



# ALLIANCE FOR MICROBICIDE DEVELOPMENT

**05 April 2007, Volume 8, Number 13**

The Alliance for Microbicide Development *News Digest* is an **unedited** compilation of:

- Media coverage of microbicides;
- Abstracts of articles on microbicides and relevant science in peer-reviewed journals;
- Material on other reproductive health and HIV prevention technologies, including HIV vaccines; and
- Matters of policy and politics with importance for microbicide research, development, and advocacy.

Its purpose is to:

- Raise awareness around the range of opinions and information about microbicides disseminated in the press and scientific journals; and
- Provide a neutral, objective basis for decision-making and evidence-based advocacy.

The *News Digest* is produced in a web-based format. Readers can view individual articles or complete issues at <http://www.microbicide.org/publications/> and may also search by keyword for articles included in issues of the *Digest* created after 27 January 2006, at <http://www.microbicide.org/publications/search.html>. Should you wish to be removed from the *Digest* distribution list, please advise us at [digest@microbicide.org](mailto:digest@microbicide.org). We welcome comments, questions, and ideas about other microbicide-relevant topics we might cover, services we might provide, and better ways of providing them!

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## 1. MONTHLY MICROBICIDE PIPELINE UPDATE

### April 2007

Each month, the *Digest* includes an update on overall progress in the field. Currently, there are 11 **microbicide** candidates in clinical development and over 30 in preclinical development. As a continued effort to maintain the most up-to-date information, we urge you to visit the Alliance website at [www.microbicide.org](http://www.microbicide.org) or contact Carolyn Plescia, Alliance Writer/Research Associate, by email ([cplescia@microbicide.org](mailto:cplescia@microbicide.org)) or by phone (301-587-3302) with any updates, questions, or comments.

<b>Candidate</b>	<b>Mechanism of Action</b>	<b>Developer</b>	<b>Phase*</b>
ACIDFORM (Amphora)	Vaginal defense enhancer	CONRAD; Instead, Inc.	1
BufferGel	Vaginal defense enhancer	ReProtect, Inc.	2/2B
Carraguard	Entry/fusion inhibitor	Population Council	3
Dapivirine (TMC120)	Replication inhibitor	IPM	1/2
Invisible Condom	Entry/fusion inhibitor	Laval University	1/2
PC 815	Combination	Population Council	1

Praneem polyherbal vaginal tablet	Uncharacterized mechanism	Talwar Research Foundation	2
PRO 2000	Entry/fusion inhibitor	Indevus Pharmaceuticals, Inc.	3
Tenofovir (PMPA gel)	Replication inhibitor	CONRAD	2B
UC-781	Replication inhibitor	CONRAD	1
VivaGel (SPL7013)	Entry/fusion inhibitor	Starpharma Ltd.	1

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\*Some candidates are in more than one phase of clinical testing. The phase listed in this table represents the most advanced clinical trial currently planned or underway for each candidate. (This table does not include trials of contraceptive efficacy). For modifications, please contact Carolyn Plescia, email [cplescia@microbicide.org](mailto:cplescia@microbicide.org), tel. 301-587-3302.

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## 2. ALLIANCE UPDATES AND COMMUNITY NEWS

### Internship opening at the Alliance

<http://www.microbicide.org/allianceinfo/employment.shtml>

The Alliance for **Microbicide** Development is offering a four-month, full-time, paid internship at our office in Silver Spring, MD from May 14 through September 14, 2007, with the potential to become a full-time position. Applicants should have an MPH or equivalent degree, or be working toward such a degree. Strong science background and familiarity with HIV prevention field preferred.

Specific duties will be determined based on the qualifications of the individual selected, but may include:

- Compiling a weekly *News Digest* of **microbicide**-relevant media and journal coverage
- Writing *News Alerts* highlighting significant events in the field
- Writing abstracts and conducting literature searches and background research for conferences and meetings
- Tracking **microbicide** clinical trials and maintaining the *Microbicide Research and Development Database*
- Contributing to articles published in *The Microbicide Quarterly*
- Updating the *Microbicide Resource Directory*
- Writing meeting reports for scientific working groups
- Εξοπλισμός βριέφς ανδ ρεπορτσ

Please send a resume and cover letter to:

Franka des Vignes, PhD  
Deputy Director

Alliance for **Microbicide** Development  
8484 Georgia Avenue, Suite 940  
Silver Spring, Maryland 20910 USA  
Tel 301-587-9690  
Fax 301-588-8390  
Email: [employment@microbicide.org](mailto:employment@microbicide.org)

The Alliance for **Microbicide** Development is an equal opportunity employer. Women and Minorities are encouraged to apply.

