The Economics of Microbicide Development

A Case for Investment

A Report of the
Pharmaco-Economics Working Group
of the
Rockefeller Foundation
Microbicide Initiative

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The Pharmaco-Economics Working Group was established as part of the Rockefeller Foundation's Microbicide Initiative, started in early 2001. This was one of four Working Groups formed to examine the key steps in creating a microbicide: (1) understand the public and private views of investment in microbicide development; (2) develop ways to ensure access to the product; (3) advocate investment in and adoption of a product; and (4) identify the scientific and technical requirements for developing a product.

The reports from the other Working Groups are contained in companion volumes within this series. The pharmaco-economic work has been completed in two sections: the private investment view and the public investment view. This report covers the private investment view of the microbicide market.

Participants and Acknowledgements

A team of six people from the public and private sectors collaborated on the private investment view, drawing heavily on information and ideas from the other three Working Groups. The members of the Pharmaco-Economics Working Group who worked on the private investment view are:

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Executive Summary

Prevention technologies are a vital weapon in the battle against HIV. Although traditional technologies such as condoms are effective against sexually transmitted infections (STIs), for many women they are not a viable option. For some women, social pressures and the need to negotiate with their partners can make condom use a difficult proposition. A microbicide, however, offers the potential for a woman-controlled defense against infection. Microbicides may also offer significant health benefits by preventing transmission of STIs other than HIV, and potentially offering another form of contraceptive.

The work of the Pharmaco-Economic group focused on developing a full understanding of the economic potential of the microbicide market, including potential size of the market, cost to develop a microbicide, and the resulting returns-on-investment as viewed by a private investor. Ensuring development of a microbicide will require participation of both public and private developers. Until now there have only been analyses of segments of the potential market, and limited understanding of the complete development costs for a product. This uncertainty about the market and expected returns has been a factor in many private investors' decisions to invest their finite resources in products other than microbicides. By reducing some of the uncertainty around microbicide economics, this analysis will help attract additional private investors and provide the donor community with valuable insight into the true financial cost of developing the current microbicide pipeline.

The potential market size for a microbicide depends critically on the characteristics of the product, and product traits are likely to evolve slowly over time. The first-generation microbicide will probably be formulated for use in the vagina, with later indications formulated for rectal use. As new microbicides are developed, both their microbicidal and contraceptive effectiveness are expected to increase. Initial estimates are that effectiveness against HIV will begin around 50 percent and improve to 85 percent, and that contraceptive effectiveness will begin around 75 percent and improve to 90 percent.

A microbicide that meets the basic needs of women in the industrialized and developing worlds could have a global market size of US$0.9 billion by 2011, and double that by 2020. This is a conservative estimate, based on an assumption that the product will be used by less than 10 percent of sexually active women. If, however, the products are able to meet a broader set of needs, including those for daily hygiene, vaginal health, and general protection against infection, there is potential to far exceed these forecasts, with a peak market size as large as US$5 billion. On the other hand, should microbicides fail to meet women's high standards of product acceptability, peak market size could be much smaller, perhaps reaching only US$0.1 billion.

Despite the potential market size, neither pharmaceutical nor biotech companies have made significant investments in the field. Microbicide development is very costly, and the risk of failure in clinical trials is still significant. The current product pipeline has many promising candidates for development, but none has progressed beyond phase 3 trials, where costs are projected to run between US$40 million and US$45 million, and there is statistically still only a 25 percent chance of success.

It is unlikely that expected returns would cover development costs or the cost of capital for the first generation of microbicides (if the product is

to be affordable in its intended markets). The firms and organizations that are currently developing products are doing so with significant support from donors. Estimates of the net present value (NPV) of investing in a first-generation microbicide range from negative US$65 million to negative US$27 million. Depending on market evolution, a second-generation product could be self-funding, with an NPV ranging from a negative US$56 million to a positive US$122 million. A third generation of products offers the first potential for significant returns. Depending on whether microbicides become a niche product or a regular hygiene product, outcomes for the third generation range from a negative US$49 million to a positive US$428 million. Donor support will, therefore, be critical through phase 3 trials and registration of the first generation of products.

Donor support for microbicide development has been driving development to date; however, there is still a large gap between required and available funding. We have estimated that it would require roughly US$775 million in direct product development costs over the next five years for the entire portfolio of potential products, whereas current estimates of public support for microbicide development from 2001 to 2005 are approximately US$230 million. While increased financial support is vital, the field can also play an important part in helping to bridge this gap through better portfolio management (i.e., phasing and/or winnowing the pipeline of products) and increased coordination to save resources. We estimate that funding requirements could be reduced by up to US$53 million by capturing economies of scope across products.

For microbicides, the transition from product registration to wide acceptance and use cannot be taken for granted. Vital advocacy and access issues must also be addressed and funded, raising awareness of microbicides and ensuring that once a product is available, there is both demand for the product and an affordable supply.

Both public and private sector donors will play an essential role in the next phase of microbicide development. They can help the field to develop and deliver effective microbicides as rapidly as possible by:

- Mobilizing additional financial support for microbicide development in both the public and private sectors
- Encouraging increased coordination within the field of microbicide developers, to help reduce the current funding gap through:
  - better portfolio management across the field
  - increased coordination to save resources by gaining economies of scale or scope (e.g., building common clinical trial infrastructure), or avoiding duplicate investment and effort
- Reducing some of the uncertainty about the potential market size by ensuring demand for a product, once it is developed
- Developing an integrated approach to development subsidies and intellectual property rights, to ensure public sector access to a successful product if it is developed in the private sector

The Likely Evolution of a Microbicide

Because no microbicide has yet completed clinical trials, the product attributes are still uncertain—but key product attributes will have a profound impact on the eventual market size. To develop a meaningful size estimate, the team made some assumptions about both product attributes and price.

One key modeling decision was to focus on when an HIV indication could be available. We chose roughly 2007. It is likely that a stepping-stone, "contraceptive-plus" microbicide could be available sooner, without an HIV indication. For example, an early microbicide might have an indication as a contraceptive, *as well as* a preventative of one or more sexually transmitted diseases such as herpes. However, these products lay outside the scope of this analysis, which focused on a microbicide's impact on HIV.

The Working Group laid out its assumptions about the product attributes in a working set of scenarios. In selecting these scenarios, the Working Group applied four principles. Scenarios should be:

- conservative and realistic;
- meaningful in impact on potential market size;
- possible to model, given the available data; and
- responsive to the community's need for an affordable, effective HIV-protective product.

