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REPORT OF A MEETING ON THE DEVELOPMENT
OF VAGINAL MICROBICIDES FOR THE PREVENTION
OF HETEROSEXUAL TRANSMISSION OF HIV

GENEVA
11-13 NOVEMBER 1993



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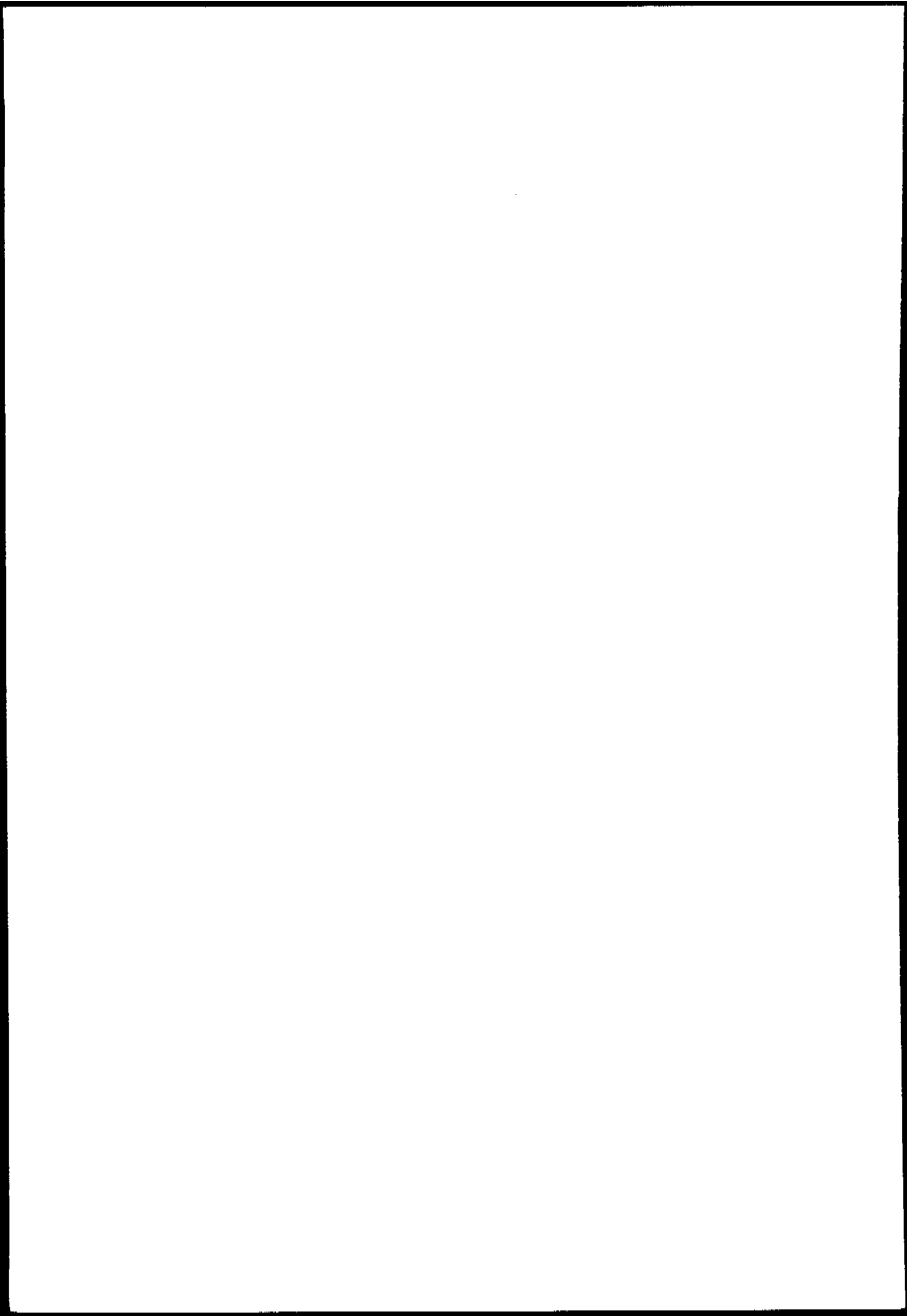
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Geneva, 11-13 November 1993

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A meeting on the development of vaginal microbicides was held from 11 to 13 November 1993 at the World Health Organization (WHO), Geneva. The objectives of the meeting were:

- to increase awareness of the need to develop new vaginal microbicides;
- to review the current scientific knowledge and regulatory requirements related to the development of vaginal microbicides;
- to identify outstanding issues for research and development of such products;
- to define a sound and rational approach to the clinical safety and efficacy testing of vaginal microbicides.

I. THE NEED FOR NEW OPTIONS TO PREVENT THE HETEROSEXUAL TRANSMISSION OF HIV

There is an urgent and worldwide need for an antimicrobial agent for vaginal use to reduce/prevent the heterosexual transmission of HIV. The World Health Organization estimates that, as of late 1993, 15 million adults and children worldwide had already been infected with the virus, leading to an estimated 3 million cases of AIDS.

Heterosexual intercourse is becoming the predominant mode of HIV transmission in most countries of the world. As of late 1993, an estimated 75% of cumulative HIV infections had been acquired heterosexually. Heterosexual transmission accounted for up to 90% of new infections in 1993. Unless the rate of spread of the pandemic can be slowed, it is projected that the cumulative number of HIV infections will reach 30 to 40 million by the year 2000.