### **Presentations from CONRAD/Alliance joint meeting on biomarkers now available online!**

[http://www.microbicide.org/microbicideinfo/biomarkers\\_conference.shtml](http://www.microbicide.org/microbicideinfo/biomarkers_conference.shtml)

In November 2006, CONRAD and the Alliance for **Microbicide** Development sponsored a meeting entitled "Biomarkers for evaluating vaginal **microbicides** and contraceptives: Discovery and early validation." This meeting was held in Reston, Virginia, and was funded in part by the Bill and Melinda Gates Foundation and the United States Agency for International Development.

The goals of the meeting were to:

- Review the current status of biomarkers in vaginal product research;
- Assess how emerging technologies might be applied to the **microbicide** field; and
- Encourage innovation and collaboration among a broad spectrum of researchers within and beyond that field.

Three main areas were discussed:

- Biomarkers of semen exposure;
- Biomarkers of cervicovaginal inflammation; and
- Biomarkers of HIV/STI infection.

The meeting was attended by 85 representatives from 42 institutions (government, academia, industry), and received accolades for bringing together a new and diverse group, addressing cutting edge research. The presentations from this meeting are available on the Alliance's website at [http://www.microbicide.org/microbicideinfo/biomarkers\\_conference.shtml](http://www.microbicide.org/microbicideinfo/biomarkers_conference.shtml) and on CONRAD's website at <http://www.conrad.org/biomarkers-conference.htm>

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### **3. MEDIA COVERAGE OF MICROBICIDES**

## "Intriguing findings from study on lubricants"

**Date:** 29 March 2007

**Source:** CATIE-News

**Author(s):** Sean R. Hosein

<http://www.catie.ca/catieneews.nsf/00a48c8905294f0b8525717f00661eb8/78143c953b0c6eac852572ad0068c934!OpenDocument>

A vital part of preventing HIV transmission is the use of condoms for both vaginal and anal sex. Many people use personal lubricants as well, for enhancing pleasure and reducing dryness. Using lubricant may also reduce the risk of condoms breaking during sex.

Lubricants may also become important in another area - **microbicides**. These are prevention products that are being developed in the form of gels, creams, films, sponges and suppositories that contain anti-HIV compounds. Worldwide, most cases of HIV are spread through unprotected vaginal sex. Therefore, it makes sense that **microbicides** are being designed to work in that part of the body.

An advantage of **microbicides** is that they could allow women the opportunity to protect themselves before having sex, without the need to get permission or approval from men. This is necessary in many parts of the world, particularly where HIV is endemic. In these regions, women may not have a great deal of power over their lives, particularly when it comes to their sexuality. This makes them vulnerable to infection from HIV positive men.

Both men who have sex with women as well as men who have sex with men engage in anal intercourse, which can also place them at risk for HIV transmission. Because the focus with **microbicides** has largely been on the prevention of HIV transmission in the vagina, the effect and activity of these products in the rectum may be understudied. However, it is likely that once **microbicides** designed for vaginal use become widely available they may also be used for anal sex.

As a foundation for future work on **microbicides** and to better understand the impact of some commonly available personal lubricants and other substances on the rectum, researchers at the Johns Hopkins University School of Medicine in the United States have begun to engage in lab experiments and tests on volunteers. Their findings are intriguing and may give other research teams pause for thought as they develop potential **microbicides**.

### *Study details*

Researchers recruited 10 men for this study. At different points in time over a period of weeks, the men had different lubricants squirted into their rectums by the research team. These lubricants were:

- ID Glide
- a mixture of ID Glide and FemGlide

These substances were tagged with a tiny amount of radioactive material so that their passage through the rectum and colon could be monitored. Within 1.5 hours after administering the lubricants, the study team began to probe the volunteers and removed tiny amounts of tissue from just inside the rectum to as deep as 40 cm (about 16 inches) from

the anus into the colon. These tissue samples were observed under the microscope and analysed for changes and damage.

In parallel with this research on people, the research team also conducted lab experiments with the following lubricants and other substances:

- Astroglide
- FemGlide (also sold as Slippery Stuff)
- Fleet enema
- ID Glide
- KY Jelly
- PrePair

Specifically, they assessed the potential of these products to either pull water out of a cell or push water into a cell. If a cell loses water faster than it can be replaced, it becomes injured and can die. If it has absorbed too much water, the cell can also become damaged. Injured or damaged cells lining the rectum can, in theory, make HIV infection easier.

### *Results*

In testing these substances in the lab, the study team found that many of them were hyperosmolar - they tended to attract and absorb water from cells lining the rectum. This has the potential to damage these cells. Indeed, the ability of the lubricants to pull water out of cells was between 4 and 14 times greater than the ability of rectal cells to retain water. The lubricant called FemGlide (Slippery Stuff) was the only product that did not have the potential to significantly pull water out of cells. The researchers classified it as hyposmolar, suggesting that it had the potential to push water into cells.

