



# ALLIANCE FOR MICROBICIDE DEVELOPMENT

11 May 2007, Volume 8, Number 18

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 complete issues of the *Digest* or search by keyword for individual articles at <http://www.microbicide.org/publications/>. If you would like to be removed from the *Digest* distribution list, please send an email to [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. MEDIA COVERAGE OF MICROBICIDES

### "New discovery raises hopes as microbicide clinical trials suffer setback"

**Date:** 10 May 2007

**Source:** *Daily Champion (Lagos)*

**Author(s):** Florence Udoh

<http://allafrica.com/stories/200705100252.html>

The year 2007 brought with it frustrations for **microbicides** scientists, who had hoped it was only a few years away to have them grinning ear-to-ear to their banks. This was when it was soon discovered in South African and India that cellulose sulphate gel, the most promising vaginal **microbicides**, in fact, could lead to an increased risk of HIV infection.

But a new discovery, mid April may have changed all that. This follows an announcement by researchers from the University of Washington in Seattle that they have found exactly how the human immunodeficiency virus (HIV) enters the female body during sex and which are its very first-target cells in the vagina. The discovery provides hope to a working on developing an effective **microbicide**, to help women protect themselves against HIV.

Now, the knowledge of how the vagina allows the virus to enter the body will provide a crucial boost for these scientists to discover the most effective **microbicide**. **Microbicides** are creams or gels that aim to block HIV from invading a woman's body. Using a unique model system they developed, the scientists found that HIV-1 simultaneously enters two different types of cells in the vaginal epithelium (outer lining of vaginal cells) associated with the immune CD4+T-cells but through different mechanisms. The scientists reported in the journal *Immunity* that both Lc and CD4+ cells move out of the vaginal epithelium after the infection. Research Julie McElrath reported, "Understanding the initial events in the establishment of vaginal HIV type-1 entry and infection has been hampered by the lack of appropriate experimental models. We have now shown that upon contact, HIV-1 rapidly penetrated both LC and CD4 + T-cells. HIV-1 entered CD4+T-cells almost exclusively by CD4 and CCR5 receptor without requiring passage from LC. By contract, HIV-1 entered LC primarily by means of multiple receptors. Our findings shed light on the very earliest steps of HIV infection and may guide the design of effective strategies to block local transmission and prevent HIV-1 spread."

Scientists have for long known that HIV-1 enter CD4+ cells by interacting with a protein called CCR5. But the researchers wanted to know what happens when women are exposed to HIV through vaginal sex. The team then used a chemical treatment to separate the outermost layer of vaginal skin from the underlying tissue. They then exposed this layer to HIV viruses that had been tagged with a glowing dye. The team could then see which cells the viruses had infected. Within two hours, HIV had attacked the CD4+ T-cells, and infected almost half of them. "Now we know that any effective **microbicide** must prevent HIV infection from entering both T-cells and LC," a NACO official said.

Women are physically more susceptible to HIV infection than men. Married women in developing countries are among those at highest risk due to their unfaithful husbands. Most new infections, about 14,000 every day, are in women. According to WHO, 17.5 million women globally have HIV.

Meanwhile, South African Minister of Health Manto Tshabala-Msimang has launched an investigation into the clinical trial that was conducted in KwaZulu-Natal, cellulose sulphate gel, following preliminary results of the trials indicating that the compound could lead to an increased risk of HIV infection. The study had been conducted amongst a group of 604 women in KwaZulu-Natal to test the effectiveness of the vaginal **microbicide** in preventing the sexual transmission of HIV.

In this regard, the Minister met with the researchers involved in at least five **microbicides** clinical trials that are taking place in South Africa last week. The purpose of the meeting was to establish the details with regard to the interim results of the cellulose sulphate study and gain further insights into the other **microbicide** trials that are underway in the country.

### "Gita Ramjee: a passion for prevention"

**Date:** 08 May 2007

**Source:** *The Guardian*

**Author(s):** Linda Nordling

<http://education.guardian.co.uk/higher/profile/story/0,,2074242,00.html>

Months have passed, but Professor Gita Ramjee still recoils at the memory of events that came close to robbing South Africa of one of its top scientists. "There came a point when I thought: is it worth my while? I have dedicated my life to finding an HIV prevention option for the women of Africa, and these recent attempts to tarnish my efforts have been very demotivating."

It is fitting that we meet on a day when freak waves and high winds are causing widespread damage along the KwaZulu Natal coastline. A storm of a different kind rocked her research unit recently. A storm less forceful perhaps, but more damaging to those inside.

In January, Ramjee, director of the HIV prevention research unit in Durban, received the news that a routine inspection by an external team of experts had discovered anomalies in data from a study of a potential new **microbicide** to protect women against HIV/Aids. Alarmingly, more women receiving the vaginal preparation of cellulose sulphate appeared to have developed HIV, compared with the group not receiving the product. Although the

numbers were very small, the external team decided to halt the trial for safety reasons.