Figure 1: Summary of microbicide market evolution scenarios

Dimension		1st generation	2nd generation	3rd generation
Launch timeframe		2007	2012	2017
Number of products		One	Three+ (2 vaginal, 1 rectal)	Multiple
Formulations		Vaginal →		
			Rectal →	
				Controlled release vaginal devices
Indications		HIV		
		1 other STI	Herpes, gonorrhea, chlamydia, and HPV	
		Possibly contraceptive	Choice of contraceptive or non-contraceptive version	
				Vaginal health
Microbicidal effectiveness	Typical use	50%	70%	85%
	Correct & consistent use	60%	90%	90% if user-applied 97% if device-driven
Contraceptive effectiveness	Typical use	75%	80%	90%
	Correct & consistent use	85%	90%	97%
Use instructions		Approved for use with a condom or vaginal device		
			Approved for use as a stand-alone	
Sales channel	Industrialized	Prescription-only	OTC	
	Developing	OTC	OTC/Social marketing	
Price US$	Industrialized	• $3 for single-pack • $1.50/dose multi-pack	• $2 for single-pack • $1.25/dose multi-pack	• $1 for single-pack • $1.25/dose multi-pack
	Developing	• $0.83/dose single-pack • $0.35/dose multi-pack	• $0.75/dose single-pack • $0.32/dose multi-pack	• $0.67/dose single-pack • $0.28/dose multi-pack

The scenarios represent the team's forecast of the likely development of a microbicide product based on literature reviews and consultation with other members of the microbicide field. In particular, these scenarios were reviewed with the other Working Groups in the Microbicide Initiative (science, advocacy, and access).

Timing of Formulations

With a number of promising candidates in late-stage development, it is reasonable to expect a

first-generation product as early as 2007. A second generation of microbicides (including a rectal formulation) could be expected within five years of the first, with a third generation to follow by 2017. Third-generation microbicides are likely to be significantly more advanced than the initial products.

Indications

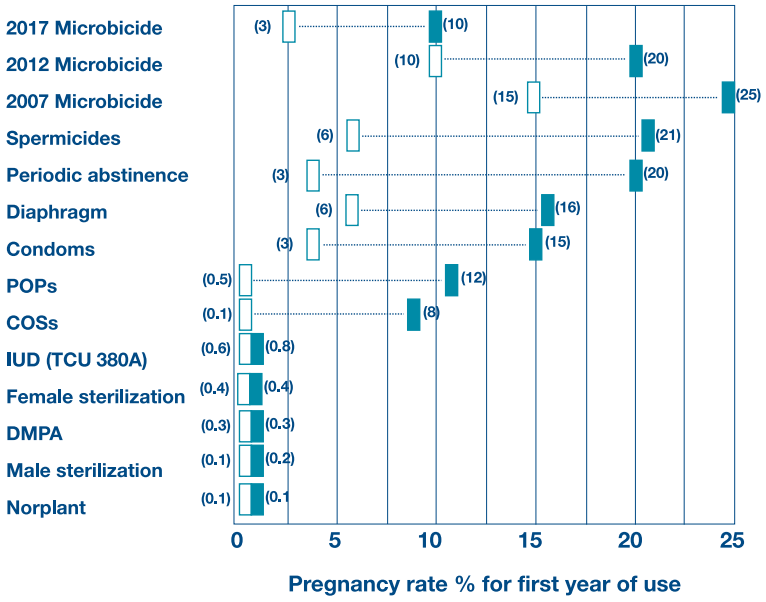
A first-generation microbicide, for vaginal use, will probably offer prevention against HIV and one other STD. Additionally, it might be contraceptive. There are both contraceptive and non-contraceptive microbicides in development, and it is unclear which version will be approved first. Therefore, two different scenarios were modeled for the first-generation product.

A contraceptive indication will have a neutral or negative effect on consumer interest in countries with low contraceptive use, and a positive effect in countries where contraceptive use is high. The markets better able to pay for a microbicide tend to have higher contraceptive use, and would likely generate more revenue. In the developing-world markets hardest hit by HIV and AIDS, however, rates of contraceptive use are quite low. In those areas, we expect that a non-contraceptive product would attract more users. Second- and third-generation microbicides should offer protection against HIV and multiple STDs *and* offer users the choice of a contraceptive or non-contraceptive version.

Use Instructions and Product Effectiveness

As with most prevention technologies, the theoretical effectiveness of products will be higher than their actual effectiveness in use. The effectiveness of any product that requires the user to apply it correctly and consistently will suffer from the effects of human error. Because AIDS is a deadly disease, consumers and health-care professionals will weigh heavily any product's effectiveness when determining whether to use or recommend it. For this reason, it is unlikely that a first-generation microbicide

Figure 2: Contraceptive effectiveness levels for microbicides and comparable products



Source: Diagram adapted from Reproline at Johns Hopkins

will be licensed for stand-alone use. To gain regulatory approval, a microbicide should offer at least 50 percent effectiveness in typical use, and be licensed for use with a condom or vaginal device. In subsequent generations, effectiveness is likely to increase significantly, potentially reaching 85 percent by the third generation, or even higher if the product is delivered by a device.

As contraceptives, first-generation microbicides are likely to be less effective than most alternatives today, perhaps achieving 75 percent effectiveness for typical use. Second-generation products can reasonably be expected to approach levels similar to those of spermicides. Ultimately, a third-generation contraceptive microbicide could be competitive with oral contraceptives if it were device-delivered.

Sales Channel

For our analysis, we assume a first-generation microbicide in industrialized countries will be available only by prescription, but that it would switch to over-the-counter in its second and third generations. In developing countries, it will be

Table 1: Summary of price scenario assumptions (US$)

	Industrialized world (willingness to pay)			Developing world (cost-plus)		
	Single use	20 dose multi-pack	Average (70% single use)	Single use	20 dose multi-pack	Average (70% single use)
First generation	$3.00	$1.50 ($30 for 20)	$1.66	$0.83	$0.35 ($7 for 20)	$0.40
Second generation	$2.00	$1.25 ($25 for 20)	$1.32	$0.75	$0.32 ($6.40 for 20)	$0.37
Third generation	$1.00	$1.25 ($25 for 20)	$1.22	$0.67	$0.28 ($5.60 for 20)	$0.32

imperative that microbicides be available over-the-counter from the outset. If first-generation microbicides in the developing world are prescription only, that could dramatically restrict access to the product.

Pricing

Ensuring equitable access to the product will require different price levels by market. In industrialized countries, product price can be based on willingness to pay, providing an attractive margin to manufacturers and developers. In developing countries, pricing will need to be cost-plus. In markets where the product is distributed through public agencies, we assumed it would be purchased at cost.

The Working Group assumed that, with each new generation of microbicide, it will be possible to achieve a 10 percent reduction in dose cost and price. Some third-generation products are expected to be device-driven, maintaining a price premium in the industrialized world. For the purposes of this analysis, we assumed the premium on device-driven products would balance continued price reductions in the standard user-delivered formulations.

Market Penetration

Market penetration is also important in understanding the rate of market growth, and hence ultimate size, at any given time. For health care products, penetration rates depend primarily on whether the product is launched as a prescription or an over-the-counter product. For a microbicide, we assumed a first-generation prescription product that switches to OTC in subsequent generations. On this basis, the group assumed 60 percent compound annual growth (CAGR) for the first five years, and 22 percent CAGR over the life of the product (from first generation to third generation).

How Big Is the Market for a Microbicide?

The group used three different methods to estimate market size. The primary method, a top-down approach, was based on translating consumer interest levels into a market size. This was confirmed using a bottom-up approach, in which we identified segments of consumers who have a need for the product, and then estimated their likely patterns of use. The bottom-up approach broadly confirmed the top-down figures, and allowed us to confirm the estimates for some key markets (for example, the U.S.). Finally, analogies with other products provided empirical boundaries for the estimates of market size. The top-down and bottom-up results demonstrate interest and need among consumers, with the analogies suggesting a wide margin of error for market projections made before product launch.