The other lubricants and substances, because they are hyperosmolar and attract and absorb water, have the potential to reduce the layer of mucus that coats the rectum.

Based on the analysis of tissue samples taken from volunteers, damage to cells lining the rectum occurred in less than two hours after lubrication was first applied. In theory, this damage may increase the risk of HIV transmission during sex. However, this study was not designed to assess such a risk and any conclusions drawn about that subject can only be theoretical possibilities.

Another finding from this study was that some lubricants, after being applied just past the anus, can migrate as far as 40 cm up the colon up to four hours after being applied. At such a distance, the lubricant becomes diluted and likely poses little threat to the health of colon cells. However, the potential for other issues (as noted below) arises.

### *What's next?*

The results from this study are intriguing and may stimulate other research teams to conduct studies to confirm and extend the initial findings of the Johns Hopkins team. The results from the present study also have implications for currently available lubricants and future rectal **microbicides** (which may or may not contain lubricants), including the following:

- Does exposure to certain commonly available lubricants in everyday use lead to rectal injury?
- How long after exposure to some lubricants will the rectum heal itself?
- How often can these products be safely applied to the rectum?
- As lubricants have the potential to migrate up the colon, will the concentration of **microbicides** still be active against HIV as they migrate and become diluted?
- Is it possible to create lubricants that do not migrate up the colon?

Overall, the results from the Johns Hopkins study show that much work remains to be done to study the potential safety of rectal **microbicides** and lubricants.

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## 4. PUBLISHED RESEARCH: MICROBICIDE-SPECIFIC

### "A comprehensive murine model to evaluate topical vaginal microbicides: mucosal inflammation and susceptibility to genital herpes as surrogate markers of safety"

**Author(s):** Galen BT, Martin AP, Hazrati E, et al

**Reference:** N/A 195(9):1332-9.

**Published Abstract:** A critical gap in **microbicide** development is the absence of surrogate safety markers. The objective of the present study was to develop a murine model to examine the mucosal response to **microbicides** and to assess the functional implication of observed changes. Mice received 14 daily intravaginal doses of nonoxynol-9, PRO 2000, or placebo gel. Nonoxynol-9 induced an inflammatory response characterized by increases in levels of cytokines and chemokines, recruitment of neutrophils and monocytes into the genital tract, and activation of the transcription factors NF- kappa B and activator protein-1. Minimal inflammation was observed in response to 2% PRO 2000. Nonoxynol-9-treated mice were significantly more susceptible to challenge with a low dose of herpes simplex

virus type 2; the response of PRO 2000-treated mice was similar to the response to placebo. These findings suggest that PRO 2000 has little deleterious effect on mucosal immunity and, if validated by clinical experiences, support the inclusion of this model in the preclinical evaluation of future candidate **microbicides**.

### "Effect of topical microbicides on infectious HIV-1 binding to epithelial cells"

**Author(s):** Roth S, Monsour M, Dowland A, et al

**Reference:** N/A Epub ahead of print.

**Published Abstract:** Topical **microbicides** (cellulose acetate 1,2 benzene dicarboxylate [CAP], PRO 2000, SPL7013, and UC781) are being investigated to reduce the sexual transmission of HIV-1. These products were shown to prevent the transfer of infectious HIV-1 from urogenital and colorectal epithelial cell lines to PBMCs. However, it was unclear if the topical **microbicides** rendered the virus non-infectious and/or reduced the binding to the epithelial cells. To test this, epithelial cells were cultured with HIV-1 in the presence or absence of topical **microbicides** or their placebos. The cells were washed, RNA lysates were made, and real-time PCR was performed for HIV-1. PRO 2000 and SPL7013 significantly ( $p < 0.0001$ ) reduced the amount of bound HIV-1 to the colorectal epithelial cell line across clades A, B, C, and CRF01-AE. While none of the products reduced the binding of HIV-1 clades A and C to the urogenital cell line, CAP, PRO 2000, and SPL7013 significantly ( $p < 0.002$ ) reduced the binding of clades B and CRF01-AE. In general, PRO 2000 and SPL7013 placebos significantly ( $p < 0.0001$ ) reduced the amount of bound HIV-1, but were less than the active products. UC781, its placebo, and hydroxyethyl cellulose (placebo for CAP) minimally affected the amount of bound HIV-1. These results suggest that rendering HIV-1 non-infectious may not correlate to the amount of HIV-1 bound to epithelial cells and possible shedding into mucosal secretions. Therefore, functional virological assays in addition to measuring viral RNA should be included when clinically evaluating topical **microbicide** use by infected persons.