A press release was issued explaining that the treatment "might" increase women's chances of HIV infection. Test products were recalled from the 1,333 women participating in South Africa, Benin, Uganda and India, and Conrad, the US-based sponsor of the trial, ordered a review to shed light on what had happened.

### *Press field day*

Ramjee wished it could have stopped there. But it didn't. The press had a field day with what was incorrectly christened a "botched" trial. Some called the women testing the drug "guinea pigs", encouraged by the scientists to have unprotected sex using the gel as an aphrodisiac. "I think the whole world was horrified that certain South African press could stoop so low. That they could misunderstand an issue so much," says Ramjee.

The articles were not just damaging to other HIV prevention efforts at the unit, but to clinical trials as a whole, she says. "Negative press such as this can destroy HIV prevention efforts. We need to have a united front, with civil society and scientists working together to address the problem and applauding volunteers who come forward to find solutions." But she admits her unit could have done more to prevent what happened. "In future, I would like to do it better, get the press involved, make them understand the science and interpretation of data."

In the aftermath, Ramjee received strong support from her colleagues, sponsors and even from participants in the trials. The last tried to put the record straight with the press. "Don't tell us that we are guinea pigs, we know exactly what we're doing, and can think for ourselves," they told the journalists. Did the press print their stories? "No."

But Ramjee's heart sank. It felt like the very people she had dedicated her life to help had turned against her. "At the time I was very, very depressed." But she did not give up. "A lot of people said to me: if you, one of the best clinical trialists in the world, don't continue with this fight against HIV/Aids, who will? So you have to motivate yourself again."

Such dedication to what she values most is a recurring phenomenon in Ramjee's life. Not for her the latte-sipping existence enjoyed by some of her contemporaries. "I'm not the type of woman who likes to spend hours at shopping centres with friends," she says. Instead, her life has revolved around her family and her career, with the former taking precedence.

Perhaps it was the many upheavals of her youth that taught her to hold on to what could always be counted on: close family and her own faculties. Growing up in Uganda, her first experience of exile came at the hands of Idi Amin, the dictator who forced all Asians out of the country in the 1970s. After a couple of years in a high school in India, the land of her ancestors, she relocated again, this time to the University of Sunderland in the north-east of England.

It was in here that she met her future husband - a South African of Indian descent. In 1981, on finishing her degree, she followed him to South Africa. It was a culture shock. In the early 80s the apartheid regime was weakening, but still held on to power, particularly in the Transvaal region, from where her husband's family came. "It was extremely difficult for somebody used to living in a multicultural, open society. As a student in England, you didn't look at colour. You looked at people as individuals."

In search of more liberal surroundings, the young couple moved to Durban. Here, Ramjee felt more at ease. She felt welcomed by people from a variety of backgrounds. "I think it was nice for them to meet somebody who wasn't thinking in the past. I felt very comfortable living in Durban at that time." She got a job in paediatrics at a local hospital.

This put her in the way of a masters degree and, ultimately, a PhD on the kidney diseases of children, which she completed in 1994.

By that time she had two sons whom she tried - sometimes in vain - to shelter from the idiosyncrasies of South African society. "I was so determined, coming from a multicultural society, that I would never put my child in a single-race school." This was easier said than done, but in the end she succeeded.

The years of her doctorate saw Ramjee make superhuman efforts to stay on top of family and career. "I used to get up at six in the morning, prepare food, wake my children, send them off to school, do a half day of practical work, come back, pick my sons up from school, help them do their homework and send them to sleep." She would then herself go to sleep at 8pm only to get up again at two in the morning to write her thesis. She kept this up for a year. "I never gave up my responsibility as a parent. Although I wanted to excel in my career, I never wanted to compromise myself as a mother."

### *Nascent technology*

The sacrifice paid off, but in a roundabout way. After her PhD, Ramjee wanted a break, but fearful of too much leisure time, she sought out a small project that would pass the time when her sons were at school. She found a small research project evaluating the acceptability of a vaginal **microbicide**, at that time a nascent technology in the armoury against HIV/Aids. This work put her in contact with local sex workers - a "reality check" as she calls it.

"It opened my eyes. These are good women, who are put in a position that people scorn." In the mid-90s, when Ramjee started working with sex workers in Kwa-Zulu Natal, 50% were HIV positive. "These women mostly aren't doing this out of choice. The stories they used to tell us were horrific. That's when I knew I wanted to be involved in the prevention of HIV infection in women."

What began as a short project evolved into a strong commitment. In the years to follow, Ramjee worked her way up through the ranks to finally head the Durban unit. She inherited a staff of 21, and quickly built this into a 300-strong organisation with an international reputation for excellence.

She is matter of fact about her success: "Because I did so well in clinical trials, I had offers pouring in for me to do clinical research. I think the key to success is my approach to capacity building, respecting each and every member of my staff, the community, and also the fact that I delivered on the contracts. It is my holistic approach to research, where I'm not just thinking science."