How the market for microbicides develops will depend on both the product itself and how the market adopts it. The Working Group examined three possible market adoption scenarios:

- Expected case – widely acceptable product
- Optimistic case – regular hygiene product
- Pessimistic case – niche product

Expected Case

The expected-case scenario represents the team's best estimate of the potential market for a microbicide, if it meets the basic needs of women in the industrialized and developing worlds. Using the bottom-up and top-down methodologies, a first-generation microbicide in this scenario could have a market size of US$0.9 billion to US$1.1 billion. This could reasonably be expected to grow to between US$1.5 billion and US$1.9 billion, as additional indications become available and the effectiveness of the product increases. Based on the group's assumptions

Figure 3: Summary of expected-case market sizing analysis by methodology

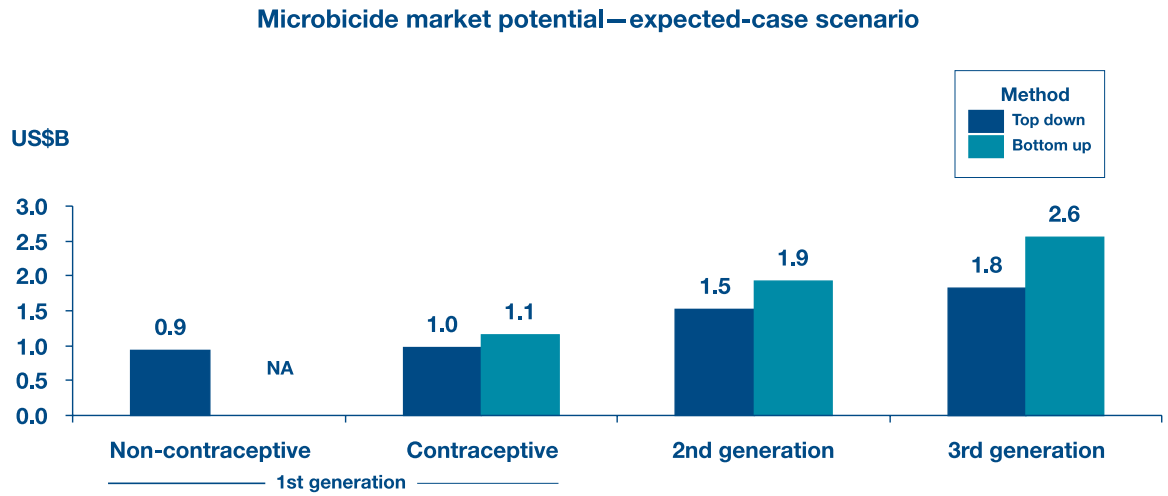
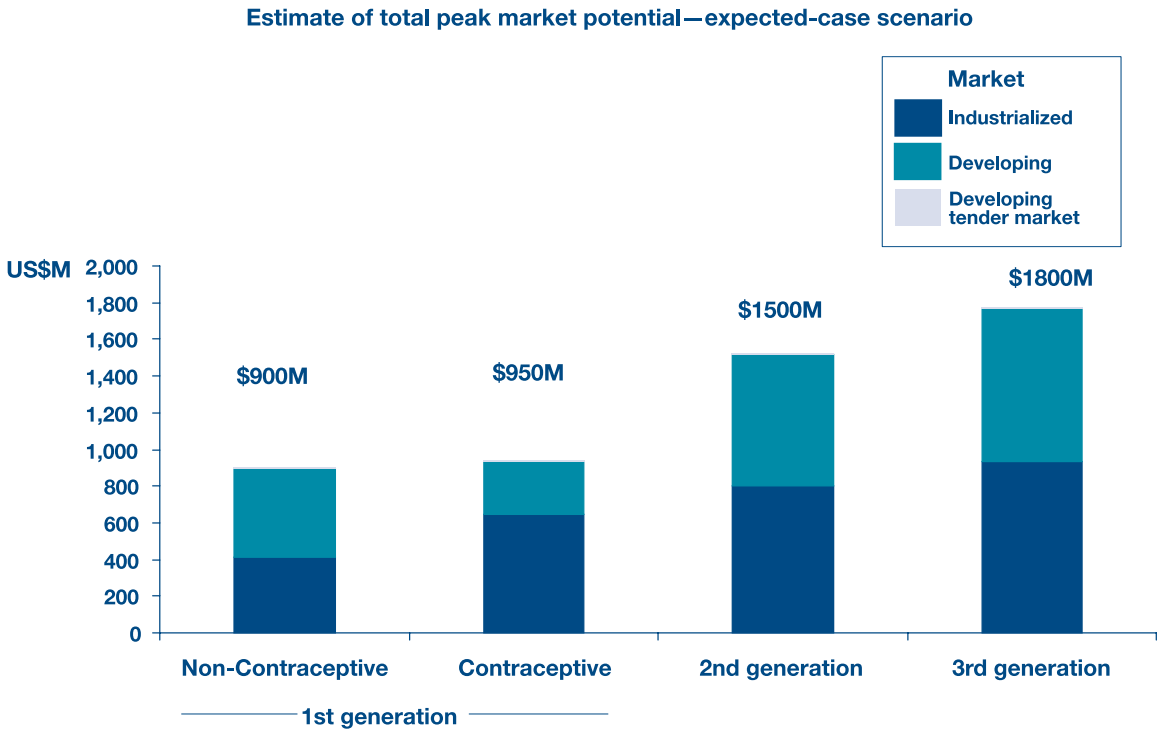


Figure 4: Summary of expected-case evolution by market



about how the product will evolve, the peak market size for a third-generation product could reach between US$1.8 billion and US$2.6 billion by 2022. The timing of peak market size will vary with the rate of market penetration and the duration of product life cycles.

Optimistic

The benefits a microbicide offers women could result in microbicides becoming part of their daily regimen. The expected-case market size estimates are based on a small proportion of women using the product 50 percent of the time when they have sex (assume one hundred coital acts per year). Under the expected-case scenario, 3 percent of women in developing countries, and 7 percent of women in industrialized countries, would be using the product, leaving plenty of room for expansion. Although it is unlikely that a first-generation product would have the attributes required to make it a regular hygiene product, a second-generation product adopted for regular hygiene use could reach US$3 billion, double the size of the expected market. For a mature third-generation product, the market could expand further, reaching US$5 billion (assuming the same growth rate between second and third generations as in the expected-case scenario).