### "The genital tract immune milieu: An important determinant of HIV susceptibility and secondary transmission"

**Author(s):** Kaul R, Pettengell C, Sheth PM, et al

**Reference:** N/A Epub ahead of print.

**Published Abstract:** HIV is generally sexually acquired across the genital or rectal mucosa after exposure to the genital secretions of an HIV-infected partner. Most exposures to HIV do not result in infection, likely due to protection afforded by an intact mucosal epithelium, as well as by innate and adaptive mucosal immune factors present in the genital tract. Another important mucosal determinant of transmission may be the number and activation status of potential HIV target cells, including CCR5/CD4+ T cells and DC-SIGN+ dendritic cells. The simultaneous presence of other genital infections, including classical sexually transmitted infections (STIs), can enhance HIV susceptibility either by breaching the epithelial barrier, recruiting HIV target cells to the genital tract, or by generating a pro-inflammatory local immune milieu. In HIV-infected individuals, genital co-infections increase HIV levels in the genital secretions, thereby increasing secondary sexual transmission. Co-infections that act as important HIV cofactors include human cytomegalovirus (CMV), Herpes simplex virus type 2 (HSV2), *Neisseria gonorrhoeae* and many others. Strategies focused on genital co-infections, such as vaccines, **microbicides** and suppressive therapy, are feasible in the short

term and have the potential to curb the pandemic.

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## 5. PUBLISHED RESEARCH: RELEVANT BASIC AND TRANSLATIONAL SCIENCE

### "Decreased condom breakage and slippage rates after counseling men at a sexually transmitted infection clinic in Jamaica"

**Author(s):** Steiner MJ, Taylor D, Hylton-Kong T, et al

**Reference:** N/A 75(4):289-93.

**Published Abstract:** PURPOSE: Our objective was to evaluate condom failure (breakage and slippage) rates before and those during a trial that provided instructions on correct condom use. METHOD: Our analysis was based on 314 men who presented with urethral discharge at Jamaica's largest sexually transmitted infection clinic and were enrolled into our 6-month trial. RESULTS: Participants reported breaking 18.5% (95% confidence interval=12.8-24.1%) of their condoms during the 7 days prior to the screening visit and having 3.5% (95% confidence interval=1.2-5.7%) of their condoms slip off completely. After the condom counseling provided during the screening visit, breakage rates decreased ( $p < .05$ ) and remained below 10% throughout the trial. During in-depth interviews, the men who reported frequent condom failures cited (1) improper storage/exposure to heat, (2) improper handling while putting on condoms and (3) use of lubricants/improper lubricants as the possible reasons for their high failure rates. CONCLUSION: Although the rates of reported condom breakage and slippage decreased significantly after counseling, we need to improve the quality of condom counseling to further reduce failure rates.

### "Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study"

**Author(s):** Coovadia HM, Rollins NC, Bland RM, et al

**Reference:** N/A 369(9567):1107-16.

**Published Abstract:** BACKGROUND: Exclusive breastfeeding, though better than other forms of infant feeding and associated with improved child survival, is uncommon. We assessed the HIV-1 transmission risks and survival associated with exclusive breastfeeding and other types of infant feeding. METHODS: 2722 HIV-infected and uninfected pregnant women attending antenatal clinics in KwaZulu Natal, South Africa (seven rural, one semiurban, and one urban), were enrolled into a non-randomised intervention cohort study. Infant feeding data were obtained every week from mothers, and blood samples from infants were taken monthly at clinics to establish HIV infection status. Kaplan-Meier analyses conditional on exclusive breastfeeding were used to estimate transmission risks at 6 weeks and 22 weeks of age, and Cox's proportional hazard was used to quantify associations with maternal and infant factors. FINDINGS: 1132 of 1372 (83%) infants born to HIV-infected mothers initiated exclusive breastfeeding from birth. Of 1276 infants with complete feeding data, median duration of cumulative exclusive breastfeeding was 159 days (first quartile [Q1] to third quartile [Q3], 122-174 days). 14.1% (95% CI 12.0-16.4) of exclusively breastfed infants were infected with HIV-1 by age 6 weeks and 19.5% (17.0-22.4) by 6 months; risk was significantly associated with

maternal CD4-cell counts below 200 cells per mL (adjusted hazard ratio [HR] 3.79; 2.35-6.12) and birthweight less than 2500 g (1.81, 1.07-3.06). Kaplan-Meier estimated risk of acquisition of infection at 6 months of age was 4.04% (2.29-5.76). Breastfed infants who also received solids were significantly more likely to acquire infection than were exclusively breastfed children (HR 10.87, 1.51-78.00, p=0.018), as were infants who at 12 weeks received both breastmilk and formula milk (1.82, 0.98-3.36, p=0.057). Cumulative 3-month mortality in exclusively breastfed infants was 6.1% (4.74-7.92) versus 15.1% (7.63-28.73) in infants given replacement feeds (HR 2.06, 1.00-4.27, p=0.051). INTERPRETATION: The association between mixed breastfeeding and increased HIV transmission risk, together with evidence that exclusive breastfeeding can be successfully supported in HIV-infected women, warrant revision of the present UNICEF, WHO, and UNAIDS infant feeding guidelines.