Today, Ramjee is looking ahead. The final results of a recently completed trial on a vaginal diaphragm will be out in the next couple of months and other trials are also nearing completion. There is a long way to go. "What people don't realise is that none of the current generation of **microbicides** or any other prevention technology is going to be 100% effective. So whether there are **microbicides** or a vaccine out there or not, there is nothing that will allow you to go have unprotected sex without the risk of infection. Not for a long, long time."

Still, the recent crisis has taught her the importance of striking a new work-life balance. "In a way, I feel that while I'm passionate about my work, it is too consuming a passion. I need to find a more balanced situation, where I do things that I enjoy as well." But finding the time to do that will be difficult, she admits. "It's in my nature to want to excel. My calling is to find a solution. If I don't succeed in my lifetime, at least I've worked towards it."

*Curriculum vitae*

Age: 50

Job: Director of the HIV prevention research unit in Durban, South Africa

Lives: In Durban with her husband, a pharmacist

Likes: spas, exotic travels

Dislikes: insincerity and dishonesty

Married:., with two sons

**"Circumcision promotion divides AIDS activists"**

**Date:** 04 May 2007

**Source:** *In These Times*

**Author(s):** Dana Goldstein

[http://www.inthesetimes.com/article/3137/circumcision\\_promotion\\_divides\\_aids\\_activists/](http://www.inthesetimes.com/article/3137/circumcision_promotion_divides_aids_activists/)

The last time circumcision made headlines in New York City, the city Department of Health and Mental Hygiene was objecting to an ultra-Orthodox Jewish practice in which mohels - professional circumcisers - sucked blood out of the wounds of newly cut infants. After three babies contracted herpes, the city tried to ban the obscure ritual in 2005, provoking an angry response from the Orthodox community and a media dust-up.

Now circumcision is news again in New York, but this time the city is promoting the practice. The April 5 *New York Times* reported that the city health department has decided to encourage male circumcision as an HIV-prevention method among at-risk populations, particularly gay and African-American men. The move comes after several clinical studies in Africa showed that circumcision of an adult male can decrease his likelihood of infection by as much as 60 percent.

But New York's campaign brings up thorny questions for AIDS researchers and activists. Many are concerned about extrapolating prevention methods for American high-risk men, many of whom are bisexual or gay, from the African circumcision studies, which were conducted primarily among heterosexual groups. Meanwhile, others question how a male partner's circumcision affects a woman's susceptibility to HIV.

Two decades of research show women are less likely to contract a variety of sexually transmitted infections when their male partners are circumcised. But a recent Johns Hopkins University study examining 997 men in Uganda found that their female partners were more likely to contract HIV following a circumcision if the men ignored doctors' orders to abstain from sex until their wounds were fully healed, which usually takes about a month. And with the continued lack of a female-controlled HIV-prevention method - **microbicide** gels have yet to advance out of the trial phase - any HIV education effort must include a heavy emphasis on condom use. Spokespeople for the New York City Department of Health and Mental Hygiene and the Health and Hospital Corporation, which operates public clinics and hospitals in the city, say the city hasn't established any formal procedures for encouraging HIV-testing prior to circumcision in light of women's increased risk, but stress that any public circumcision efforts will be just one part of a multi-pronged HIV-prevention program.

Cultural stigma against circumcision also remains, especially among immigrant groups like Caribbean Americans. Though about 60 percent of American men are circumcised, the practice is relatively rare worldwide. And it has become less popular in recent years as parents have come to see circumcision as a painful surgery that removes an integral part of the male sexual anatomy. According to the CDC, in 2003, the American circumcision rate dropped to a postwar low of 55.9 percent.

Marjan Hezareh, scientific director of the Los Angeles-based AIDS Research Alliance, is cheered by New York City's decision to explore circumcision as what she terms an "additional prevention strategy" to condoms. For Hezareh, the health benefits for women of having a circumcised partner have been sufficiently proven and the medical benefits should outweigh any stigma against both adult and infant circumcision. "We must disassociate circumcision from a sign of belonging to a specific religion or culture, and show it to people as another medical prevention strategy," she says. "I bet people will be very open about this."

But Tokes Osubu, executive director of Gay Men of African Descent in New York, is not so confident. He says he is baffled by the city's decision to focus on circumcision. "We might be sending the wrong message to people who are already circumcised," he says. "They might think, 'Oh, because I'm circumcised, I might be okay!' We are still dealing with the effects of HIV being misunderstood 25 years ago as a gay disease. Now I'm afraid people will say, 'I don't have a problem because Mayor Bloomberg said so.'"

AIDS activists also fear that a circumcision drive will undermine their long-term strategy to emphasize condom use. Indeed, homosexual anal sex is so risky that doctors agree circumcision provides little protection against HIV for gay men.

Ronald Goldman, a psychologist and founder of the Circumcision Resource Center, makes the point that "the U.S. has the highest circumcision rate and the highest HIV-infection rate in the developed world." A longtime anti-circumcision advocate, Goldman says, "If you're treating a problem, medical ethics would say use the least invasive method available. And condoms are more effective, plus they're cheaper."