Pessimistic

Unfortunately, there are a number of well-documented cases where products were launched with high market expectations that were never realized. In the case of a microbicide, a relatively strong product scientifically could nonetheless result in a niche market if the product fails to meet women's standards of acceptability, or if it is not marketed effectively. The group drew heavily on analogies of other products that have faced similar challenges, in order to estimate the size of a niche market for microbicides. Both the female condom and the Today sponge were thought to have substantial market potential prior to actual launch. However, the peak sales of

the female condom, at US$6 million, and the Today sponge, at US$20 million, are dwarfed by the expected microbicide market projection of US$1.8 billion. The smaller markets can be attributed to issues of product acceptability. Female condoms are expensive and difficult to use; and the Today sponge, although popular among users, is hard to learn to use. Drawing on the analogy of the Today sponge, a first-generation microbicide that fails to meet standards of product acceptability could have a market size of US$20 million. The group agreed that a second-generation product in this scenario could reasonably be expected to be comparable with the peak market for spermicides, US$55 million. A third-generation product, with market potential comparable to douches, could be expected to peak at US$100 million in the third generation. Based on product improvements over time, a third-generation product would be a scientifically robust product that fails on one or more dimensions of product acceptability.

What Is Holding Private Investors Back?

Private investors have been hesitant to invest fully in microbicide development, despite a full and promising pipeline of potential products and significant market potential. In large part, this hesitation is due to the large investments required to ensure a high probability of success.

Expected returns for pharmaceutical and biotech companies cover neither development costs nor the cost of capital. Firms that are developing products are doing so with significant support from donors and the public sector. Our analysis suggests that such support will continue to be critical through phase 3 trials and registration of the first generation of product, even for those developers currently on the cusp of phase 3 trials. The amount of subsidy required will depend on the probability that the pessimistic market scenario will occur. A second-generation product may get to market without subsidy, with third-generation products likely to be positive investments. The increased potential for profitability in later products is attributable to the increased market size and reduced development costs. Once a product has been approved, phase 3 clinical trials will be reduced in cost by a third (the condom-only arm will be eliminated, and trials will be a comparison of the new product versus the existing standard of care.).

By our estimation, expected returns will not cover development costs or the cost of capital for the first generation of microbicides. For example, with a discount rate of 12.5 percent, the devel-

Figure 5: Summary of return-on-investment for different scenarios (US$)

	Pessimistic case "Niche product"	Expected case "Widely acceptable product"	Optimistic case "Regular hygiene product"
1st generation • launch 2007 • 8 yr lifecycle • 100% share	Market $20M NPV = ($65M) IRR = N/A	Market $900M NPV = ($27M) IRR = 7%	Unlikely scenario
2nd generation • launch 2012 • 15 yr lifecycle • 50% share	Market $40M NPV = ($56M) IRR = N/A	Market $1500M NPV = $37M IRR = 18%	Market $3000M NPV = $122M IRR = 24%
3rd generation • launch 2017 • 33% share • 3% growing perpetuity	Market $100M NPV = ($49M) *(of which terminal value = $6M)* IRR = N/A	Market $1800M NPV = $117M *(of which terminal value = $112M)* IRR = 14%	Market $5000M NPV = $428M *(of which terminal value = $307M)* IRR = 26%

Negative NPV at 12.5% cost of capital Positive NPV at 12.5% cost of capital

oper of a first-generation product could expect a net present value (NPV) of between negative US$65 million and negative US$27 million (this assumes the first product will have no competition, so will capture 100 percent of the market). Depending on how the market evolves, a second-generation product could potentially be self-funding, with potential NPVs ranging from a negative US$56 million to a positive US$122 million. It is with the third generation of products that we first see significant returns. Potential NPVs range from a negative US$49 million to a positive US$428 million, depending on whether microbicides become a niche product or a regular hygiene product.

Although commodity purchasing will play an important role in ensuring access to products in some parts of the world, it is unlikely to affect returns in the microbicide field significantly, unless the prices are structured to pass on additional margin to developers. Even if this is the case, it is unlikely that the quantities purchased through this mechanism will be large enough to have a significant effect on overall returns. Following the current trends for commodity purchasing in the contraceptive market (industrialized-world commodity spending not included), and assuming that microbicides capture between 5 percent and 10 percent of this spending, it would expand the potential market by only US$8 million to US$16 million.

Conclusions

Although it is uncertain how the market will evolve, the most likely scenario suggests a peak market size of US$1.8 billion. The biggest uncertainty surrounding the market size is how consumers will receive the product. In the upside scenario, microbicides become a regular hygiene product with a peak market of US$5 billion. The downside scenario, a niche product, is considerably less attractive, with peak sales of only US$100 million. Based on expected retail sales, the industrialized and developing worlds will be equally significant (52 percent and 48 percent of the retail market, respectively). However, on a per-user basis, demand in the developing world (70.5 million women) is expected to far outstrip demand in the industrialized world (16.5 million women).

Current expectations about returns, and the uncertainty about development success, have discouraged independent, private-sector investment. Public-sector support has been instrumental to the progress made so far, and will continue to be essential, even after the first microbicide is registered.

Sizing the Market

The market size for microbicides was estimated by triangulating from three methods:

Top-down: Consumer Products Approach

This approach started with the available consumer survey data on interest in a microbicide. The European Commission's study (Vaginal Microbicides for the Prevention of HIV/AIDS: Assessment of the Potential Market, 2000) provided the most conservative base case for stated interest, with the Hardy (Women's Preferences for Vaginal Antimicrobial Contraceptives, 1998) and Alan Guttmacher Institute (Women's Interest in Vaginal Microbicides, 1999) studies providing more demographic breakdowns. Data were available only for a subset of the countries with a potential market for microbicides. To infer microbicide interest in additional countries, we developed a regression model.

Interest in microbicides was found to be predictable from common country indicators. Regression analysis generated a 0.75 R^2 when microbicide interest (at 5x condom prices) was regressed

Table A1: Summary of different market sizing approaches

Approach	Methodology	Strengths	Weaknesses
Top-down consumer product approach	• Use consumer surveys and correlation with country-level statistics to derive product interest level • Translate interest level to users and $ market value	• Microbicide-specific • Easy to generalize to whole world	• May generalize away key cultural differences
Bottom-up medical model approach	• Use demographic risk factors to derive product interest levels • Translate interest level to users and $ market value	• Can use more existing knowledge of population segments • Helps confirm stated interest levels from top-down method	• Must tailor each population • tradeoff between richness and reach of model • Many markets have poor data about sexual behavior
Analogies	• Compare similar products • Sanity-check market sizes	• Creates empirical boundries	• Comparability of products • Wide margin of error

against: the percentage of the adult population living with HIV/AIDS (likely a primary demand driver); the birthrate (potential indicator of unprotected sex); and condom prevalence (potential indicator of willingness to use product) in each country. Regression models also worked for interest at 2x and 1x condom price, although the R^2 for 1x condom price is lower (0.68 versus 0.75).

Survey data and interest inferred from the regression model indicated broad interest in microbicides in a number of countries.