Over the last decade the HIV epidemic has increasingly affected women. In 1983, 80% of those infected were men, but by 1993, 50% of new infections worldwide occurred in women. An increase in the number of infections in young women of childbearing age is already having an impact on rates of HIV infection in children.

The development of new options for preventing the heterosexual spread of HIV in both developing and industrialized countries is becoming a major research priority as the proportion of new infections contracted through heterosexual sex continues to rise. One of the key criteria for a new prevention method is that women be able to control its use.

Current efforts to decrease the spread of HIV infection consist primarily of widespread condom promotion, the promotion of other safer sex practices, and the prevention and treatment of other sexually transmitted diseases (STD). Although individual projects have shown that the incidence of HIV infection can be reduced in this way, at a global level the epidemic continues to spread.

Condoms are a highly effective means of preventing HIV transmission and their use is increasing in many parts of the world. However, even where HIV prevalence is high, condom promotion projects, involving constant condom availability and regular counselling, have been unable to attain levels of use above 50% to 60%. In many countries, significant numbers of heterosexuals have two or more sexual partners each year but never use condoms. Among those who do use condoms, use is often inconsistent, even with new partners.

Women are biologically more vulnerable to most STD than men. Furthermore, in many societies, women's inferior status and lack of power in relation to men exacerbates this vulnerability. All currently available methods for protecting women against infection require the cooperation of their male partner. This cooperation is not always forthcoming and women in many parts of the world are not in a position to control or negotiate safer sex, including use of a condom. An HIV prophylactic which is under women's control and which, ideally, can be used without their partners' knowledge or consent, is therefore urgently required.

The female condom is becoming more widely available. This is a welcome addition to current protection methods and may prove an acceptable alternative to the male condom, for some women. However, it does not fully meet the requirements that have been identified – it is relatively costly, not always easily accepted, and requires the partner's consent.

A vaginal microbicide could meet these requirements. In order for women to exercise control with this method, the microbicide would have to be more or less undetectable by the male partner. Experience from family planning shows that women are willing to use contraception without their partner's knowledge. Furthermore, it has been shown that compliance is better, and effectiveness therefore enhanced, with contraceptive methods which are *strictly* under women's control. It is likely that the same would be true for HIV prophylaxis – provided that women are aware that their own survival and their family's well-being are at stake.

A vaginal antimicrobial agent offers a number of additional advantages over the condom. For example, a long-acting microbicide could be inserted well before intercourse and would not, therefore, interfere with spontaneity. Furthermore, as a microbicide is not a physical barrier, it would not diminish intimacy or interfere with sexual pleasure. Other factors determining the acceptability and value of a vaginal microbicide to women and men include the following: ease of application, removal and disposal (the product should not be messy to use); and stability at high temperatures and humidity.

Women's needs and perspectives must underlie the development of a female-controlled method of HIV prevention. It may be necessary to develop a range of products which will be acceptable in different circumstances and cultural contexts. Research into the acceptability of a variety of vaginal microbicides to suit different criteria in different cultures, should begin at an early stage of development. For example, most cultures place a high value on motherhood and indeed women's status in many cultures depends on the number of children they have borne. One of the tragedies of AIDS is that in fulfilling their reproductive expectations, women risk not only HIV infection due to unprotected vaginal intercourse, but also HIV transmission to the child. Women may wish to protect themselves against HIV but

not against pregnancy. An important acceptability criterion for some women may be that the vaginal microbicide should not impair fertility.

New technology by itself will not empower women to protect themselves. In order for women to take control of, and protect their sexual health, they may have to confront deeply entrenched, stereotypical views of the role of women in sexual relationships. Prevention programmes promoting the use of vaginal microbicides will need to address these issues sensitively, providing appropriate education, accurate information and ongoing support to women.

For a vaginal microbicide to have any measurable impact on the HIV pandemic, and for reasons of social justice, the product must be accessible to women worldwide, in both developing and industrialized countries. The ideal product should be inexpensive and easily produced in large quantities using technology available in all parts of the world.

Products already licensed in some countries for vaginal use as a spermicide have been shown *in vitro* to have activity against HIV and other sexually transmissible pathogens. These include nonoxynol-9, menfegol, octoxynol-9 and benzalkonium chloride. These compounds act by disrupting membranes. There is some evidence of *in vivo* efficacy in reducing the incidence of some other sexually transmissible pathogens. For example, reductions in transmission of *Neisseria gonorrhoeae* of 24% to 87% have been reported. It has not yet been shown that these compounds reduce sexual transmission of HIV as no data from properly randomized, controlled efficacy trials are available.

There is, however, growing evidence from several studies that, when used frequently or at a high dose, these compounds may produce vaginal and cervical lesions or inflammation. Such lesions could increase the risk of HIV transmission. Lesions may not only be due to the active compound. One safety study found a high percentage of lesions in the group using a matching placebo, implying that the vehicle may also be harmful to the cervical and vaginal mucosa.

New products which can be used frequently without adverse effect are needed and their development is an urgent priority. However, it may take 5 to 10 years to bring a new product to the market. In parallel, studies should be conducted to evaluate the clinical safety and efficacy of existing licensed products against HIV alone and in combination, and in various formulations, to provide data on their optimal use.

Rapid progress in the development of a microbicide will only be possible through collaborative international effort, involving private and public sectors, research institutions, and regulatory bodies.

