/day, HIV pos (U.S.)	•29	•2002	•2006
	♂	•7 day, 1x/day, HIV neg (U.S.)	•24	•2000	•2001
		•7 day, 1x/day, HIV pos (Belguim)	•24	•2003	•2005
MRI		•2 volumes (U.S.)	•6	•2001	•2003
Safety with Diaphragm		•6 Months with intercourse (Zimbabwe)	•79	•2004	•2005
Contraception		•True Efficacy, 1 month with intercourse (U.S.)	•33	•2004	•2006
		•Phase II, 6 months with intercourse (U.S.)	•200	•2005	•2006

The safety studies in women and men varied in terms of control group (inactive sexual lubricant such as K-Y® Jelly or active spermicidal gel such as Conceptrol®), frequency of use (once, twice, or four times daily), duration of use (6-14 days), sexual activity (abstinent or active), and HIV status of participants (infected or uninfected). Endpoints included signs and symptoms of genital irritation, colposcopic findings, changes in vaginal microflora and, in some cases, vaginal inflammatory markers, and responses on acceptability questionnaires. The contraceptive studies used the prevention of pregnancy as the primary endpoint. The results of these studies have indicated that CS was as safe, acceptable, and effective as marketed spermicides and sexual lubricants.

The initial safety study was begun in 1999 and the contraceptive effectiveness trial was completed in July, 2006. The results of all eleven clinical studies to date have indicated that CS was as safe, acceptable, and effective as marketed spermicides and sexual lubricants.