Regression Model for Microbicide Interest

$$y = 154.7x_1 + 2.0x_2 + 2.4x_3 - 29.6$$

y = % of women interested in a microbicide at 5x condom price
x_1 = HIV prevalence in the adult population
x_2 = Birthrate (per 1,000 population)
x_3 = condom prevalence

Adjusted R^2 = 0.747

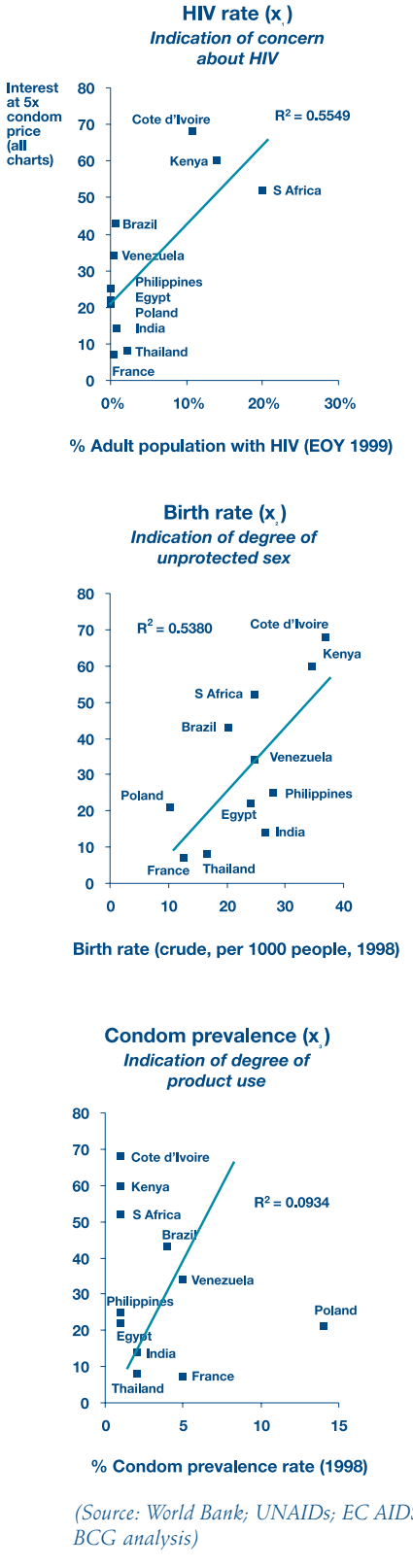
P-values:

Intercept	0.125
HIV rate	0.027
Birthrate	0.014
Condom prevalence	0.086

The next step was to determine at what multiple of condom prices a microbicide would be available in each country (interest levels were stated in terms of condom price multiples), and hence, what the interest levels for microbicides were likely to be. The weighted average retail price for a microbicide in an industrialized or a developing country was used to calculate at what multiple of a condom price a microbicide would be sold. We based average condom prices on four tranches of national income.

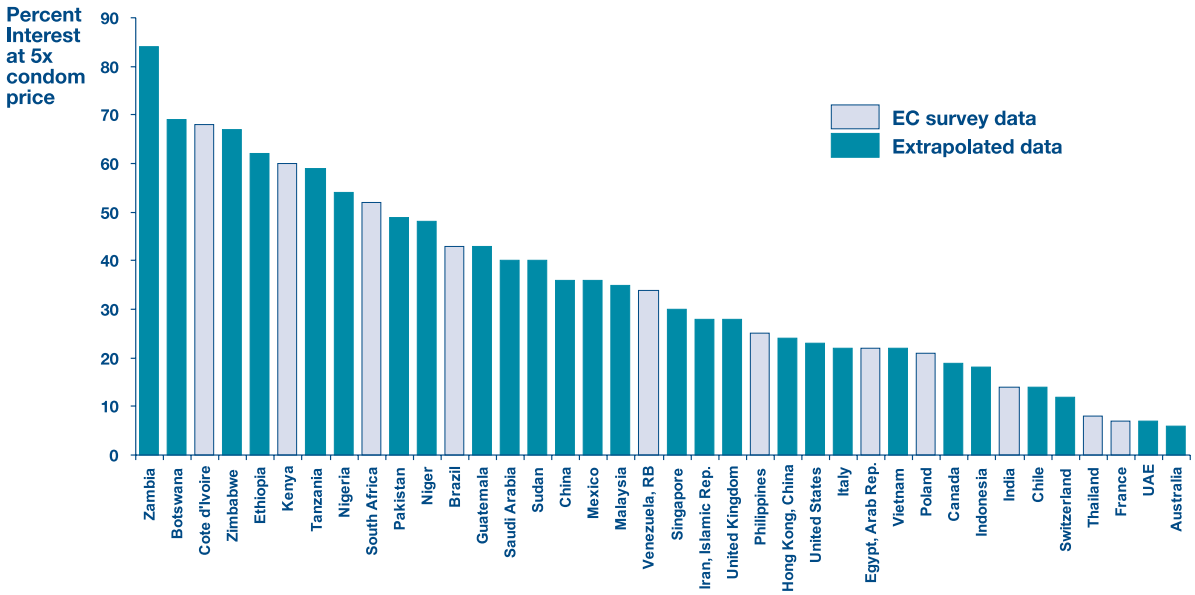
For some countries, it was necessary to extrapolate from the demand curve to determine consumer interest at price points representing multiples not asked about in the survey. (The surveys asked only about 1x, 2x, and 5x condom price.) In extrapolating demand curves for each country, we assumed that they were "kinked," with the greatest drop-off in interest occurring as soon as microbicides become more expensive than condoms.

Figure A1: Regression results for microbicide interest against HIV rate, birth rate, and prevalence of condom use.



(Source: World Bank; UNAIDs; EC AIDS survey; BCG analysis)

Figure A2: Microbicide interest level by country



(Source: World Bank; UNAIDs; EC AIDS survey; BCG analysis)

The final step in determining market size in each country was to apply a conversion rate from stated interest to actual purchase. The surveys estimated the percentage of consumers who stated they were "very interested" in a microbicide, but not all women who state interest will actually become users. Part of this gap can be attributed to how consumers take surveys: there is a tendency to overreport "desirable" behaviors and to underreport "undesirable" ones. In this case, safe sex may be seen as a desirable behavior, and hence, consumers may overreport their interest in a microbicide. Also, sex surveys are often poor indicators of actual behavior because of the discomfort many people feel about discussing their sexual behavior. A second issue more specific to microbicides, which could lower conversion rates, would be insufficient access or advocacy resulting in limited product availability and/or adoption.

Examples from outside of the health-care arena suggest that conversion rates depend on both the product and the purchasing process. At one extreme, a new brand of potato chips—a fast-moving, low-priced, immediate purchase—can expect a conversion rate of 70 percent of "very interested" consumers (based on A.C. Nielsen BASES benchmarks). At the other end of the spectrum, an electric car—with a multi-year purchase cycle, a high price, and an unproven technology—would expect conversion rates on the order of only 10 percent of

Table A2: Condom price assumptions (US$)

	Four tranches of national income	Assumed average condom price
Industrialized	High income (e.g., France)	$1.00
Developing	Upper middle income (e.g., Argentina)	$0.40
	Lower middle income (e.g., South Africa)	$0.20
	Low income (e.g., Uganda)	$0.10

Table A3: Conversion rate assumptions and rationale by generation

	First generation		First generation		Second generation		Third generation	
Industrialized markets	Rx product	10%	Rx product, high contraceptive prevalence	15%	OTC switch improved effectiveness	20%	Very good product effectiveness	25%
Developing markets	Inefficient distribution channels	15%	Inefficient distribution, low contraceptive prevalence	10%	Improved distribution, improved effectiveness	20%	Wide distribution, very good product effectiveness	25%

those who state strong interest. For a microbicide, conversion rates will probably be low at the start and improve over time, as both access and product effectiveness improve.