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## 6. EPIDEMIOLOGY

### "HIV infections in Asia could more than double in 5 years"

**Date:** 30 March 2007

**Source:** *Associated Press*

<http://english.pravda.ru/news/world/30-03-2007/88837-aids-0>

The number of people in Asia infected with the HIV virus that causes AIDS could more than double to 20 million over the next five years without a better government response and more funding, officials warned Friday. "At the current level of inadequate response, it is expected this number will rise to about 20 million in the next five years," said the independent Commission on Aids in Asia that is funded by the Joint United Nations Program on HIV/AIDS or UNAIDS. There are currently around 8.6 million people infected in Asia with HIV.

It said the number of deaths currently average around 500,000 yearly and financial losses to the Asian region are estimated at US\$10 billion (EUR7.5 billion) annually. But that economic cost is predicted to rise to as high as US\$29 billion (EUR21.72 billion) per year if the epidemic is not controlled within the next five years.

Despite these projections, investments on HIV control in the region remain extremely low at ten percent of the required US\$5 billion (EUR3.74 billion) per year, it added. UNAIDS data show the number of infected people receiving antiretroviral therapy, which inhibits the replication of the HIV virus, has increased more than threefold since 2003, but they represent only 16 percent of the total of those in need of treatment in Asia. Only Thailand is providing treatment to at least 50 percent of those in need, UNAIDS said.

The nine-member commission of economists, policy makers and civil society members was created in 2006 to analyze the socio-economic impact of HIV/AIDS and make policy recommendations on how it can be mitigated. The commission is holding its two-day Southeast Asia Sub-Regional workshop in Manila until Friday.

Chakravarthy Rangarajan, chairman of Indian Prime Minister Manmohan Singh's economic advisory council and head of the commission, told reporters that while the prevalence of HIV/AIDS is low in Southeast Asia, the region is populous, making the number of infections high. It also has a huge number of mobile workers, who risk spreading

HIV. He also said there was a need to mobilize domestic funds to control HIV/AIDS in the region, because more than 80 percent of funding currently comes from foreign aid organizations.

In Southeast Asia, Laos and the Philippines are among those which have low HIV prevalence rates, while Cambodia, Myanmar and Thailand are among those which have a high prevalence of the virus, according to J. V. R. Prasada Rao, a UNAIDS director and a member of the commission.

The commission said the reasons for the inadequate response in the region are manifold, ranging from low levels of awareness and understanding among policy makers of the long term impact of HIV/AIDS to a difficulty in predicting the dynamics of the disease progression, and a lack of funding.

Sex remains taboo, with very little encouragement for sex and family education for young people. Multi-partner sex and injecting drug use, which mainly drive the epidemic, are criminal acts in the eyes of the law, resulting in infected populations remaining highly stigmatized and deprived of even limited health care services, it added.

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## 7. POLITICS AND POLICY

### "Drug makers set lobbying record"

**Date:** 03 April 2007

**Source:** *The Los Angeles Times*

**Author(s):** Ricardo Alonso-Zaldivar

<http://www.latimes.com/news/nationworld/politics/la-na-lobby3apr03,1,268236.story?ctrack=1&cset=true>

Drug makers spent \$155 million lobbying the federal government from 2005 to mid-2006, setting a record that they could top this year as Congress considers high stakes legislation for the industry and consumers, a public interest group said in a report Monday.

Researchers at the nonpartisan Center for Public Integrity said that the drug industry spent nearly \$111 million on lobbying in 2005, a record for the sector in any one year. The record pace appeared to be sustained in the first half of 2006, the report said.

Pharmaceutical industry officials said the report distorted the industry's role in Washington, which they say is primarily educational and scientific. They said industry spending was designed to ensure that new drugs for intractable illnesses get government approval to be marketed. "The Center for Public Integrity's report, not surprisingly, misses the mark when it comes to efforts by America's pharmaceutical research companies to educate policymakers," said Ken Johnson, senior vice president at the Pharmaceutical Research and Manufacturers of America. "Our priority has always been to help advance patient health and... we have supported policies and programs that bolster patient access to safe and effective medicines."

Lobbying is only one facet of the industry's influence. Drug company sources also accounted for more than \$19 million in political contributions to candidates in last year's congressional election, mainly Republicans. And user fees paid by drug makers make up more than half the budget of the Food and Drug Administration centers that evaluate new drugs. The industry's budget enabled drug makers to field about 1,100 agents to lobby congressional committees and administration offices in each of the last two years, the study said. The industry achieved several of its major objectives, the report added, including upholding the government's ban on imports of lower-cost medications from abroad. "Essentially what they did is they blocked any legislation," said M. Asif Ismail, director of the center's project to monitor the drug industry. "There have been several attempts to revisit this issue, and importation is still illegal." With strong support from the Bush administration, the industry also appears to be in a position to make sure the prohibition against Medicare negotiating drug prices for seniors in its prescription program remains intact.