But in battling a disease that continues to grow at alarming rates in urban areas (one in 20 Washington, D.C. residents is HIV-positive, and in New York City, African-American and gay men have infection rates as high as 10 to 20 percent), New York City's proposed circumcision drive is at the vanguard of public health efforts. Whether HIV/AIDS activists will get on board remains to be seen.

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## **2. PUBLISHED RESEARCH: MICROBICIDE-SPECIFIC**

**"Molecular umbrellas: a novel class of candidate topical microbicides to prevent HIV and HSV infection"**

**Author(s):** Madan RP, Mesquita PM, Cheshenko N, et al

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

<http://jvi.asm.org/cgi/content/abstract/JVI.02851-06v1?ct=ct>

**Published Abstract:** Molecular umbrella compounds may function as novel topical **microbicides** to prevent HIV and HSV infection. In a preliminary structure-activity investigation, one umbrella compound, designated Spm8CHAS, was identified which inhibited both HIV and HSV infection with no cellular toxicity. The objectives of the current studies were to define its spectrum of antiviral activity, characterize its mechanism of action, and explore the possibility of combining Spm8CHAS with HIV-specific reverse transcriptase inhibitors. Spm8CHAS inhibited infection by laboratory and clinical R5 and X4 clade B and clade C HIV strains in cell culture. Ectocervical tissue explants exposed to HIV-1BaL in the presence of Spm8CHAS were completely protected (IC<sub>50</sub>=13.6 ug/ml), and transfer of virus to target T-cells via migratory cells was abolished (IC<sub>50</sub>=3.8 ug/ml). Spm8CHAS inhibited HSV-2 infection of epithelial cells 10,000-fold if present throughout the infection. Notably, adding Spm8CHAS to cultures following HSV entry significantly reduced viral infection, indicating that the drug also acts post-entry. Subsequent studies indicate that Spm8CHAS blocks cell to cell spread of HSV. Confocal microscopy using a fluorescently labeled analog of Spm8CHAS demonstrated that this conjugate crosses the plasma cell membrane and is transported to the nucleus. Combinations of Spm8CHAS with UC-781 or PMPA *in vitro* exhibited additive anti-HIV activity with preserved anti-HSV activity. The ability of Spm8CHAS to inhibit primary isolates of HIV, block HSV infection post-entry, and cross cell membranes supports the development of a combination **microbicide** containing Spm8CHAS with an HIV-specific reverse transcriptase inhibitor to prevent both HIV and HSV by multiple mechanisms.

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

#### "Women have significantly better response to HIV therapy than men"

**Date:** 03 May 2007

**Source:** *AIDSmap.com News*

**Author(s):** Adam Legge

<http://www.aidsmap.com/en/news/70262B3E-200F-4BFA-AE80-2DF75277E2E5.asp>

Women have a significantly better response to HIV treatment than men say the Spanish authors of the latest big study into gender bias in HIV outcomes published in the April 23rd edition of *AIDS*.

The first suggestions that men and women differ in their responses to HIV infection were made over 15 years ago. A number of studies since have reported conflicting findings. The researchers behind the new study have attempted to clarify the issue by concentrating on a large group of patients from 69 Spanish hospitals who all started on similar treatments. They collected data on 2,620 HIV-infected people - 72% of them men - for twelve months after they started taking similar nelfinavir-based antiretroviral regimens.

Among those who were taking potent HIV therapy for the first time, the women's average CD4 cell count was higher than the men's ( $p = 0.01$ ). Although the women were more likely to achieve undetectable viral loads the difference was

not statistically significant ( $p = 0.6$ ). The gender difference was more marked in the treatment-experienced group where again women's average CD4 cell counts were higher than men's, but the difference was of only borderline statistical significance ( $p = 0.06$ ) At twelve months 49% of the treatment-experienced women had undetectable viral loads compared to 40% of the men ( $p = 0.01$ ).

At every time-point studied throughout the twelve months women had consistently better virological and immunological responses than men despite the fact they were significantly more likely to experience side-effects to the regimen. HIV disease also progressed more slowly in women.

None of these differences could be explained by women being more adherent to the drug therapies, the researchers concluded (Collazos 2007).

In general the women tended to have lower viral loads and higher CD4 cell counts when they began therapy but the differences seen in this study are also due to stronger immunological responses to therapy, they add.

Previous studies into a possible gender bias in HIV outcomes have produced varying conclusions. Some have found higher CD4 counts in men and others in women while others have found no difference.

The authors of this study say it has several advantages over others, including its size. Ethnic or racial factors are less likely to have an influence as 90% of the individual studied were white Spanish. And the fact that 69 hospitals across Spain were used minimises the risk of treatment bias from one centre.

#### *Reference*

Collazos J et al. Sex differences in the clinical, immunological and virological parameters of HIV-infected patients treated with HAART. *AIDS* 21: 835-843, 2007.