These calculations resulted in a percentage of women who would be expected to adopt the product in each country. The ultimate number of users was then calculated from the number of sexually active urban women (ages 15 to 49) in a particular country, multiplied by their frequency of use of the product, and finally multiplied by the price assumed for that country. For this calculation the group assumed one hundred coital acts per year, per woman, and use of the product 50 percent of the time. We employed the price stipulated in the product scenario. The total market size was determined by summing all countries, excluding those with markets smaller than US$5 million. Markets smaller than US$5 million are unlikely to be pursued by investors, as returns would not cover the cost of entry (registration, marketing, etc.).

Limitations of the Analysis

The main sources of data for this analysis were the EC survey and the regression model developed by the Working Group. Although these are both good starting points, it is important to recognize their limits.

The EC survey has a sample bias toward urban populations; the regression analysis mimics this bias. The product in the EC survey does not exactly match the scenarios selected by the Working Group, and it covers only eleven countries. As with all such surveys, there is an inherent difficulty in accurately gauging interest in a product that exists in concept only.

The regression analysis has predicative value only for countries whose indicators lie within the range of those surveyed. For example, the country must have HIV incidence no higher than that of South Africa (20%), a birth rate no higher than Kenya's (35 per 1000) and a condom prevalence rate no higher than Poland's (14%). For countries with higher or lower figures, our analysis caps the country's indicator to fall within the survey range. Although an R^2 of 75% is very strong for social sciences, there is still a 25% probability of results being the result of chance.

In general, the top-down approach is most sensitive to changes in the assumptions about stated interest in a microbicide and sales conversion rates. Market size changes in almost direct proportion to changes in either interest or conversion rate.

Bottom-up: Medical Model Approach

For this method the first step was to identify which segments of the population have a need for the product, as determined by:

- risk of becoming infected with HIV
- risk of unwanted pregnancy
- both

Table A4: Assumed conversion rates for potential users by risk group

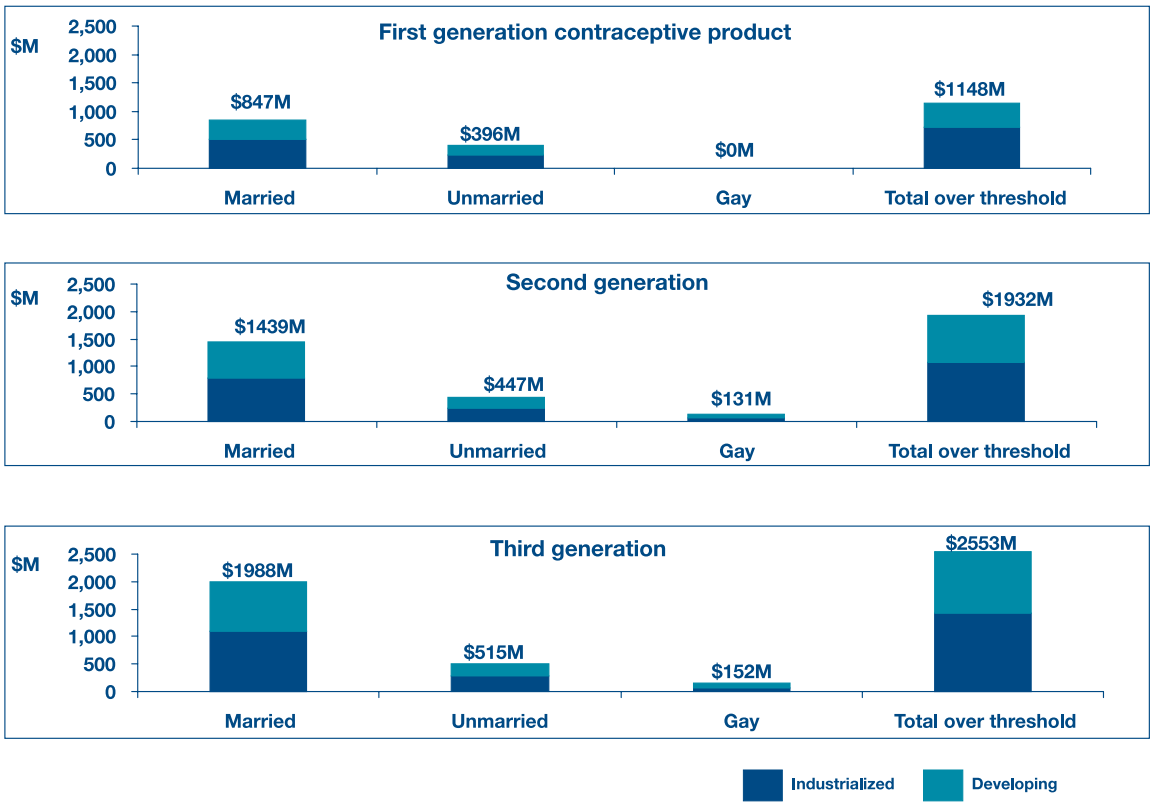
	Potential users (worldwide)	First generation	Second generation	Third generation
Married women	231M	10%	20%	30%
Unmarried women	38M	30%	40%	50%
Gay/bisexual men	23M	N/A	40%	50%

Three segments were considered: married women, unmarried women, and urban men. For each segment, those likely to need and use a microbicide were identified. Within these groups, it was necessary to narrow further the potential users, based on the limited worldwide data available on sexual behavior. The group agreed that, among women, the potential users would be married women practicing modern methods of contraception (~47% of married women) and sexually active unmarried women practicing modern methods of contraception (~15% of unmarried women). Among men, the target market was assumed to be men who have sex with men (MSM) in any twelve-month period (~3% of men).

As with the top-down approach, a conversion rate was applied to convert implied need to actual purchase. Again, the initial conversion rates are expected to be low, and should increase as prices drop, product effectiveness increases, and access improves.

The market size was calculated assuming all segments would use fifty doses per year (married

Figure A3: Bottom-up market sizes by potential user group



women, one hundred coital events per year, product used 50 percent of the time; single women and MSM, seventy-five coital events per year, product used two-thirds of the time) and would be purchasing the product at the same prices used in the top-down scenario. As with the top-down analysis, markets estimated to be below US$5 million were assumed to be subscale. The bottom-up results were slightly higher than those generated by the top-down method, with the results being most sensitive to changes in the assumptions about sales conversion rates. The market size changes in almost direct proportion to changes in conversion rate.

Additional analysis of key markets (such as the U.S.) using the bottom-up approach yielded results comparable to those from the top-down analysis, increasing our confidence in our estimates of market potential.

Product Analogies

As a third method we employed analogies to compare different product market sizes with those projected by the top-down and bottom-up methods. Analogies provide a useful sanity check on the estimates of market size based on other methodologies. They create empirical boundaries for a market size. Our microbicide analogies were drawn from feminine hygiene products, contraceptives, and consumer products focused on hygiene. Worldwide and U.S. market sizes were compared with the peak projected sales for a microbicide under the "expected" market scenario. The tables on this page indicate that there is considerable variation in the size of the different product markets. The comparability of products limits the applicability of this method for determining a market size, because no two classes of product are identical. Therefore, there is likely to be a wide margin of error when using this method to estimate the market for a microbicide. For example, while the product attributes for a microbicide and a spermicide may be similar, the availability of substitutes for spermicides could result in dramatically different market sizes for the two classes of product.

