Challenges of producing a drug primarily for use in developing countries: microbicides for HIV prevention

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Diseases largely confined to the developing world are under-researched in part because of the limited commercial potential for products used in these settings. The need for an alternative model has led to the establishment of product-development partnerships in which the intellectual property and technical expertise of the private sector is combined with both public and private funding to create a not-for-profit drug-development effort. The production of products for developing countries presents many other challenges, including product design, the design and conduct of clinical trials and registration with regulatory agencies. Once they have been registered, there are additional challenges to the marketing and distribution of such products. An overview of these issues is presented within the context of microbicides, which are self-administered vaginal products for the prevention of HIV transmission that, if proven to be efficacious, will represent one of the most promising strategies for combating the HIV/AIDS epidemic.

Keywords: developing countries, HIV/AIDS, microbicides, prevention, women

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It is estimated that only 10% of the world's medical research is devoted to conditions that account for 90% of the global disease burden [101]. This 10/90 gap, as it is known, highlights the need for greater resources to be devoted to the development of medical interventions for diseases that occur primarily in developing countries. In addition, there are diseases that, although present in both developed and developing countries, require different types of interventions in the different regions. This may be owing to differences in the prevalence of a disease, socioeconomic factors, risk:benefit profiles, limitations in healthcare infrastructures or other concerns. One such disease is HIV/AIDS.

It is estimated that almost 40 million people worldwide are now HIV infected [102], and that 63% of all adults and children with HIV live in sub-Saharan Africa. Increasingly, it is women who bear the greatest impact of the epidemic, particularly in developing countries. In sub-Saharan Africa, there are an estimated 13.3 million women living with HIV/AIDS, and they account for nearly 60% of infected adults in this region [102]. In several African countries, women aged 15–24 years are more than three-times more likely to be infected than men the same age [103]. In South Africa, one in four women is infected by age 22 years [1]. Globally, more than 17.7 million women are now living with HIV/AIDS [102].

Clearly there is an urgent need for female-initiated HIV-prevention options for developing countries, and one potential strategy for combating the epidemic is microbicides. Microbicides are self-administered products that that can be applied vaginally to impede sexual transmission of HIV. They can be formulated in a variety of ways, including gels, films, vaginal tablets, sponges and intravaginal rings. The potential additional benefits of including microbicides with other prevention methods are numerous. For example, abstinence is not a viable option for married women or for those who are victims of sexual violence. Being faithful in a monogamous relationship will not protect women whose partners are unfaithful. In reality, in many countries, being a married and monogamous woman is one of the highest risk factors for infection [2]. The consistent use of male and female condoms is highly effective in preventing infection [3,4,104], but in many developing countries women have little or no say in their sexual practices, and their male partners are often not amenable to the use of condoms [5]. In addition, the ability of a woman to bear children is often critical to her status within her marriage and within society [6], and neither abstinence nor condoms are practical options for these women.

There are currently two microbicides (Carraguard® and PRO 2000) in Phase III clinical trials and another two (BufferGel® and Tenofovir Gel) in Phase II/IIB clinical trials [105]. VivaGel™, Invisible Condom™, UC-781, dapivirine (TMC120) and Praneem are in Phase I or II trials, and a number of products are also in the preclinical stage of development.

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Traditionally, pharmaceutical development has been driven by the potential for meaningful financial returns offered by successful products in developed-country markets. Estimates of the cost of drug development vary widely [7], but there is no doubt that it is an expensive and time-consuming process. Given the costs involved, drug development is typically performed by large pharmaceutical companies. In cases where novel drug candidates are discovered by smaller organizations such as biotechnology companies or academic institutions, the needed financing to take a candidate from discovery to the market place is commonly obtained through venture capital or licensing agreements with established pharmaceutical companies.

By contrast, products developed primarily for developing countries may produce little, if any, profit. In addition to the lack of financial incentives, such efforts require a huge commitment of human resources, thus incurring a substantial opportunity cost. Therefore, even large pharmaceutical companies with corporate social-responsibility programs have historically invested relatively little in products primarily for developing countries.

The need for an alternative development model for products aimed primarily for developing countries led to the creation of 'public/private partnerships', or 'product-development partnerships'. The principle of this model is to draw upon the intellectual property and technical expertise of pharmaceutical and biotechnology companies and academic institutions, and combine them with funding from public and private sectors such as foundations, governments and nongovernmental bodies in a nonprofit environment. Such partnerships provide a means for private companies to contribute to the development of new products (e.g., by providing access to compound libraries), while limiting costs and development-related risks. In return, product-development partnerships have sought licensing agreements containing provisions that include intellectual property rights to support the future supply of successful products at affordable prices.