The pharmaceutical industry can contribute expertise in production, distribution and marketing of therapeutic agents worldwide. Industry will require a reasonable return on investment and one aspect of the advocacy role of public sector organizations is to outline the large potential market for a vaginal microbicide. The pharmaceutical industry recognizes the benefits of collaboration with the public sector in clinical studies, for example, in terms of

access to suitable trial populations. In addition, WHO and other agencies can provide the organizational infrastructure to undertake multicentre clinical trials under Good Clinical Practice conditions, thus generating data that can be used for regulatory purposes, particularly from trials conducted in developing countries.

The regulatory authorities can accelerate the process and encourage industry to proceed in the development of a promising product, by producing clear guidelines for preclinical and clinical data requirements. In view of the urgent need that has been identified for a vaginal microbicide, these applications should receive priority review by regulatory agencies.

II. THE SCIENTIFIC AND TECHNICAL BACKGROUND

Summaries of available information relating to the development of a vaginal microbicide to prevent heterosexual transmission of HIV were presented. The session covered vaginal ecology, mechanisms of sexual transmission of HIV, mechanisms of infection with other sexually transmissible agents, laboratory and animal models for the evaluation of candidate microbicides, review of candidate microbicides and formulations of microbicides and vaginal drug delivery systems, and the design of clinical trials for the evaluation of the safety and efficacy of microbicides.

1. Vaginal ecology

Normal vaginal flora offer resistance to infection – the genital candidiasis which can occur during antibiotic therapy is the commonest proof of this. In the healthy vagina, pH is maintained at about 4 to 4.5 by hydrogen peroxide-producing lactobacilli. This low pH may offer some protection since the viability of HIV is reduced at such levels of acidity. Changes in vaginal flora may lead to the acquisition of organisms such as *Gardnerella vaginalis*, *Chlamydia trachomatis* and *Mobiluncus* spp. and conditions such as bacterial vaginosis. Bacterial vaginosis may have sequelae, for example an increased risk of obstetric problems and intra-uterine infections, and possibly a greater likelihood of upper reproductive tract infections which may lead to infertility. There have been reports that the use of nonoxynol-9 results in destruction of lactobacilli and increases colonization with *Escherichia coli*.

2. Mechanisms of sexual transmission of HIV

Much remains unknown about the mechanism(s) and point(s) of entry for heterosexual transmission of HIV and the many factors which might affect individual susceptibility and infectivity. Research on these topics will provide useful information for the development of a vaginal microbicide.

Oral sex is a frequent practice amongst both heterosexuals and homosexuals and there is some evidence that anal sex is at least an occasional practice amongst heterosexuals. (About 25% of sexually active women in the United States of America practise anal sex occasionally.) Unless a microbicide has been shown to be safe for oral and anal use, it will have to be clearly labelled "for vaginal use only".

The vaginal environment is complex and many factors may affect the likelihood of HIV transmission. For example:

- changes in vaginal flora
- infection with other STD
- vaginal pH
- amount of secretory IgA (local immunity)
- amount of cervical mucus (neutral pH)
- menstruation
- condition of the epithelia
- extent of cervical ectopy
- endogenous and exogenous hormones
- drugs
- use of contraceptive methods.

Age affects susceptibility to infection, as changes in endocrine function influence the genital mucosa. The vaginal epithelium is thinner in prepubescent girls and post-menopausal women. Cervical ectopy, which may increase the risk of infection, is greatest during adolescence.

Questions remain about which region of the female genital tract is the most important point of entry for HIV infection. Simian immunodeficiency virus (SIV) can be transmitted across intact genital epithelia of rhesus macaques, and hysterectomized females have been infected by this route. HIV can infect intact vaginal and cervical mucosae but the presence of epithelial disruption probably increases the risk of infection. The vulva is also a potential point of entry for infection, particularly in the presence of ulcers.

In women, virus is probably shed from both the vagina and the cervix, although HIV is more frequently detected in cervical than vaginal secretions. HIV has been identified in lymphocytes, monocytes/macrophages and epithelial cells in cervical tissue. In female macaques, virus is found in the mucosa and submucosa of both the cervix and vagina and the number of SIV-infected cells is raised at sites of inflammation.

It is unclear whether HIV is transmitted primarily as cell-free or cell-associated virus and the major route may vary according to circumstances. Cell-associated virus could be transmitted through syncytium formation or through release of virus as cells die. Cell-associated and cell-free SIV is present in the semen and vaginal fluids of infected macaques.

Reported rates of HIV detection in genital secretions and semen (in people known to be HIV-infected) are generally about 30%. This may indicate low levels of virus in genital secretions, intermittent shedding or problems with detection methods in genital fluids. The severity of HIV disease may affect the amount of virus in genital tract secretions although this has not been demonstrated unequivocally. Some studies have suggested that anti-retroviral therapy decreases viral shedding.

Semen contains CD4-positive lymphocytes and monocytes/macrophages which are important carriers of HIV. Virus is more frequently cultured from semen in samples with elevated numbers of white blood cells. Cell-free HIV is probably also important – studies in macaques have shown that cell-free SIV can cause infection.

A question to address, given the desirability of a microbicide which is not also a spermicide, is whether HIV infects or attaches to sperm. The evidence is equivocal. Other sexually transmissible pathogens have been described attaching to spermatozoa, and spermatozoa have been shown to express HIV gp120 receptors. However, a recent study has been unable to detect virus on sperm. Successful insemination without seroconversion of 10 women with processed semen from HIV-positive men has been reported, also suggesting that HIV does not attach to sperm.