These battles are expected to be fought more fiercely this year because Democrats now control Congress. In the past, senior Republican leaders were able to keep import legislation from getting a floor vote. "The industry is going to spend more money this time than the record amount that is reported by the center," said Dr. Sidney M. Wolfe, director of the consumer watchdog Public Citizen's Health Research Group. "From the perspective of the industry, this money is extremely well spent, because they have used it to win virtually every important battle."

The industry's clout will be severely tested in coming months. Legislation authorizing the FDA's user-fee system will expire this year unless Congress acts. Such must-pass legislation often attracts amendments. Reforms to strengthen the FDA's drug safety system are expected to be part of the bill. And supporters of lifting the ban on pharmaceutical imports also are eyeing the user-fee bill as a vehicle.

Sens. Byron L. Dorgan (D-N.D.) and Olympia J. Snowe (R-Maine) have introduced legislation that would allow U.S. consumers to import cheaper prescription drugs from Canada. "They have a history of looking for vehicles to attach this legislation to, and I would expect that to continue," said Barry Piatt, a spokesman for Dorgan.

The industry is approaching the debate by offering carrots and sticks. It has agreed to hefty user-fee increases that would pay for new safety reviewers at FDA and help set up a computerized surveillance system to aid in detecting harmful side effects in new drugs. But it is vowing to fight legislation allowing imports, arguing that it would lead to a flood of fake drugs. "The bills will in all probability end up importing what has become a counterfeit epidemic around the world into the United States," W.J. "Billy" Tauzin, a former Louisiana congressman who is the industry's top lobbyist, said during a recent discussion with reporters. "Congress is looking at an importation bill that would bust open the biggest safety protections we have." Asked if the industry would withdraw its support for an extended user-fee agreement if Congress added on objectionable amendments, Tauzin said it was too early to say.

### **"NIH grantees under the microscope?"**

**Date:** 02 April 2007

**Source:** *The Scientist*

**Author(s):** Ted Agres

<http://www.the-scientist.com/news/home/53048/>

Federal investigators are examining how the National Institutes of Health (NIH) oversees financial conflicts of interest among thousands of extramural scientists and grant recipients -- a decision biomedical research groups warn may lead to restrictions on industry-academic collaborations, ultimately inhibiting the translation of biomedical discoveries into therapies and diagnostics.

"There have to be interactions between those doing the research and those doing the translation," said David Korn, senior vice president for biomedical and health sciences research at the Association of American Medical Colleges (AAMC), which has prepared policy recommendations for academic and clinical researchers. If COI rules for extramural researchers are too Draconian, "you run the risk of interfering with" the search for cures and other health benefits, Korn told *The Scientist*.

"This is something we need to be very concerned about," said Howard Garrison, public affairs director at the Federation of American Societies for Experimental Biology, which has issued guidelines on industry interactions. "I would not want to see a situation where academic-industry collaborations are treated as something to be avoided or considered illicit, unwarranted, or bad," he told *The Scientist*.

In a March 23 letter made public last week (March 30), Department of Health and Human Services Inspector General Daniel R. Levinson said that the Office of the Inspector General (OIG) has started a study "to determine the extent to which the NIH oversees grantee institutions' financial conflict-of-interest issues." The letter was addressed to Rep. Joe Barton (R-TX), ranking member of the House Committee on Energy and Commerce. The topic was discussed in the pages of *The Scientist* in February.

At present, extramural researchers are not subject to the same federal laws and regulations that since 2005 have banned NIH staff and intramural scientists from consulting with or receiving other compensation from pharmaceutical and biotech companies. Rather, it is up to each university and research institute to establish and enforce COI guidelines and report infractions to NIH.

In his letter, Levinson also revealed that his office was re-examining 103 COI cases involving NIH intramural researchers, to determine whether further investigations are warranted. The NIH had previously examined those cases following reports that numerous agency scientists and senior officials had received hundreds of thousands of dollars in consulting and other fees. Only one case, involving Trey Sunderland, former chief of the Geriatric Psychiatry Branch at the National Institute of Mental Health, ended in a successful conviction. "We welcome the additional review," said NIH spokesman John Burklow. "We are confident in the process we used and the rigor in which we processed [investigations of intramural researchers] already," he told *The Scientist*.

However, not all officials are pleased with the NIH's previous efforts. "The NIH specializes in great science, not detective work, and it shows," Barton said in a statement. "I hope the inspector general's inquiry will finally sort things out so everyone can have confidence that the public's interest is being fully served."