Table A5: Analogies for U.S. market, most recent data available between 1998-2000

Product	US market (manufacturers' sales), $M
Female condom	$1M
Feminine towelettes	$11M
Bacterial vaginosis	$25M
Deodorant sprays	$29M
Spermicides	$55M
Douche	$80M
Dental floss	$154M
Denture cleanser	$179M
Chlamydia products	$264M
Microbicide, 3rd generation *(Manufacturers' sales assumed 80% of retail)*	$274M
Male condom	$295M
Mouthwash	$668M
Herpes products	$900M
Candidiasis products	$950M
Shampoo	$1,360M
Toothpaste	$1,966M

(Source: Market research reports and company annual reports)

Table A6: Analogies for products worldwide, most recent data available between 1998-2000

Product	US market (manufacturers' sales), $M
Female condom	$6M
Spermicides	$17M
Non-oral pharma contraceptives	$230M
Dental floss	$354M
Denture cleanser	$688M
Microbicide, 3rd generation *(Manufacturers' sales assumed 80% of retail)*	$1,440M
Mouthwash	$1,700M
Oral contraceptive	$2,240M
Male condom	$4,000M
Shampoo	$10,992M
Toothpaste	$12,978M

(Source: Market research reports and company annual reports)

The characteristics of each product and its particular challenges can, however, provide insight into specific market challenges. In the case of microbicides, analogies provide useful insight into the pessimistic case of market evolution. If we examine the market size of other products that were launched with high market expectations, but which failed to meet product acceptability standards on some dimension, we get a good understanding of the potential downside. The female condom, with peak retail sales of US$6 million, illustrates the case of a strong scientific product that is expensive and difficult to use. The Today sponge provides another example of how the market might evolve for microbicides. The sponge reached a peak market of only US$20 million in retail sales, despite its high potential, because it was difficult to learn to use.

Table A7: World contraceptive donor support

Product	Current % of commodity spending
Foam/jelly/others	0.1%
Vaginal foaming tablets	1.5%
IUD	5.0%
Implant	6.5%
Injectable contraceptives	24.1%
Condoms	29.0%
Oral contraceptives	33.9%

(Source: UNFPA commodity database; Interim Working Group on Reproductive Health Commodity Security (IWG))

Impact of public spending

For public spending, we considered world contraceptive donor support, and projected spending out to 2015. Worldwide support from donors could reach US$166 million by 2007 and US$210 million by 2015. (These numbers do not include industrialized-world commodity spending). If a microbicide captured between 5 percent and 10 percent of this spending, it would generate US$8 million to US$16 million in supported sales.

Appendix B

Product Pricing

Cost estimates were derived by projecting the mix of product packaging (proportion sold as multi-packs versus single-use application) and manufacturing cost. Product cost information reflects manufacturer estimates for an applicator-based gel product.

Packaging Assumptions

Microbicides are most likely to be available with an applicator, and could be sold either as single-dose applications or in multi-packs. The projections in this report assume that 70 percent of unit sales are single-use applicators and the remainder are multi-packs. Manufacturer cost estimates were based on twenty doses per multi-pack.

Manufacturer Price

Manufacturer price estimates are US$0.60 per dose for a single-use applicator and US$0.25 per dose for multi-packs, resulting in a weighted average manufacturer price per dose of US$0.29. These prices assume use of a contract manufacturer and include manufacturer margin. They do not include margin for product developers.

Retail Price

Retail prices were estimated for both the industrialized and the developing world. For the developing world, they were derived on a cost-plus basis. For the industrialized world, retail price was based on willingness to pay. Average retail prices reflect the weighted average retail price, assuming 30% of units purchased are multi-packs and 70% are single doses. Note that because multi-packs are assumed to contain twenty doses, the percentage breakdown *per dose* is 89.5% purchased in multi-packs and 10.5% purchased as a single dose.

Developing-world average retail price buildup

Manufacturer price	$0.29
Distribution and marketing (10%)	$0.04
Retail markup (17%)	$0.07
Average retail price per dose	$0.40

Industrialized-world average retail price buildup

Manufacturer price	$0.29
Distribution and marketing	$1.10
Retail markup (20%)	$0.28
Average retail price per dose	$1.66

Note: Does not add due to rounding. $1.66 is the weighted average of $3.00 for a single-dose package and $1.50 per dose for a multidose pack priced at $30 for 20 doses.

Market Penetration

The penetration rates used to estimate the growth of each generation of product and the timing of cash flows were based on analogies with existing products. First-generation rates were modeled on prescription launches, where successful products typically achieve 15 percent of their fourth- or fifth-year sales in their first year. Sales and marketing spending are assumed to match those of a prescription product being launched for the first generation. Later development of the market (second and third generation) was assumed to be much like that for a consumer product, once the product makes the switch to over-the-counter. Sales and marketing expenses are assumed to adjust correspondingly.

Table C1: Market penetration scenarios

	First generation	Subsequent generations
Launch conditions	Prescription launch	OTC switch
Examples	• Claritin • Flonase • Imitrex • Lescol	• Advil • Gyne-Lotrimin • Monistat • Tavist
Sales in year one	15% of year 4-5 sales	Previous year's sales plus 15% of incremental market potential
Growth after first year	60% CAGR until peak	25% CAGR until peak
Sales and marketing spending	Year 1 89% of sales Year 2 33% of sales Year 3 28% of sales Year 4+ 19% of sales	Year 1 68% of sales Year 2-4 37% of sales Year 5+ 24% of sales

(Source: IMS, Kline & Company)

Appendix D

Product Development Costs and Timing

Expectations for when a first-generation product will be available are based on a probabilistic model developed to analyze the current microbicide pipeline. The model combines the current number of compounds in each phase, the cost and time of each phase, and the probability of compounds completing individual phases. This generates an estimate of the investment needed to develop a product, an estimated time to launch, and the probability of success. (Duration of the phases of development, probabilities for success, and costs are based on industry averages and interviews with microbicide experts.)

At each phase of drug development, a compound has an expected probability of succeeding and moving on to the next phase, and a corresponding probability of failure. The probabilistic model uses Monte Carlo simulation to run the current pipeline through the development process five thousand times, yielding a probability distribution of potential outcomes and the resulting costs and time frame for launch. We used this model as the basis for our launch dates and input costs.