3. Infection with other sexually transmissible pathogens

Infection with sexually transmissible pathogens other than HIV may have adverse sequelae such as pelvic inflammatory disease, infertility, adverse outcomes of pregnancy, and cervical cancer. For all compounds in development, it is important to ensure that reducing the transmission of HIV does not increase the efficiency of transmission of another pathogen.

Studies have shown that infection with other STD can increase both susceptibility to HIV infection and infectivity. Ulcerative STD have been shown to increase the risk of HIV infection by a factor of 10, and diseases causing genital discharge increase the risk 3 to 5 times. The genital discharge diseases are more prevalent and so may be more important in increasing population attributable risk. Thus, an agent which was directly active against HIV and against other STD could also indirectly reduce HIV transmission through decreasing the incidence of other STD.

Chlamydia. This is perhaps the most prevalent sexually transmissible pathogen in most parts of the world including developing countries. The organism attaches to the cervical epithelium within 5 minutes of entering the cervix and so an effective microbicide would need to be fast acting. Infection produces erythema and a mucous discharge and CD4+ cells are recruited to the site.

Gonorrhoea. On average, an ejaculate contains 10^5 viable organisms. Efficient killing would be necessary because only 250 to 1000 organisms are required to infect a woman. As well as a white mucopurulent exudate, the woman has a red and irritated cervix. Since the late 1970s, more and more strains of *Neisseria gonorrhoeae* have become penicillin-resistant, suggesting that microbicide-resistant organisms could become a problem in the future.

Trichomoniasis. Women have both cervical and vaginal lesions. There are fewer data on increased susceptibility to HIV infection, but it probably arises because of the presence of inflammation.

Chancroid, syphilis, herpes simplex. All have been implicated in promoting HIV transmission, both through increased virus shedding and recruitment of CD4-positive target cells to the sites of ulcers. A vaginal microbicide would protect the vagina, cervix, and penis but would not protect against infections occurring at extra-genital sites.

Human papillomavirus. The virus is not enveloped and so it may be possible to develop agents which attack the viral capsid but do not attack cell membranes.

4. Laboratory models for evaluation of candidate microbicides

Assays have been developed to measure *in vitro* the pH stability of the virus, the selectivity index of candidate microbicidal agents and the activity of agents against cell-free virus. The latter is achieved by attaching virus to a microtitration plate by poly-L-lysine. After treatment with candidate microbicide, the compound can be washed off and target cells added. Following incubation, the number of syncytia in the cell monolayer is a measure of the amount of infectious virus present.

In these assays, the virus was found to be less sensitive to low pH than has previously been reported. Virus was stable for 2 hours at pH 5 to 8. There was no reduction in the amount of infectious virus following incubation for one hour at pH 4.5 although the amount was reduced by 50% after 2 hours. The virus was more sensitive to lower pH, with a half-life at pH 3.5 and 4.0 of 6 minutes and 10 minutes respectively. Maintaining low vaginal pH is an important consideration in the development of a vaginal microbicide.

The selectivity index of anti-HIV activity compared to cytotoxicity was determined in cell culture for nonoxynol-9, octoxynol-9, benzalkonium chloride and chlorhexidine. In each case, it was less than 10. This low selectivity is to be expected, as these compounds act by membrane disruption. It is not clear how relevant cytotoxicity in cell culture will be to safety *in vivo* as other factors may play a role locally. For example, cells of the vaginal and cervical mucosa may be protected to some extent by the mucus. No specific anti-HIV activity was found in cervical mucus. Seminal plasma was found to inhibit HIV markedly. The reasons for this inhibitory activity are being investigated currently.

5. Animal models for evaluation of candidate microbicides

Three animal models have been used to test the ability of nonoxynol-9 to protect against sexually transmissible viruses: herpes simplex virus (HSV)-2/mouse, feline immunodeficiency virus (FIV)/cat, the simian immunodeficiency virus (SIV)/rhesus macaque. The results are summarized in Table 1. It has been shown that the presence of seminal plasma reduces the dose of SIV required to infect female macaques. This may be because the neutral pH buffering capacity of seminal fluid protects the virus from the low pH of the vagina.

Studies are currently under way to assess whether chronic vaginal exposure to nonoxynol-9, which produces inflammation in macaques, increases the efficiency of SIV transmission. The effectiveness of products which lower vaginal pH in reducing SIV transmission is also being investigated in macaques.

6. Review of candidate microbicides

A wide variety of agents exist which may have more selective anti-HIV activity than the licensed spermicides. These have potential for development as antimicrobials for vaginal use to prevent HIV transmission. Agents need not necessarily be virucidal but could target early stages in HIV infection. For example, inhibitors of virus adsorption, inhibitors of fusion and uncoating or reverse transcriptase inhibitors could be considered. Agents which cover the HIV glycoproteins and prevent binding to the CD4 receptor would also inhibit syncytium formation. Some of these agents are in clinical use already but not topically in the vagina: others are anti-HIV agents whose development has been abandoned because of systemic toxicity, poor oral absorption or rapid emergence of resistance. Good communication between research institutes and the pharmaceutical industry is needed to ensure that existing compounds with potential for vaginal anti-HIV use are not overlooked.

A summary of types of agents which can currently be considered is presented in Table 2. A potential strategy would be to combine agents with different modes of action to produce a series of chemical barriers to HIV infection. In combining these agents in a formulation, their widely differing physicochemical properties should be considered. In addition to their anti-HIV activity, a number of these agents have high viscosity and so would aid retention of the product in the vagina. However, their ability to spread and cover the cervical and vaginal epithelia must be assessed.