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## **4. EPIDEMIOLOGY**

### **"Socioeconomic, biological factors placing women in Pakistan at increased risk of HIV, Health Minister says"**

**Date:** 06 May 2007

**Source:** *Kaiser Daily HIV/AIDS Report*

[http://www.kaisernetwork.org/daily\\_reports/rep\\_index.cfm?DR\\_ID=44716](http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=44716)

Women in Pakistan are at increased risk of contracting HIV because of socioeconomic and biological factors, Minister of Health Muhammad Nasir Khan said recently at a workshop at Quaid-i-Azam University in Islamabad, Pakistan, *The International News* reports. Nasir said gender disparities in literacy, education, economic empowerment and control of resources also are fueling the spread of the disease among women in the country. According to Nasir, men are seen as the "decision-makers" in Pakistani society, and women, particularly those in rural areas, depend on men for access to outside information, *The News* reports.

According to Nasir, 85,000 people in the country are living with HIV, which is 0.1% of the population. He added that the majority of those living with HIV are men, who are transmitting the virus to their sexual partners. Injection drug use in several cities also is exacerbating the problem, Nasir said. Fifty-two percent of IDUs in Karachi and 82% of IDUs in Lahore reuse needles, he said. He also noted that drug use has shifted to urban areas, causing a concentrated epidemic in cities, such as Karachi, where HIV prevalence among IDUs has risen more than 25% in the last three years. Nasir added that male and female commercial sex workers are engaging in unsafe sex practices in part because of social marginalization and a lack of access to HIV/AIDS education. Qasim Jan, university vice chancellor and workshop chair, stressed the need for greater HIV/AIDS research and awareness. He said the university would welcome collaborative projects between institutions to study HIV/AIDS epidemiology and new approaches to fighting the disease (Khalid, *The International News*, 5/3).

### "Surge in senior HIV survivors prompts new treatment studies"

**Date:** 27 April 2007

**Source:** *MedicalNewsToday.com*

<http://www.medicalnewstoday.com/medicalnews.php?newsid=68717>

Many patients diagnosed with HIV in the 1980s and 1990s have survived and now are entering their golden years. AIDs cases among the over-50 crowd reached 90,000 in 2003, and according to the Centers for Disease Control and Prevention, will account for half of all HIV/AIDS cases in the United States by 2015.

Consequently, health care providers and social service workers are pioneering new ground to treat the growing number of HIV-positive older adults. Timothy Heckman, an Ohio University health psychologist, has been on the forefront of research involving HIV-infected older adults. Heckman recently received a \$1.5 million, four-year grant from the National Institute of Mental Health and the National Institute of Nursing Research to nationally test the effectiveness of a telephone support group for older adults with HIV.

Seniors often feel embarrassment or out-of-place among what is usually a gathering of young people at traditional AIDS support groups. The seniors have different needs, which may not be met, or they may be uncomfortable talking about issues, such as sex, among younger people. "The telephone, as a tool for delivering support, is financially and psychologically easier for many older adults," said Heckman, who has spent the past eight years conducting AIDs research among the elderly and in rural populations.

A project four years ago found that a telephone support program reduced depression for rural seniors. The results of that study were published in the *Annals of Behavioral Medicine* last year. Now Heckman plans to expand the geographical scope of the study and increase the number of participants. "A separate study we conducted of older adults found that support groups which are designed to teach them skills to handle stress, obtain social support and cope more adaptively are more effective than brief therapy sessions initiated by the person or support groups where participants only discuss problems but do not receive what is called coping intervention treatment," Heckman said.

He will further test that concept through the telephone support group study. Nearly 400 participants of the project will be divided among three therapy models, ranging from a 12-week telephone-delivered support group with sessions designed to improve the participants' coping skills to less active therapy sessions in which participants receive

individual guidance only upon request.

Other Ohio University research, led by Heckman, has found that seniors living with HIV also report problems such as suicidal thoughts, depression, stress and ignoring other age-related health issues. He and two graduate students presented these and other related findings at the annual conference of the Society of Behavioral Medicine, held in Washington, D.C., last month.

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## 5. POLITICS AND POLICY

### "Senate approves new power for F.D.A. on drugs"

**Date:** 09 May 2007

**Source:** *The New York Times*

**Author(s):** Robert Pear

<http://www.nytimes.com/2007/05/09/washington/09cnd-drug.html>

By a vote of 93 to 1, the Senate passed a bill this afternoon that gives the Food and Drug Administration sweeping new power to police drug safety, order changes in drug labels, regulate advertising and restrict the use and distribution of medicines found to pose serious risks to consumers. The bill calls for a fundamental change in the philosophy and operations of the F.D.A., requiring the agency to focus on the entire life cycle of a drug - not just the years prior to its approval, but also the experience of patients who later take it. Under the bill, the government would establish a surveillance system to track the adverse effects of prescription drugs. Scientists would analyze data on tens of millions of patients, looking for signals that particular drugs posed serious risks.