"There is a giant hole in the way NIH conducted its investigation," said Ned Feder, an investigator with the Project on Government Oversight (POGO), which describes itself as an independent nonprofit group that exposes government corruption. "They were looking for documented evidence that the NIH had given its prior approval to paid consulting and other outside arrangements and not examining whether those arrangements actually created a conflict of interest," Feder told *The Scientist*.

Burklow and others said they unaware of any particular issue that may have triggered the IG's interested in extramural researchers. Donald White, spokesperson for the OIG, told *The Scientist* he had "no way of knowing" whether the decision to look into the NIH's oversight of conflicts of interest among extramural researchers will lead to any changes in rules about partnerships between academia and industry.

FASEB plans to release a set of COI proposals for NIH-funded extramural researchers during a summit in July with several dozen other research organizations.

### "The vaccine conundrum"

**Date:** 31 March 2007

**Source:** *The Scientist*, Volume 21, Issue 4

**Author(s):** Dan Zimmerman, Ken S. Rosenthal, Eyal Talor

<http://www.the-scientist.com/article/home/52982/>

**EDITORS' NOTE:** *Due to the length of this article, we have included only any excerpt below. The full text can be found at* <http://www.the-scientist.com/article/home/52982/>

They've eradicated smallpox, and all but eradicated polio. Their successes in lowering the disease burden of any number of other diseases are well known. Vaccines have joined an elite group of public health and medical approaches such as penicillin, pasteurization, and insecticides that have virtually eliminated diseases such as syphilis, bovine tuberculosis, and malaria from many regions of the world.

Because they're administered a few times at most, they're also more cost-effective than many drugs that treat the same conditions. In recent years, economists such as David Bloom have argued convincingly that the cost savings are even more impressive because they go beyond the costs of medical care, and should include income lost to illness and its sequelae (see *Why vaccines are a good investment*). It's therefore more than a bit puzzling why vaccines are either not seriously considered or completely ignored as marketable products by most pharmaceutical and biotech companies, and by most persons or groups who could invest in them.

Simply stated, the reason is limited profit and large risk. At best, vaccines bring in \$6 billion worth of revenues, about 1.5% of the current total annual pharmaceutical market worldwide. The market is splintered among more than a dozen pediatric vaccines and another dozen or so for travelers, other at-risk individuals, and the military. As a result, the market for any given vaccine is substantially below the \$500 million per year threshold that a pharmaceutical company considers as a viable product to develop.

While companies may start to see an expanded return on R&D investments for certain products due to the over-the-counter market, that is not currently possible for vaccines due to requirements for parental administration (except for some oral and nasal) and the requirement for a "cold-chain" of most vaccines due to stability issues. Thus, the current average cost of bringing a vaccine to market is larger than can be borne by the market for most of the current vaccines. Although there are some vaccines which have the potential for a greater than \$1 billion dollar market (e.g., hepatitis B virus, human papilloma virus), the total vaccine market is so limited that the required return on investment for commercial pharmaceutical and biotech companies does not justify investment in vaccine development.

All this means that a dire need exists for more vaccines and vaccine development programs, but stimulating research and development of highly effective vaccines is no small task. Still, we believe great progress could be made by addressing three major areas of research funding. First, we need to reassess the way in which the US government funds vaccine research. Second, we need to provide public-private partnerships with more incentives to collaborate with industry. Finally, we need to work out ways of funding vaccine research through healthcare costs. In this article we aim to outline the barriers in funding that are stifling vaccine research and development, and we will propose solutions to these issues...

### **"Glaxo asks Cervarix approval"**

**Date:** 30 March 2007

**Source:** *The Philadelphia Inquirer*

**Author(s):** Thomas Ginsberg

[http://www.philly.com/inquirer/business/20070330\\_Glaxo\\_asks\\_Cervarix\\_approval.html](http://www.philly.com/inquirer/business/20070330_Glaxo_asks_Cervarix_approval.html)

The race for prestige and profits in cervical-cancer vaccines intensified yesterday when GlaxoSmithKline P.L.C. formally asked U.S. regulators to approve its vaccine, Cervarix. The long-expected application to the Food and Drug Administration - for use in adolescent girls and possibly young women - puts Cervarix at least 16 months behind Merck & Co. Inc., maker of Gardasil.

Cervarix has been tested and prepared for market partly at GlaxoSmithKline facilities in Upper Merion and Philadelphia, part of the U.S. headquarters of the London-based company. Gardasil is made and marketed in West Point, Montgomery County, home to the vaccine division of Merck, which has headquarters in Whitehouse Station, N.J. Both vaccines have been shown to completely block at least two strains of the human papillomavirus, or HPV, blamed for roughly 70 percent of cervical cancers.

