

# MDP 301: PRO 2000 Advocates' Brief

Last Updated: 7 December 2009

*The Global Campaign for Microbicides designed this document for HIV prevention advocates, to help us prepare for the announcement of the results of the MDP 301 microbicide trial results, scheduled for 14 December 2009.*

## What will we know from the trial data?

MDP 301 is designed to provide data on PRO 2000's safety and effectiveness. Regarding safety, the trial should tell us whether women in the PRO 2000 arm of the trial experienced any more side effects than women in the placebo gel arm.

MDP 301 is examining the issue of safety very carefully. All the used applicators were collected and participants were grouped into 'high' gel users (those using gel frequently) and 'low' gel users (who used it less frequently). If it turns out that more genital side effects occurred among the high gel users, this will influence the decision as to whether to proceed with development of PRO 2000, and the pace at which to do so.

In terms of effectiveness, MDP 301 is designed to tell us if PRO 2000 reduces women's risk of HIV infection by 35% or more.

## If PRO 2000 works, will it be licensed by regulatory agencies?

That's a big question. There are several possible scenarios:

1. PRO 2000 belongs to a company called Endo Pharmaceuticals, a US-based company focused mainly on branded and generic prescription pain medication. If PRO 2000 proves to be effective, Endo plans to seek one partner or set of partners (a private company or not-for-profit organization) to develop the product for sale in the industrialized world and another to work on getting it licensed for use in the developing world. More information on the investment required -- and the complexity involved in doing this -- is available in the backgrounder.

The UK government's Department for International Development (DFID) and the UK Medical Research Council (MRC) funded MDP 301. As a part of the clinical trial agreement, Endo agreed it would give MRC and/or DFID or their agents the right to manufacture and distribute PRO 2000 for use in countries with low-income economies if Endo decides not to do that itself. If the MRC decides to pursue licensure, its technology transfer unit would work to identify commercial or not-for-profit developers to work with them and negotiate contracts to pursue this development and licensure of PRO 2000.

### Important Note:

**Please read the "MDP 301 Clinical Study Testing PRO 2000 Background Information"**

**available on line at**

**<http://www.global-campaign.org/MDP301.htm>**

**before proceeding with this document.**

**The following assumes that the reader has this background.**



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Even if PRO 2000 is licensed, distribution would require substantial additional financial investment from the private, public or philanthropic sectors. So one big question is whether these funders will decide that a moderately effective product (one showing 30-50% effectiveness in a standard analysis) is worth the investment. They might choose, instead, to wait and hope that an ARV-based microbicide or oral PrEP shows greater effectiveness in preventing HIV.

## If someone does decide to pursue licensure, when is the soonest that PRO 2000 might be available in low income countries?

The short answer is at least 3-4 years. Some of the steps listed below could occur simultaneously. But they are not likely to occur in a rapid or in a coordinated way unless someone makes a substantial commitment to moving PRO 2000 forward. Pressure from civil society and advocacy groups is also going to be needed to make this happen. Some “next steps” toward access include:

1. The regulators may require additional data on the effects of PRO 2000 use by pregnant and breast-feeding women; as well as on the impacts of rectal use and high frequency vaginal use of the product.
2. More PRO 2000 gel will have to be made. Endo only made enough to complete the MDP 301 trial and perhaps one of the additional studies listed above. Endo or some other manufacturer would have to scale up production to manufacture PRO 2000 in large quantities. That manufacturing process would have to be “validated” (this means verifying that it makes a high quality product consistently) as a part of the regulatory application for licensure. This is likely to take at least two years.
3. Operations and marketing research will be needed to determine how a moderately effective product could be safely delivered in various settings. Logistics and supply chains also need to be developed and/or strengthened. PRO 2000 would likely be introduced first in just a few settings. Access to it would increase as programs, providers and users gain more experience with it.
4. National and international policy makers would have to be persuaded to make it a high priority in their HIV prevention programs, which may be a challenge, especially in severely under-resourced countries.

Meanwhile: A limited amount of PRO 2000 could be made available to women participating in additional clinical or operations research or other pre-introductory studies.

PRO 2000 trial participants will likely demand to receive the gel immediately (if it is proven effective) based on the principle of “compassionate use.” This principle has been used for years to justify providing access to an HIV treatment drug, once it is found effective, to HIV-positive people who participated in the clinical trials to test it. This principle has never been applied to participants in HIV prevention trials. Whether ethicists would judge that it applies in the case of something like a microbicide, especially prior to the product being licensed, remains to be seen. Even if the concept of “compassionate use” can be applied to PRO 2000, the particular provisions will vary based on different countries’ regulations and policies.