Senators said the bill was a response to a widespread loss of confidence in the ability of the F.D.A. to protect consumers against the dangers of drugs like Vioxx, a popular painkiller withdrawn from the market in 2004. The bill, which would carry out many recommendations from the National Academy of Sciences, is likely to become law. It appears broadly acceptable to the House, which is working on its own version of the legislation, and is unlikely to be vetoed by President Bush. The administration has not actively opposed the measure, although it says the F.D.A. already has all the regulatory authority it needs. Within the agency itself, officials have been divided about whether they have the power needed to do their job. The bill is widely seen as "must pass" legislation because it renews authority for the government to collect fees from drug companies to speed the review of their products. Without action by Congress, the authority would expire Sept. 30.

Billy Tauzin, president of Pharmaceutical Research and Manufacturers of America, the main trade group for brand-name drug companies, applauded passage of the bill, saying it "will preserve and even strengthen the F.D.A.'s ability to do its job."

Drug company executives succeeded in their efforts to block a provision of the bill that would have legalized imports of lower-priced medicines from Canada. And they were happy that the final Senate version of the measure sidestepped a multibillion-dollar question: how to give consumers access to lower-cost copies of biotechnology drugs that now cost

tens or hundreds of thousands of dollars a year. But lawmakers from both parties said they intended to create a procedure for federal approval of such copycat drugs, sometimes called generic biologics.

Work on the bill began long before Democrats took control of Congress. At a time when bills often pass or fail on party-line votes, the Senate drug bill was a triumph of bipartisan cooperation. Republicans were full partners in drafting it.

The single no vote on Wednesday was cast by Senator Bernard Sanders, the Vermont independent who is an outspoken critic of the pharmaceutical industry who said he was "extremely disappointed" that the bill did not legalize imports of lower-priced medicines from Canada.

"This legislation will make a major difference for families in America, ensuring the safety of our prescription drug system," said the chief sponsor of the bill, Senator Edward M. Kennedy, Democrat of Massachusetts.

Senator Michael B. Enzi, Republican of Wyoming, said the bill was the "most comprehensive drug safety overhaul in more than a decade."

Just minutes before passage of the bill, the Senate voted, 64 to 30, to double the maximum civil fine that could be imposed on a drug company for violating a drug safety plan approved by the F.D.A. The maximum fine would now be \$2 million. "If fines are nothing more than the cost of doing business, you cannot deter bad behavior," said Senator Charles E. Grassley, Republican of Iowa, who proposed the increase.

To minimize risks to patients, the government could order changes in a drug's label and could require the manufacturer to conduct more studies and clinical trials of a drug already on the market. Under current law, the government and drug companies sometimes haggle for months over changes in drug labeling, and the F.D.A. can request but not compel manufacturers to perform studies after approval of a drug. "For Vioxx, it took 14 months to change the drug's label to warn doctors and patients of the danger," Mr. Kennedy said. "Companies routinely promise to conduct studies that are never even started, much less completed."

The bill would require the government to establish a public database of clinical trials and their results. Lawmakers said this would make it difficult for drug companies to hide evidence of safety problems, as they said some had done in the past. The database would also make it easier for patients to learn of clinical trials testing drugs that could save their lives.

The bill would not compel the food and drug agency to be a more aggressive regulator. But the Senate sent a strong signal that it wanted stronger action by the agency to protect public health.

Dr. Sidney M. Wolfe, director of Public Citizen's Health Research Group, a consumer organization, said: "The bill's improvements in F.D.A. authority are important but inadequate. The bill would increase collaboration between the agency and the drug industry, by increasing the agency's reliance on user fees to finance drug reviews."

But Senator Richard M. Burr, Republican of North Carolina, praised the measure as "a well-balanced drug safety bill."

Mr. Enzi said the bill could speed the approval of new drugs by giving the F.D.A. more tools to protect patients after treatments were approved. The agency would no longer have to rely on "the nuclear option, which is pulling a drug

completely off the market" - an extreme step that may disrupt the care of patients, Mr. Enzi said. The F.D.A. could instead require a manufacturer to adopt a "risk evaluation and mitigation strategy" for a drug that posed serious risks. As part of a risk-management plan, the agency could require that any television or radio advertisements for a drug describe its risks "in a clear and conspicuous neutral manner," with fines for false or misleading commercials.

To make sure patients could get access to drugs with extraordinary risks - like thalidomide, for a type of cancer, and Tysabri, for multiple sclerosis - the F.D.A. could require additional safety precautions, like special training for doctors and close monitoring of patients.

Senator Judd Gregg, Republican of New Hampshire, said that any restrictions on the use or marketing of a drug would have to be based on "sound science."

The bill would give financial incentives to drug companies to study the effects of their products in children, but the reward would be scaled back for drugs that already had sales of more than \$1 billion a year in the United States. Experts estimate that two-thirds of the drugs prescribed for children have not been studied or labeled for pediatric use.