In general there is likely to be an inverse correlation between specificity and toxicity. Compounds with specific anti-HIV activity are likely to show less toxicity than those with broader antimicrobial activity. The disadvantage of more specific compounds is that they are not active against other STD. Furthermore, they may be more likely to lead to the development of viral resistance.

7. Formulations of microbicides/vaginal drug delivery systems

Safety issues applying to the active compound also apply to the formulation. There is considerable evidence that infection with any of several other STD increases the probability of HIV infection. Thus, a formulation which inhibits infection with other STD-causing organisms would be very desirable. Conversely, one which enhances infection with another STD would be problematic.

Irritation to the genital tract must be avoided – even asymptomatic micro-ulcerations could be points for HIV entry. As the point(s) of HIV entry are not yet known, the product must be designed to coat the entire lower genital tract.

Among pharmaceutical considerations, compatibility with latex (and with other materials used in physical barrier methods) and stability at high temperatures are very important. Another important consideration in formulation is cost. Among those at highest risk of HIV infection are some of the poorest people in the world. The product, therefore, must be inexpensive. Acceptance of the product by the local population is essential and is likely to vary considerably between countries and cultures.

Gels, creams and foams. These can be formulated with a variety of properties. For example, it is possible to make a cream which feels like a gel. Foams give a good coating and are generally well accepted but they are more costly to produce than gels or creams because they need to be dispensed from a can.

Vaginal suppositories and ovules. These are designed to disperse in an aqueous environment or by the action of pH or enzymes. Suppositories can be hard or soft. The need to position the suppository correctly during insertion, and the time taken to dissolve and coat the vagina and cervix are potential drawbacks. Foaming suppositories which give a more rapid coating can be made, but this causes a burning sensation which some women find unpleasant.

Sponges. A vaginal sponge creates an extra physical barrier and thereby provides excellent protection for the cervix – a likely point for HIV entry. However, sponges can cause irritation and discomfort. As they are individually wrapped, they tend to be expensive.

Vaginal ring. The vaginal ring is in phase III efficacy trials as a hormone delivery system. It is a sustained delivery device and so its use is dissociated from intercourse. The device can be left in place and protect the user for several months, provided it contains a sufficient quantity of the active ingredient. Such a device would require an active ingredient that is effective at relatively low concentration.

Microspheres and microcapsules. These are slow-release products and so could be used in advance of coitus. There have been difficulties obtaining consistent release rates in repeat batches. Those which are currently available are hard and so could cause discomfort, but it should be possible to develop softer formulations.

Hydrogels and hydrofilms. These formulations absorb water and release the active ingredient when inserted in the vagina. An advantage of the hydrogel and the hydrofilm is that they can be made very small. Different versions of these delivery systems can be designed with different rates of release and other properties.

8. Issues in clinical trial design

Safety

Safety studies should be carried out in populations at low risk of HIV infection. It cannot be assumed that safety in a low-risk population is equivalent to safety in a high-risk population, who may for example have a higher prevalence of other STD. For this reason, full safety evaluation must be included, at least in the early stages, in efficacy trials.

There are issues to consider about whether dose frequency should be fixed or related to frequency of sexual acts, which may be more representative of user safety. Dose frequency in safety trials should relate to both high and low frequency use. Ideally safety trials should include a vehicle-only placebo group and a no-treatment group to distinguish between active compound and vehicle effects.

Careful colposcopic evaluation of both the vagina and cervix is essential because studies have identified vaginal and cervical lesions in women who reported no symptoms. Standardized reporting of lesions must be adhered to. It will be necessary to consider what would be an acceptable level of toxicity, taking account of the risk/benefit for women (in terms of acquiring or avoiding infection) of using the product. Clinical trials of existing spermicides may give a better understanding of the clinical significance of lesions observed.

Efficacy

It will be necessary to carry out efficacy trials in high-risk populations in order to achieve sufficient end-points. All trial participants must be counselled to protect themselves from infection by using condoms and condoms must be supplied to all trial participants. Reported condom use will need to be included as a variable in the analysis.

The sample size will need to be very large and its determination should allow for a high rate of loss to follow-up. There is likely to be an association between compliance with microbicide use and condom use and this will also be a factor in the sample size calculation.

Efficacy trials will be expensive and so it will only be possible to carry out a small number. For this reason, criteria need to be agreed to select the most promising compounds to go forward to phase III trials. Efficacy trials should recruit low frequency as well as high frequency users. Toxicity will have to be weighed against the protective effect of the product, for high and low frequency users, in high and low prevalence areas, separately.

III. REGULATORY REQUIREMENTS FOR VAGINAL MICROBICIDES

Before microbicial products can be marketed for the prevention of transmission of HIV and other STD, regulatory requirements must be satisfied. The regulatory bodies of the European Community and the United States aim to facilitate bringing such a product to the market as rapidly as is consistent with the need to demonstrate safety and efficacy.

1. Regulatory procedures in the United States

New drugs have to go through the new drug application (NDA) process. Safety and efficacy must be determined in adequate and controlled trials conducted according to standards specifically defined in regulations.

Generic drugs must demonstrate bioequivalence with an existing licensed drug. Standards for demonstrating bioequivalence have not been developed for topical agents.