HPV is carried by hundreds of millions of men and women worldwide. Each year, the cervical cancer it causes kills about 4,000 women in the United States and 270,000 worldwide, where Pap smears to detect and treat it are rarer. Both vaccines' huge health benefits, however, have been mirrored by unusual and sometimes controversial marketing campaigns as the companies compete for a global market expected to be worth \$2 billion to \$4 billion within three years.

Merck, first to market with Gardasil last June, has triggered a backlash over its state-by-state lobbying for mandatory-vaccination laws. Mandatory vaccination, besides saving more lives, could significantly boost sales, up to half paid by taxpayers. Sexual-abstinence groups and vaccine skeptics have opposed mandatory-vaccine laws, saying parents should decide individually. Some experts also have voiced concern that such laws could lead to fewer Pap screens. In making the case for its vaccine, Merck has said Gardasil prevents genital warts and other dangerous HPV strains. The firm is also studying Gardasil's use in boys.

GlaxoSmithKline counters that Cervarix is more powerful and may prevent up to 80 percent of cancers, thanks to the company's proprietary adjuvant, AS04, a key booster ingredient. It also is funding an unusual head-to-head comparison to try to prove Cervarix is more potent than Gardasil.

And then there is the price. At \$360 for a three-shot course, Gardasil is the most expensive vaccine ever marketed, part of an industry effort to push up profit margins in the notoriously risky business. GlaxoSmithKline declined to disclose what it would charge for Cervarix, if approved as expected sometime between October and January.

Doctors and policymakers who expect competition automatically to bring down vaccine prices are likely to be disappointed, at least initially. Jean Stephenne, president of GSK Biologicals, the company's Belgium-based vaccine division, said in an interview last month that GlaxoSmithKline aims to win over physicians and others by proving Cervarix is better, not by selling it for less. "If you start a price war, you give the impression that your product is of lower quality," Stephenne said during a trip to Philadelphia. "For sure, at a certain point, we will compete to get a bigger market share" based on price, Stephenne said. But he indicated the initial strategy would be matching Merck on price and beating it on effectiveness.

The strategy, while good for vaccine-makers and potentially the Philadelphia pharmaceutical sector, could prolong financial headaches across the nation's health-care system, where physicians and patients already face a cash crunch over Gardasil. While most health insurers are covering Gardasil, some have limited their reimbursements and administrative expenses. In turn, some doctors have been slow to offer the product, likening Gardasil to handling expensive crystal with no margin for error. "If you drop a \$120 vial of Gardasil on the floor, that's a problem," said Joseph Bocchini, chief of pediatric infectious diseases at Louisiana State University and a HPV expert at the American Academy of Pediatrics. The academy is planning an expert meeting to consider the cost squeeze, he said.

Insurers caught in the middle want all sectors of the health-care system to share the burden. "If the question devolves entirely to reimbursement, it misses the broader issue of rising vaccine costs," said Susan Pisano, a spokeswoman at the trade group America's Health Insurance Plans. "We think there is need for a broader discussion."

Administrators of the federal immunization program last year were able to win a 20 percent discount on Gardasil - \$288 per three-shot course, instead of \$360, said Lance Rodewald, head of immunization services at the U.S. Centers for Disease Control and Prevention. But he described it as a tougher-than-usual negotiation with Merck, then the sole HPV vaccine-maker. "We really don't know the effect of competition on prices, whether it gives us a better negotiating position. We think it does, but we don't have hard evidence," Rodewald said.

So far, physicians and health officials have embraced Gardasil, even with its cost and legal issues. Merck reported \$155 million in sales in the fourth quarter, considered a strong launch. The next test is how it fares a year from now with competition from Cervarix. "If they have equal efficacy, then the physician's decision on which to use is going to be made more on price and convenience," said Bocchini, the pediatric academy HPV expert.

Yesterday, GlaxoSmithKline shares closed at \$54.55, up 51 cents, or 1 percent. Merck shares closed at \$43.95, up 72 cents, or 1.7 percent.

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## **8. ANNOUNCEMENTS**

## **Job Opening: NIH Office of AIDS Research Health Scientist Administrator**

The Office of AIDS Research has the responsibility for a broad range of scientific, budgetary, legislative, and public policy matters relevant to the conduct and future development of AIDS research at the NIH, including its programs, policies, and operations. The subject position serves as the principal advisor to the OAR Director on **microbicide** research and coordinator of the NIH **Microbicide** research program which offers one of the most promising areas for HIV prevention research. The incumbent is responsible for the direction and management of OAR's **Microbicides** planning, budget, evaluation, and policy activities through the establishment and maintenance of working relationships with other government and non-government organizations.

For more information, please visit <http://www.usajobs.gov/> and search for Job Announcement Number OD-07-181895-DE.

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