The model we developed estimates that it would require roughly US$775 million (US$267 in early-stage funding and US$508 in late-stage funding) in direct product development costs over five years for the entire portfolio of potential products. Typically, within a commercial pharmaceutical company, a portfolio committee manages the pipeline, making decisions about which compounds do and do not advance, priorities for investment, and relative funding levels. The microbicide field is relatively fragmented, with many smaller players; however, there is no common forum for rationalizing the portfolio of

Figure D1: Model inputs for time, probability of success, and cost for each stage of microbicide development

		Late discovery	Pre-clinical	Clinical phase 1	Clinical phase 2	Clinical phase 3	Registration	Total
Time	Average R&D time (month)(1)	12	12	22	30	60	6	
	Microbicides estimates (2) (month)	12-24	12-24	12-24	12-24	36-48	6-18	
	Model inputs	18	18	18	18	36-48(3)	12	Avg 126 mos (10.5 yrs)
Probability of success	Average of various industry benchmarks(1)	27%	30%	57%	47%	70%	87%	
	Median of various industry benchmarks	29%	36%	70%	50%	65%	91%	
	Microbicide estimates(2)	25%-35%	40%-60%	70%-80%	70%-80%	10%-40%	90%	
	Model inputs	30%	50%	75%	75%	25%	90%	1.9%
Cost (for one comp)	Development cost OECD countries(1)	$2M	$3M	$1M	$3M	$23M	$1M	
	Manufacturing	n/a	$1M	$2M	$3M	$5M	n/a	
	Total industry average	$2M	$4M	$3M	$6M	$28M	$1M	
	Microbicides estimates(2)	$1M-$3M	$2M-$3M	$1M-$3M	$1M-$5M	$30M-$50M	$1M	
	Model inputs	$2M	$2.5M	$2M	$3M	$43-49M(3)	$1M	Avg $56.9M

(1) RTI estimate
(2) Based on the mean derived from interviews with team members and biotech companies
(3) Model incorporated a range of inputs for phase III trial due to the significant proportion of development costs associated with phase III trials

Source: RTI Cost report, MMV business plan, Parexel R&D Sourcebook, interviews with team members and biotech companies

products. Every institution naturally optimizes decisions within its own budget and organizational constraints, but this may very well lead to a solution that is sub-optimal for the field as a whole. Depending on the degree of portfolio management across the field, the current estimates of funding could be significantly reduced.

The model also incorporated expected reductions in the cost of phase 3 trials, once the first product is successful. We assumed that the need for a three-arm trial—the product, a placebo, and a condom-only arm—would be eliminated after the successful phase 3 trial; and that subsequent trials would have only two arms—the product and the comparison. There may be additional opportunities to reduce development costs by running combination phase 3 trials that leverage the placebo and condom-only arm across two products. Selective combining of four product trials could save an estimated US$53million. Initial phase 3 trials being planned by the HPTN are pursuing this approach.

Appendix E

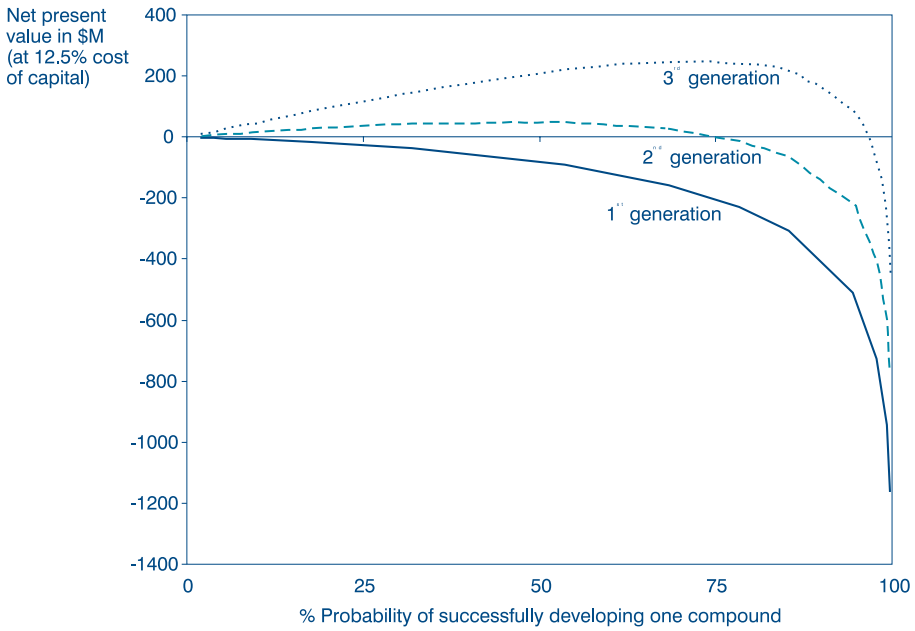
Return on Investment

Return-on-investment calculations weigh development costs against expected payouts from the perspective of one organization investing in microbicide development. Inflows and outflows of cash (cost of goods sold and sales and marketing expenses) for each year were calculated for each generation of product and each market scenario. These cash flows were then discounted by the probability of occurrence and by the cost of capital. When the NPV is positive, the project is a financially sound investment.

The group considered a range of discount rates for developers, including a representative pharmaceutical company and two different biotech scenarios. A pharmaceutical company was expected to have a discount rate of 12.5%. A biotech would likely have a higher discount rate—for example, 25%—due to the increased risk associated with such a business, as compared to a traditional pharmaceutical company. However, in a situation where a developer is receiving a subsidy from a donor or the public sector, their discount rate could be substantially lower, e.g., 5%.

For any developer, both development costs and expected return depend on the number of compounds put into development, and on the consequent probability of success. If a developer puts only one compound into late discovery, its development costs will be low, but its probability of success will be only 1.9%. To compensate for this, the risk-adjusted value of the market for that developer is reduced to only 1.9% of the total projected market. For each generation of product, returns were calculated across the range of probabilities for success from 0% to 100%. Calculations were based on achieving a 100% share of a US$0.9 billion market in the first generation; a 50% share of a US$1.5 billion market in the second generation; and a 33% share of a US$1.8 billion market in the third generation. Returns would be lower if the market were smaller or if the share were less. Higher discount rates yield less negative NPVs in certain instances of large planned future negative cash outflows because development costs are more certain than revenues.

Figure E1: Net present value (US$) for developing and marketing a microbicide, by probability of development success



Source: RTI Cost report, MMV business plan, Parexel R&D Sourcebook, interviews with team members and biotech companies

Table E2: Impact of discount rate on return-on-investment for subsequent generations of microbicides in different market scenarios (US$)

	Discount rate	Peak market size		
First generation		*Low ($20M)*	*Expected ($900)*	*High (N/A)*
	5%	($85M)	$18M	N/A
	12.5%	($65M)	($27M)	
	25%	($47M)	($38M)	
	IRR	N/A	7.0%	
Second generation		*Low ($20M)*	*Expected ($900)*	*High (N/A)*
	5%	($67M)	$185M	$435M
	12.5%	($56M)	$37M	$122M
	25%	($43M)	($22M)	($4.5M)
	IRR	N/A	18%	24%
Third generation		*Low ($20M)*	*Expected ($900)*	*High (N/A)*
	5%	$15M	$158M	$4,469M
	12.5%	($49M)	$117M	$428M
	25%	($43M)	($17M)	$30M
	IRR	N/A	14%	26%
One product on cusp of phase 3		*Low ($20M)*	*Expected ($900)*	*High (N/A)*
	5%	($40M)	$85M	N/A
	12.5%	($37M)	$33M	
	25%	($32M)	($2.8M)	
	IRR	N/A	23%	