Representative John D. Dingell, Democrat of Michigan, the chairman of the House Committee on Energy and Commerce, said Tuesday that he shared the goals of the Senate bill. "Incidents like the recall of the arthritis drug Vioxx have created a crisis of confidence in the Food and Drug Administration," Mr. Dingell said.

Representative Frank Pallone Jr., Democrat of New Jersey, the chairman of the panel's health subcommittee, said the House would hold several hearings this month and write its bill in June, with a vote by the full House likely to come in July.

### **"EMEA launches GMP database"**

**Date:** 08 May 2007

**Source:** *in-Pharma Technologist.com*

**Author(s):** Anna Lewcock

<http://us-pharmatechnologist.com/news/ng.asp?id=76316>

An online database detailing information on all manufacturing and importation certificates and authorisations issued within the European medicines network has been launched by the European Medicines Agency (EMA). The system has been set up to ease the strain of exchanging vast amounts of information on compliance with good manufacturing practices (GMP) within the European Economic Area.

This first version of the database - currently going by the name EudraGMP - will only be available to national competent authorities (i.e. EU member states, Iceland, Liechtenstein and Norway), the European Commission and the EMA. However, by the summer the system will be available online to the general public free of charge, with only commercially or personally confidential information restricted.

The database itself will contain information on all manufacturing and importation authorisations issued by the appropriate agencies within the European network, as well as information on GMP certificates issued by the aforementioned authorities for facilities both within the network and in third countries. Authorities in the member states

will have to enter results into the database within 90 days of the completion of an inspection, and manufacturers will also have to submit any certificate changes within a set time period (currently under discussion, but likely to be within 30 days).

"The legislative and database requirements introduce a harmonised approach to the receipt and recording of manufacturing authorisations and GMP certificates," says the EMEA. "The facility to exchange inspection related information will assist the EMEA and the member states in planning their inspection schedules."

The database will also include information on GMP certificates for excipient manufacture, if and when such regulations are introduced in the EU, in-PharmaTechnologist.com was told. Combine this with information generated following the introduction of GMP requirements for active ingredients and third-country inspections, and the EMEA is justified in expecting that the database will grow rapidly over the coming years.

With EMEA estimates putting the number of importers and manufacturers in the countries concerned at around 15,000, with 7,000 or so new GMP certificates added each year, the EudraGMP system is being seen as a mechanism to greatly reduce the duplication of work between national authorities, as well as increasing efficiency and cooperation between the different parties.

As well as the impact the database could have on increasing efficiency in information exchange regarding GMP compliance, the EMEA has said that discussions are ongoing with a view to replacing paper certificates used between Mutual Recognition Agreement (MRA) partners. MRA partner countries include Australia, Canada, New Zealand and Switzerland.

With the first version of the database already live and accessible by relevant authorities, and the second, publicly accessible version due to come online in the summer, there are two further updates scheduled to be released at later dates to allow the system to expand and accommodate more information. "In the future, the database will include negative as well as positive inspection results," Francisco Penaranda of the EudraGMP development team at the EMEA told in-PharmaTechnologist.com. "So the system will be able to alert member states to non-compliance, as well as making things more transparent to the general public."

### **"WHO moves to boost online data of clinical trials"**

**Date:** 04 May 2007

**Source:** Reuters

**Author(s):** Stephanie Nebehay

[http://today.reuters.com/news/articlenews.aspx?type=internetNews&storyID=2007-05-04T162434Z\\_01\\_L04683898\\_RTRUKOC\\_0\\_US-WHO-TRIALS.xml](http://today.reuters.com/news/articlenews.aspx?type=internetNews&storyID=2007-05-04T162434Z_01_L04683898_RTRUKOC_0_US-WHO-TRIALS.xml)

The World Health Organization (WHO) said on Friday it was improving access online to data on clinical trials in the wake of high-profile cases of drugs being tested with possibly harmful side-effects. A new Web site aims to help researchers, doctors and patients obtain reliable information on high-quality clinical trials, it said in a statement.

Currently a "significant proportion" of trial research is never published, meaning doctors can lack information about treatment options, according to the United Nations agency. Another problem is the selective reporting of clinical trial findings, which can end up being misleading, WHO officials say. "WHO believes that the registration of clinical trials is a scientific, ethical and moral responsibility."

Initially, data from 50,000 clinical trials provided by three registers -- in Britain, Australia/New Zealand and the United States -- have been put on the WHO site, which is [www.who.int/trialsearch](http://www.who.int/trialsearch). Registers submitting data must ensure they meet a minimum quality standard and that all trials are registered before any participants are recruited. Data will not be accepted directly from drug companies.

"The Clinical Trial Search Portal is a collaborative international initiative led by WHO that facilitates the identification of all clinical trials, regardless of whether or not they have been published," said Tim Evans, assistant WHO director-general for information evidence and research.