Since 1962 it has been a requirement that over the counter (OTC) products demonstrate efficacy as well as safety. Products already available were reviewed and those generally thought safe and effective were classified as category 1. For category 1 agents, monographs are published and new products must be manufactured to the standards of the monograph. Nonoxynol-9 and octoxynol-9 are category 1 agents. The monograph on vaginal

spermicides is shortly to be published and will identify when an NDA is required. Although new products are generally approved initially as prescription drugs, it is possible to obtain an immediate OTC licence.

New products containing nonoxynol-9 or octoxynol-9 would be treated as new drug applications, despite being category 1 OTC agents, because contraceptive experience shows that efficacy is highly dependent upon formulation. Full animal toxicity studies would not be required but data on vaginal irritation would be helpful because levels which are acceptable for contraception may not be for STD prophylaxis. Data obtained from studies outside the United States will be acceptable in support of a new drug application.

As the precise dataset needed for regulatory approval will be discussed for each New Drug Application, it is advisable to start discussions with the Food and Drug Administration at an early stage in product development.

2. Regulatory procedures in the European Community

The legal framework for the regulation of medicines in the EC is laid down in the *Pharmaceutical Directives*. Regulatory requirements are detailed in a series of published Guidelines, part of the ongoing work of the EC Committee on Proprietary Medicinal Products (CPMP). These guidelines are not legally binding but any departure from them needs to be justified. Of particular relevance to a vaginal microbicide are guidelines on the following subjects: in the preclinical area, pharmacotoxicity and non-clinical local tolerance testing; and in the clinical area, good clinical practice, drugs for long-term use, biostatistical methodology and data sheets for antibacterial medicinal products.

The *Notice to Applicants* provides guidance on the presentation of licensing applications within the EC. One important aspect is the requirement for expert reports. The clinical expert report should include an analysis of the clinical problem, discussion of compliance of the application with EC guidelines, evaluation of the risk/benefit ratio, and justification for statements in the summary of the product characteristics.

Under current EC procedures, licensing applications can be made in three ways. At present, marketing authorization is granted on a national basis, and an application may be submitted in one EC country alone. If a product is already licensed in one member state, a multi-state application may be made to extend the licence to two or more member states. Alternatively the concertation procedure allows simultaneous consideration of an application in all or a number of member states, with one state acting as rapporteur. This route is mandatory for biotechnology-derived products and is also available for medicines which represent a significant therapeutic advance. A new vaginal microbicide for the prevention of transmission of HIV would fall into this category.

Major changes in the regulation of medicines in the EC are imminent. Recent "Futures Systems" legislation replaces current arrangements and sets up two new licensing procedures: a centralized procedure based on the concertation procedure and operative from 1995; and a decentralized procedure similar to the multi-state procedure, fully operative from 1998. A

European Medicines Evaluation Agency (EMEA) is being established which will handle all centralized applications from 1 January 1995. The new systems embody tight deadlines for decision-making (a CPMP opinion within 210 days for a centralized application) and an important new provision for binding arbitration to resolve differences between member states.

EC regulatory requirements

The overall data package in support of an application for a vaginal microbicide will depend on whether the active ingredient is a new active substance or whether it is already in use in a licensed product. An abridged application may be made under certain circumstances if the product is essentially similar to another licensed product. There are various types of abridged applications known as "hybrid" abridged applications. Each case needs to be considered individually, and early contact with the regulatory authorities is recommended to clarify the nature of the data package required.

Preclinical data

Quality issues

Both the active ingredient and the vehicle are directly linked to the safety and efficacy of a vaginal product. (For complex polymers, there is no requirement for a single product, but the mixture must be characterized.) An important issue is compatibility with latex rubber used in barrier contraceptive devices, for example, condoms and diaphragms. Data will be required to show that the formulation has no effect on the integrity or performance of the barrier. The clinical data submitted should relate to the product proposed for marketing since clinical safety and efficacy cannot be extrapolated from one formulation to another.

Pharmacology and toxicology

Information should be provided on local concentration/time relationships, taking into account the effect of dilution on biological fluids. Microbial activity may be affected by changes in pH and viscosity of female genital secretions and semen.

Local tolerance testing should include an assessment of the potential for irritation, sensitization and hypersensitivity of all surfaces which could be exposed to the product, including the rectal and oral mucosae.

Systemic absorption, through the vaginal (oral or rectal) mucosa should be monitored and target organ toxicology evaluated where indicated. Absorption via inflamed or broken mucosa should also be considered. Reproductive toxicity needs to be assessed in view of the possible use of the microbicide either inadvertently or deliberately during pregnancy. Mutagenicity and carcinogenicity studies will be required for a new active substance and possibly for products which are the subject of abridged applications.

In vitro studies need to be carried out to predict efficacy in conditions that mimic the vaginal environment. Until the mechanism of heterosexual HIV transmission is more clearly understood, animal model efficacy data may be needed before proceeding to efficacy trials. Where the proposed indication relates to a life-threatening disease, studies in animal models may be conducted in parallel with phase I clinical trials.

Clinical data

Phase I

Phase I studies should be carried out in a population at low risk of HIV infection and pregnancy. The aim will be to assess local tolerance, by subject reporting and colposcopy, and the relationship of any irritation to dose and frequency of use. The local concentration/time relationship should be evaluated, as should use of the microbicide with and without accompanying devices.

Phase II

Phase II trials could be a useful pilot for the large phase III trial, particularly in clinical centres with no previous trial experience. The aim is to assess product use in the trial population, compliance, and longer-term acceptability of the product, and to add to the safety database.