Researchers could also provide access after licensure by conducting a Phase IV study. Phase IV trials are initiated after a drug is licensed to gather additional information about a drug’s benefits, risks and optimal use.



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## Is it really possible that a microbicide with proven effectiveness could be identified but no one would be able to get it?

Yes, that is one possibility. The arguments for and against moving forward with PRO 2000 development and licensure (assuming it is a moderately effective product, showing 30-50% effectiveness) are complex. The following is a summary of some key points.

ACCESSIBILITY	
<i>When could PRO 2000 be available and to whom?</i>	
<i>For moving forward</i>	<i>Against moving forward</i>
<ul style="list-style-type: none"> <li>• PRO 2000 does not contain anti-retroviral drugs (ARVs) so it may be able to be distributed without a prescription. If so, it could be sold in shops and handed out in public health clinics. Women would not have to get HIV testing to use it.</li> <li>• Most of the other microbicide candidates in clinical trials are ARV-based. This means that, until more is known about how they affect HIV positive women, these products could only be distributed by health care providers and women could only get them if they are also getting regular HIV tests.</li> <li>• Currently, no other non-ARV based microbicides are in early safety clinical trials. While some candidates are being explored in pre-clinical studies, it is not clear when or whether any of them will be moved forward into clinical trials. This means that – if PRO 2000 is not developed – we are likely to wait for a decade or more for another chance to advance a non-condom, non-ARV based HIV prevention tool that could be made available “over the counter” in shops and from community health outreach workers.</li> </ul>	<ul style="list-style-type: none"> <li>• Development and licensing of PRO 2000 will take time. It will likely be 3-4 years before women actually have access to this product, even if it moves ahead now.</li> <li>• Most of the PRO 2000 supply was used to do the clinical trials. The remaining supply is very small. Even if we move forward toward getting PRO 2000 licensed, developers will need a few years to get the manufacturing process validated and make more product.</li> </ul>

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## PARTIAL EFFECTIVENESS

*PRO 2000 will only be moderately effective in reducing HIV risk.  
Won't people just assume that it replaces the need to use condoms?*

### *For moving forward*

- It could be packaged and sold together with condoms to encourage people to use both.
- It could be marketed specifically to people whose condom use is already very low –such as those in on-going partnerships, adolescents, and others.
- The marketing message could be: “this is what you use with your spouse or regular partner” or “this is what you use when you can't use condoms.”

### *Against moving forward*

- How do we make sure that people understand that this product isn't as effective as condoms?
- If people may think PRO 2000 is protective, they may increase their number of partners and/or reduce condom use. It could undermine existing HIV prevention strategies.

## WILL WOMEN USE THIS PRODUCT?

*Clinical trial participants said they liked PRO 2000,  
but will women in other settings want to use it?*

### *For moving forward*

- In the HPTN 035 and MDP 301 trials, 90% of participants said they would want to use PRO 2000 if it is effective. But more research on women's demand for – and use of – a moderately effective product is needed to estimate the “real world” demand for moderately effective microbicides, now and in the future.
- Trial participants have said that the lubricating effect of trial gels increases sexual pleasure for both partners. Some have said that it makes condom negotiation easier (e.g. “I'll use the gel if you use the condom”).
- At one South African trial site where nearly half of young women are already infected, demand for new prevention methods to protect those still negative is very strong. Trial participants, study staff and CAB members surveyed said they wanted PRO 2000, even if it was only 30-50% effective.

### *Against moving forward*

- We don't know whether women will really want to use PRO 2000.
- We don't really know enough about the factors that may affect women's demand for PRO 2000 and their willingness and ability to use it, especially in countries hardest hit by AIDS. Other issues such as cost or stigma associated with using it might inhibit women's demand for it.
- It is possible that we could dedicate substantial time and resources to making PRO 2000 available and then find out that there is very little demand for it.
- MDP 301 is examining the issue of safety very carefully – particularly to see if there is any reason to think that PRO 2000 may be safer for women who use it occasionally than for women who use it frequently (once a day or more). This is crucial information because, if it is not safe for frequent use, it may not make sense to move toward making it publicly available.