Since Merck & Co Inc's 2004 recall of painkiller Vioxx, after a clinical trial found it increased the rate of heart attacks among long-term users, concerns have grown about side effects of some prescription medicines. In 2004, the U.S. Food and Drug Administration advisory panel began requiring a black box warning on prescriptions for selective serotonin reuptake inhibitors (SSRI), a type of antidepressant, based on reports that fluoxetine (Prozac) increased suicidal thoughts in children and adolescents. Such cases have led to growing pressure for greater transparency.

"You can go to one place (online) and search all registers at once and identify clinical trial research underway around the world," Davina Ghersi of WHO's department of research policy and cooperation said.

The network of registers, which are required to disclose their ownership, governance structure and for-profit status, will be expanded to make it more comprehensive.

## **"Scientists, NIH in conflict over precious HIV samples"**

**Source:** *Nat Med.* 2007 Apr 26;13(5):515. News.

**Author(s):** Apoorva Mandavilli

<http://www.nature.com/nm/journal/v13/n5/full/nm0507-515.html>

The US National Institutes of Health (NIH) is refusing to fund grants that directly compete with the aims of its own HIV vaccine project: that's the allegation of a group of AIDS researchers who say they are being effectively forced to collaborate with the Center for HIV-AIDS Vaccine Immunology (CHAVI), the NIH's \$350 million scheme. "A lot of people are being told to link up with CHAVI or you'll lose your funding. I mean, that's not the way to do science," says one insider who requested anonymity.

At issue are samples of 'acute infection' collected from individuals in the first weeks after HIV infection. Among CHAVI's goals is understanding how the body responds to infection during that time, which could help design an effective vaccine. Last year, CHAVI approached research teams all over the world, asking them to share their collections of acute infection samples. But the request confused scientists, many of whom complained that it was

unclear what they could expect in return for their contribution (*Nat. Med.* 12, 865; 2006).

Some consortia, including South Africa's CAPRISA and the University of North Carolina, agreed to share their samples. Last year, the group also organized EuroCHAVI, which pooled 600 samples from Europe and Australia. But many others came away with the impression that they would have to give away their samples, with nothing to show for it in return - and, naturally, declined the request. "We thought, no way. We have invested in these cohorts for 20 years, this is something we want to do ourselves," says Hanneke Schuitemaker, a researcher at the University of Amsterdam's Academic Medical Centre.

Schuitemaker's project has support from the Dutch government and, in the end, she says, she may collaborate with CHAVI. "But it was funny to see how surprised they were at the negative reaction," she says. "They must realize what they're asking for."

Part of the problem, some researchers say, is that CHAVI was launched in 2005 without already having any samples in hand (*Nat. Med.* 11, 588; 2005), and now needs them to justify its hefty coffers to Congress. "I can understand why CHAVI needs control of the samples," says Bruce Walker, professor of medicine at Harvard University. "I can also understand why people are so reluctant to give them away, particularly at a time when people are not sure of their own survivability." Walker, who declined to share his acute infection samples, has an NIH grant that's up for review in May, but is hoping to raise money from the Gates Foundation.

Julie Overbaugh's team at the Fred Hutchinson Cancer Research Center has been collecting samples in Kenya for more than 12 years. She also declined CHAVI's request. Although she may have to write multiple grants to keep her project afloat, she says, members of her team need the samples for their own research. "For those of us who work with graduate students, if we just say [CHAVI] have the money, we'll give them the samples, how do we train our grad students?" Overbaugh asks.

Others are in even more dire straits. A dozen members of Doug Richman's lab at the University of California in San Diego have spent more than a decade collecting nearly 120,000 specimens from 500 participants. The large NIH grant that supports the project is up for review in May. If it's not funded, Richman says, he may be forced to give up his samples, something he initially declined to do. "If I'm in a collaborative relationship, I'm happy to share, but it's the first time that someone has asked me for specimens in which the agreement is not collaborative," says Richman. "I haven't been given the opportunity to have intellectual input so I didn't feel comfortable sharing."

Duke University researcher Barton Haynes, who leads CHAVI, says these researchers' perception is the result of a misunderstanding. "I am sorry if this was the impression given during some discussions," Haynes says. "We learned, we got better at having these discussions. I'm certainly sorry if the impression is remaining that that's the only way CHAVI would work."

Haynes says those who have contributed samples so far are "full participants and full collaborators, both intellectually and for authorship." The investigators also all receive support from CHAVI for the work, he adds.

Even beyond the few researchers directly affected by the fracas over acute infection samples, CHAVI has created a bitter divide among HIV vaccine researchers. Much of the criticism against the project is given anonymously-for fear, the scientists say, of retaliation from the NIH.

But the idea that the NIH will not fund grants that compete with CHAVI is completely unfounded, says Carl Diffenbach, acting director of the NIH's division of AIDS. "Funding is tight, we're all in agreement on that," Diffenbach says. "That's the nature of peer review. It has nothing to do with CHAVI, period."

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