Product attributes for developing countries

A microbicide that is not used correctly and consistently will not be effective in preventing infection. Therefore, it is crucial to determine the product characteristics that will support good product adherence. These characteristics can include the mode of delivery, appearance, smell, feel, ease of use and secondary therapeutic activities, such as contraceptive properties and activity against other sexually transmitted diseases. Developers should not assume that a product with characteristics that make it appealing to one population will be similarly acceptable to other populations. Therefore, it is important that market-research studies be conducted in populations where the product will ultimately be marketed to establish what the appropriate characteristics should be.

In fact, variations in cultural preferences and sexual practices suggest that no single type of microbicide product will be universally acceptable [8]. Therefore, alternative delivery formulations are being investigated, including gels, films, intravaginal rings and solid-dosage forms such as fast-dissolving vaginal tablets, as well as novel polymers and biologically triggered drug-release approaches. These formulations are being developed with the goal of providing sustained protection over days to months.

A drug product must also be stable under conditions that are feasible for those regions in which it is to be marketed. Many developing countries are subject to high temperatures, while also having weak distribution networks and cold chains. Therefore, products requiring refrigerated storage may not be practical for such markets.

Clinical trials

The safety and efficacy of a pharmaceutical product may vary in different ethnic groups [9]; therefore, it must be tested in individuals representative of the populations where the product will ultimately be marketed. For products intended for developing countries, this means addressing the challenges of conducting large clinical trials in regions where clinical research centers may be scarce and resources limited.

Informed consent is an essential component of ethical clinical trials and is required by international guidelines [10]. Informed consent is a process that is continuously reinforced throughout the trial to ensure that participants are fully aware of the risks and benefits. Because of the potential that some trial-related benefits, such as financial compensation or access to health services for participants, may be regarded as undue enticements in resource-poor settings, guidance is sought from local ethical-review committees and community advisory groups to ensure that trial benefits are appropriate.

It is important that the community in which the trial takes place fully understands and supports the trial. Without such informed support, false perceptions or information may easily be propagated, trial participants may face discrimination, high dropout rates may occur and trials may even close [11]. Investigators routinely meet with community advisory groups, key opinion leaders and the media to maintain open channels of communication throughout the trial to keep the community and its leaders informed of progress.

Clinical trials in developing countries need to be conducted to high ethical standards [11,12]. In the case of microbicide trials, the standard of care for participants currently includes the provision of HIV prevention, diagnostic and treatment services [13]. As health-service capacity and access to medicines is limited in many developing countries, forward planning and partnerships with local stakeholders are necessary to ensure these obligations are met, particularly those that extend beyond the duration of a trial.

Regulatory issues

Once the testing of a pharmaceutical product has been completed, it must be approved and registered by the drug regulatory authorities in those countries in which it is intended to be marketed. It is important to understand early in the development process what the target countries are and what the registration procedure and requirements will be, as these factors may influence the development strategy.

For drugs that are intended primarily for use in developing countries, this can be complicated because the regulatory resources and experience in these regions are generally limited and the appropriate pathways may be unclear. This is particularly the case for microbicides, which represent a new class of pharmaceutical product. The review of regulatory dossiers for first-in-class products requires a level of resources that authorities in developing countries may lack [14]. New pharmaceutical products in developing countries are often approved on the basis of prior approvals and use in the USA or Europe [15].

However, obtaining registration of a microbicide first in Europe or the USA may be affected by the context of its use in the population. In developed countries, where the risk of infection is low and treatment for infected individuals is readily available, a risk:benefit assessment of a microbicide may indicate that there is insufficient benefit to support registration. By contrast in developing countries, where the risk of infection is high, the risk:benefit ratio is likely to be much more favorable.

Article 58 of Regulation (EC) No. 726/2004 established a mechanism whereby the European Medicines Agency (EMEA), in cooperation with the WHO, is able to give a scientific opinion on certain medicinal products intended exclusively for markets outside the EU) [16]. Developing-country authorities can then use the scientific opinion as the basis on which to decide whether a drug should be approved. However, to date, this procedure has only been used three times, and in all cases this was for antiretroviral products that are duplicates of products already approved and used in the EU [106–108], this new mechanism appears to offer the most promising pathway for the product registration of microbicides in the developing world.