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**INTRODUCING PRO 2000 AS PART OF HIV PREVENTION FOR WOMEN**  
*How would PRO 2000 be integrated into current prevention programs?*

<i>For moving forward</i>	<i>Against moving forward</i>
<ul style="list-style-type: none"> <li>If PRO 2000 works, the gel could be provided to women along with condoms. Having a new tool to present would give public health clinics and HIV prevention educators a chance to refresh and intensify their HIV prevention messages to women. Providing PRO 2000 and female condoms – in combination with intensified counseling on male condom use – could generate new interest among women at high HIV risk</li> </ul>	<ul style="list-style-type: none"> <li>Health systems and health care workers are already over-burdened and stretched beyond capacity. We must choose strategically which products to introduce and integrate – since we cannot afford to do everything.</li> <li>We do not yet know when/if a developer will want to move PRO 2000 into large scale production, in what countries it might get regulatory approval or how introduction of it would be designed or funded.</li> </ul>

**OTHER RESULTS ARE COMING SOON**  
*Should we move ahead on this one or wait for the next?*

<i>For moving forward</i>	<i>Against moving forward</i>
<ul style="list-style-type: none"> <li>Women at high-risk of HIV infection can't wait. They have a right to access to anything that can reduce their risk now.</li> <li>Even if ARV-based microbicides are shown to be more effective, women have expressed a strong desire to be able to choose between ARV-based and non-ARV based HIV prevention options.</li> <li>PRO 2000 is safe for use by HIV-positive women. Unlike ARV-based products being tested, this means that women who do not know their HIV status could use PRO 2000 safely.</li> <li>Any new HIV prevention method that is safe and effective should be deployed to give people more options for prevention and help stem the epidemic</li> </ul>	<ul style="list-style-type: none"> <li>We cannot afford to do everything, and it would be better to wait and use our resources for newer products that may be more effective</li> <li>Within the next two to four years, trial results will tell us whether oral PrEP and the first ARV-based microbicides are effective. If PRO 2000 is introduced now -- and people develop exaggerated ideas about how effective it is -- this could generate disappointment and scepticism about the next new prevention tools to be introduced. People may think, "They said PRO 2000 would work but I know women who got infected while using it. So why should I believe that this next new product would work?"</li> </ul>

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## FUNDING AND RESOURCES REQUIRED

*Product development and delivery requires a lot of financial investment and resources. Is PRO 2000 where funders should direct their efforts?*

<i>For moving forward</i>	<i>Against moving forward</i>
<ul style="list-style-type: none"> <li>Resources exist, and donors should pull together to provide the necessary funding to develop PRO 2000. It is an ethical responsibility to the women who need it.</li> <li>In 1998, total global investment in microbicide R&amp;D was under US \$35 million. By 2008, that annual figure had grown to US \$244 million, 85% of which was supplied by public-sector funders. The philanthropic sector supplied 14% of the 2008 total only 1% came from the commercial sector. Clearly, public funding follows political will and can be mobilized.</li> <li>Investing in the development and delivery of this product will teach us important lessons about how to move other products forward in the future.</li> </ul>	<ul style="list-style-type: none"> <li>It is wiser to wait and put the funding and other resources toward advancing products once they show higher demonstrated levels of effectiveness.</li> <li>Since the available pool of resources is limited, the field must make careful and strategic decisions about how to use them.</li> </ul>

## WHEN DOES “GOOD” = “GOOD ENOUGH”?

*How will trial communities react if the first microbicide shown to work is never made available to the public?*

<i>For moving forward</i>	<i>Against moving forward</i>
<ul style="list-style-type: none"> <li>Suppose PRO 2000 is shown safe and effective, but is not developed further. Will women be willing to volunteer for future trials knowing that, even though more than 10,000 women participated in PRO 2000 trials, the product will never be publicly available?</li> <li>How will communities respond to future placebo controlled microbicide trials if they know that an effective microbicide exists? Is it ethical to ask them to participate in such trials?</li> <li>If the international health community chooses NOT to develop PRO 2000 once it is proven to be safe and effective, isn't it breaking its commitment to those in urgent need of new prevention methods?</li> </ul>	<ul style="list-style-type: none"> <li>Not every product that is proven effective is developed and introduced into markets. PRO 2000 gave the field renewed hope in microbicides, but it is not good enough to invest in further.</li> <li>Women will not have immediate access to PRO 2000 in any event. In the time it would take for this product to reach women, we may have evidence that other products are more effective.</li> </ul>



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## Finding common ground:

As microbicide advocates, we believe that more research is needed on the needs and preferences of targeted end-users of microbicides. The expected results of MDP 301 have raised critical questions around the level of protection women want before they will use a product consistently for HIV protection; how a partially protective product would be packaged and marketed; and how potential findings of a safe and partially effective microbicide might impact ongoing and planned prevention research.

At GCM, we believe the field must invest the necessary funding to support innovative social science research and build new partnerships with social marketing organizations. Whether PRO 2000 becomes the first safe and effective microbicide that moves toward licensure or the field has to wait for another product, the microbicide field must take actionable steps now to encourage the research needed to ensure we keep the needs and preferences of the users up front and center in all the work we do.



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