Phase III

The main phase III clinical trials aim to assess efficacy of the microbicide in the prevention of transmission of disease. Clinical evidence of efficacy will be required for each pathogen named in the licensing application. The trial population should be uninfected women at high risk of HIV infection. Ethical considerations require careful attention to the education and counselling of trial participants. The expected trial design would be a comparative study of microbicide plus condom versus placebo plus condom. Other control options include: condom alone group where a satisfactory placebo cannot be found, a "waiting list" control group if there is a large screened population and the trial is to be implemented in stage. The randomization of populations rather than individuals may be acceptable. Monitoring of compliance will be required, for example via direct subject and partner reporting, assessment of the quantity of product used, or surrogates of compliance such as pregnancy.

The safety database should include comprehensive monitoring of at least 100 patients for one year, according to long standing current EC guidelines. Work is ongoing between Europe, the United States and Japan to establish worldwide harmonization of clinical safety requirements for products for long-term use. The latest consensus is that 300-600 subjects should be followed for a year. The summary of safety in the product licensing application should include a global analysis of all adverse events which have occurred during clinical trials.

IV. ONGOING RESEARCH AND DEVELOPMENT ACTIVITIES

A brief outline of the research activities (under way or planned) of public sector research institutions, relevant to vaginal microbicide development, was presented. The need for coordination and collaboration, involving sharing of information, methodologies and, where appropriate, resources, was underlined by all representatives.

Contraceptive Research and Development Program (CONRAD)

The primary objective of CONRAD is to develop and promote contraceptive technology for use in developing countries. Its activities relevant to vaginal microbicide development include:

- studies on the detection of HIV in the fluids and tissues of the reproductive tracts of men and women;
- development of new formulations, for example films with increased stability, containing either nonoxynol-9 or benzalkonium chloride, and a polymeric excipient which is designed to reduce the vaginal irritation caused by nonoxynol-9 and other products;
- screening of new candidate microbicides, including their activity against cell-free and cell-associated virus, and cervical mucous penetration;
- use of animal models to test microbicidal safety and efficacy.

CONRAD has the capacity to conduct phase I and II trials.

Family Health International (FHI)

The Family Health International research programme on vaginal microbicides includes:

- clinical trials to assess the safety of nonoxynol-9 suppositories and to compare the acceptability and efficacy of contraceptive film versus foaming suppositories;
- a double-blind, placebo-controlled efficacy trial of nonoxynol-9-containing film against sexual transmission of HIV (currently in the planning stage);
- a prospective study to compare compliance in the use of condoms versus spermicides among oral contraceptive users at a family planning clinic, who are at risk of STD;
- development of *in vitro* methods to measure the speed of dissolution of vaginal preparations under wet and moist conditions;

- exploring the feasibility of testing microbicides for activity against human papillomavirus (HPV).

Medical Research Council (MRC)

The Medical research Council is working towards development of a vaginal microbicide as part of the AIDS Research Initiative. The strategy adopted involves a two-pronged approach directed at safety and efficacy studies on existing licensed spermicides in parallel with the development of novel agents. The strategy covers:

- development of *in vitro* assays for evaluating candidate microbicides under conditions which mimic the physicochemical environment of the vagina;
- *in vitro* assessment of activity against virus in genital secretions from HIV-infected women volunteers;
- safety studies in the rabbit model and phase I trials of promising candidate microbicides in low-risk, uninfected women;
- *ex vivo* assay of the effect of microbicide use on virus levels in genital secretions of volunteer HIV-infected women;
- phase III efficacy studies in populations at high risk of HIV infection.

National Institutes of Health (NIH)

The National Institutes of Health research programme works in close collaboration with the Centres for Disease Control and the Food and Drug Administration. The National Institute of Allergy and Infectious Diseases and the National Institute of Child Health and Human Development are both actively involved in research and development of a vaginal microbicide. The programme includes:

- *in vitro* assays of activity against sexually transmissible viruses, bacteria and protozoa;
- evaluation of new agents as vaginal microbicides;
- formulation of new delivery systems for agents currently licensed as spermicides – this work is currently focused on nonoxynol-9;
- clinical assessment of safety and efficacy of vaginal microbicides against sexually transmissible pathogens and effect on vaginal flora;
- assessment of the effect of vaginal microbicides on reproductive biology;
- studies on animal models;

- studies of sexual behaviour, particularly in adolescents, which will be important for implementation of prevention programmes.

Population Council

The Population Council programme includes:

- screening of antiviral agents;
- formulation of products – work is currently in progress formulating sulfated polysaccharides, the aim being to try simple formulations initially and move rapidly to phase I trials;
- safety, efficacy and acceptability trials with promising products are planned;
- acceptability trials of a number of placebo formulations in developing and industrialized countries are planned;
- working with women's advocacy groups to tackle issues related to the successful development of topical microbicides and their introduction into prevention programmes.

World Health Organization

The World Health Organization has supported one safety trial of a vaginal product. Lessons learned from this trial were that symptoms were not reliable indicators of the presence of lesions and that standardized criteria for the reporting of lesions were needed. Following a workshop held in Thailand in July 1993, a manual detailing a standard procedure for colposcopy and terminology for reporting colposcopic findings, is being produced. In collaboration with the pharmaceutical industry and regulatory bodies, WHO aims to produce prototype protocols for clinical trials and criteria for selecting compounds to bring to efficacy trials. WHO will continue to conduct safety trials and prepare the infrastructure for efficacy trials.