Alternative processes, including the Conditional Marketing Authorisation (CMA) established by the EMEA under Regulation (EC) No. 726/2004 [109], and the Notification of Compliance with Conditions (NOC/c) instituted by Health Canada [110], may also be useful for the registration of microbicides. Both processes reduce the burden of clinical data required for an initial registration, providing that a commitment is made to the provision of further data postregistration. However, the utility of these procedures has yet to be established for products for developing countries.

Introduction, use & future access

Historically, new technologies are developed for launch in high-value, predictable, developed-country markets [1101. Access for developing countries often follows many years later, if at all. Health systems are weak, human resources limited and financing is insufficient and unpredictable. In sub-Saharan Africa, less than a third of people have regular access to essential medicines [17], and only one in five people in developing countries currently have access to HIV-prevention services [112]. A new paradigm for product introduction will be required if the potential of future microbicides to reduce HIV-transmission rates in developing countries is to be realized.

Successful product introduction will require an understanding of the potential role of microbicides as part of HIV/AIDS programs in different countries. This will depend both on the characteristics of microbicides and also on country-specific contexts, including the nature of the

epidemic, demographic factors and social and cultural practices. Policy makers will need a range of evidence to inform their decisions on if, when and how to introduce future microbicides in their own countries. In addition to robust clinical-trials data, studies to model the potential impact and cost–effectiveness of different microbicide strategies in specific country settings will be needed. International technical agencies, such as the WHO and UNAIDS, will have a crucial role in providing technical guidance and recommendations.

As important as technical evaluations of potential impact and cost–effectiveness are the practical issues of ensuring that dependable product supply, financing, appropriate distribution infrastructure and trained human resources are in place to reliably and affordably deliver microbicides and supporting programs to women in developing countries. This will require considerable forward planning and the mobilization of a wide range of public, private and civil society stakeholders. Public health and business investment cases will be needed to persuade potential funders and partners to support microbicide introduction. Most important is the need for strong political commitment by developing countries' policy makers, donors and international agencies to support and fund microbicide introduction as part of HIV-prevention programs.

In addition to these technical, health-system and political requirements, it is essential to build understanding of, and generate demand for, microbicides among women and their partners. Market research to design microbicides that meet women's needs must be an integral part of the product-development process. As the characteristics of products that will be approved become clearer, marketing strategies must be developed that are relevant to the social and cultural contexts into which microbicides will be introduced. The prevalence of HIV-related stigma and gender inequality require particular attention in positioning, branding and marketing strategies and program development.

Conclusion

There are many challenges associated with the development of drug products intended primarily for the developing world. Successfully overcoming these challenges requires the establishment of new paradigms for funding, research and development, clinical research, product registration and distribution/commercialization. This is clearly demonstrated in the

Executive summary

Funding

- Diseases of the developing world are under-researched because products largely limited to these markets may not be commercially viable.

Product attributes for developing countries

- In order to be successful, pharmaceutical products for developing countries must be designed to meet the specific needs and preferences of the regions in which they will be marketed.

Clinical trials

- Conducting clinical trials in populations in developing countries requires overcoming the complexities of working with limited resources, maintaining high ethical standards and involving the local communities.

Regulatory issues

- Limitations in regulatory resources present challenges for obtaining approval to conduct clinical trials and for product registration in developing countries.

Introduction, use & future access

- The logistical problems of marketing and distributing products in these markets must be addressed well in advance of product launch.

Conclusion

- New paradigms for funding, research and development, clinical research, product registration and distribution/commercialization need to be established.
- Product-development partnerships provide a means of combining the intellectual property and technical expertise of research organizations with funding from public and private sectors for the development of affordable products to address neglected diseases in developing countries.

field of microbicides for prevention of HIV infection in women. In order to efficiently address these issues, close collaboration among many parties, including scientists, regulatory authorities, policy makers, funding organizations, community members and activists, is necessary. Product-development partnerships provide a means of addressing some of these issues, by combining the intellectual property and technical expertise of research organizations with funding from public and private sectors, for the development of affordable products to address neglected diseases in developing countries.

Future perspective

In the next 5–10 years, it is likely that the conduct of clinical trials in developing countries will become more commonplace. More clinical research centers will be established and the experience gained by the centers will make the process of conducting trials in these regions more streamlined. The process for registration of products for these markets should also become better defined.

For the microbicide field, the results from ongoing trials will be available. These will largely define that the direction the field will take.

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