V. RECOMMENDATIONS

1. Appropriate studies to determine the safety and efficacy of existing spermicides with antimicrobial activity in preventing HIV transmission should be undertaken immediately. Any eventual recommendation about the use of such agents should take into account their relative benefits and risks, bearing in mind the urgency and gravity of the HIV/AIDS epidemic in many countries.
2. New products for intravaginal use that can prevent sexual transmission of HIV must be developed. Ideally, such products would also prevent transmission of other STD, but this aim should not hamper development of compounds with more selective anti-

HIV activity. Great preference was expressed for products that would not impair fertility.

3. Research is needed to develop formulations for intravaginal use which provide good coating of the vaginal mucosa, are non-irritating and long-acting.
4. Current *in vitro* systems to evaluate anti-HIV activity and cytotoxicity allow for rapid identification of promising compounds. Use of appropriate animal models to elucidate mechanisms of transmission and evaluate potential compounds could expedite product development. Animal studies, however, should not replace safety and efficacy studies in humans.
5. WHO, in collaboration with others, should develop prototype protocols for the clinical evaluation (phase I-III trials) of vaginal microbicides. In doing so, the following should be taken into account:
 - a) To avoid undue risks, the safety of existing and new compounds must first be evaluated in a population at very low risk of HIV infection. Only after adequate safety studies in low-risk populations may a product be evaluated for efficacy in a high-risk population. Safety should continue to be assessed in efficacy trials and after marketing of a product.
 - b) Safety studies should include three groups: one using the active drug, one using a placebo, and a no-treatment group.
 - c) The assessment of the safety of vaginal microbicides requires thorough and standardized clinical examination for and reporting of genital tract lesions. In view of its accuracy and sensitivity in detecting mucosal lesions, colposcopic evaluation is recommended.
 - d) All study participants should be provided with education about and access to condoms.
 - e) If possible, surrogate efficacy end-points for phase II trials should be developed.
6. WHO should establish a mechanism to foster collaboration between all parties involved, including the pharmaceutical industry and women's health advocates, to coordinate research and other activities, and mobilize resources to ensure the most rapid and rational development of appropriate intravaginal antimicrobial agents that would prevent heterosexual transmission of HIV and other STD.
7. Vaginal microbicides are not intended to replace condoms; condom promotion remains an essential strategy to prevent transmission of HIV and other STD.

Table 1 Summary of results in animal models used to test the ability of nonoxynol-9 to prevent transmission of viral STD

Model	Formulation	Concentration	% of animals infected on challenge	
			Treated animals	Control group
HSV-2/Mice	Gel	5% by vol.	50%	100%
FIV/Cat Vaginal	Gel	5% by vol.	0%	80%
FIV/Cat Rectal	Gel	5% by vol.	0%	100%
SIV/Rhesus Macaque	Foam	12.5% by vol.	50%	100%*
SIV/Rhesus Macaque	Gel	3% by weight	66%	100%*

* Dose of cell free SIV used had previously infected 6 out of 6 animals.

Table 2 Summary of classes of compounds identified as potential antimicrobials with specific anti-HIV activity

A. VIRUCIDAL AGENTS

- | | |
|-----------------------------|--|
| Non-ionic/ionic surfactants | <ol style="list-style-type: none"> 1. Act by membrane disruption 2. Vaginal irritation may be dose-limiting 3. Dose and conditions of use will be important 4. Use at sub-optimal concentrations may give benefit 5. Readily available in a commercial form |
|-----------------------------|--|

B. INHIBITORS OF VIRUS ADSORPTION

- | | |
|----------------------------------|--|
| Sulfated polysaccharides | <ol style="list-style-type: none"> 1. Active against HSV-1 and 2 as well as HIV 2. Only medium potency against syncytium formation 3. Anticoagulant side-effects 4. Clinical experience but not as topical agents 5. Readily available – some in phase I/II trial 6. Need to characterize production – complex mix of polymers |
| Sulfated polymers | <ol style="list-style-type: none"> 1. Active against HSV-1 and 2 as well as HIV 2. Increased potency against syncytium formation 3. Lower anticoagulant activity 4. Need to characterize production – complex mix of polymers |
| Carboxylated polymers | <ol style="list-style-type: none"> 1. Increased potency against syncytium formation 2. Lower anticoagulant activity 3. Low-cost production 4. Need to characterize production – complex mix of polymers |
| Sulfonated compounds | <ol style="list-style-type: none"> 1. Medium potency 2. No anticoagulant activity 3. Clinical experience but development abandoned because of systemic effects 4. Have not been formulated as topical agents 5. Readily available 6. Large-scale production possible |
| Negatively charged glycoproteins | <ol style="list-style-type: none"> 1. High potency 2. Low immunogenicity 3. No anticoagulant activity 4. Biodegradable and non-toxic 5. No data on formulation, <i>in vivo</i> effects, stability 6. Easy and inexpensive large-scale production |

C. INHIBITORS OF VIRAL FUSION AND UNCOATING

Bicyclams

1. High potency
2. No data on systemic or local toxicity
3. Not known if large-scale production feasible
4. May be costly

D. REVERSE TRANSCRIPTASE INHIBITORS

Nucleosides/non-nucleosides

1. Some systemic absorption could occur
2. Resistance may be a problem
3. Clinical experience
4. Topical formulation and local effects are being investigated
5. Pharmaceutical industry already developing such drugs
6. Large-scale production is possible

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