Campaign project

I - RATIONALE

The 20th century began with infectious diseases dominating medicine and witnessed scientific advances that promised control over them; it ends with abundant reminders that the history of infectious diseases far from finished. The development of effective antimicrobial drugs and a wide variety of vaccines has led to the cure and prevention of many infectious diseases, and the eradication of one ancient scourge: smallpox.

But infectious diseases have always been and continue to be the leading cause of death in developing countries (17 million deaths in 1996). A large number of new infectious agents have recently been discovered, some with consequences no one could have foreseen. HIV/AIDS must be considered the ‘mother of all emerging diseases’. Within ten years of its discovery it had begun to wipe away hard-won gains in child survival programmes in many african cities, and has been responsible for a doubling or tripling of tuberculosis in some countries.

Of the 30 million persons in the world currently infected with HIV, 86% (26 million) live in the 34 sub-Saharan countries.

There has also been the new threat of some infections which were previously well controlled. The former Soviet Union has suffered a severe epidemic of diphtheria as well as a severe resurgence of syphilis. An important but neglected epidemic of human african trypanosomiasis is currently claiming lives in central Africa. Cases of urban yellow fever in Western Nigeria in 1986 were the first anywhere in the world for 40 years. Having been absent from East Africa for decades, cases have recently also been seen in Kenya.

Many advances in the fight against diseases have been cancelled by the development and spread of drug resistance. Multi-drug resistant tuberculosis (MDR TB) was seen in New York City in the early 1990s, but the spread of resistant strains to developing countries has the potential to make tuberculosis once more an incurable disease. When half a million or more refugees streamed into Zaire from Rwanda following the genocide of 1994, cholera and shigellosis epidemics occurred. The shigella bacteria were resistant to all drugs except ciprofloxacin. Chloroquine-resistant malaria and penicillin-resistant gonorrhoea and pneumococcal infection are other examples of diseases with large public health implications that are affected by drug resistance.

An effective curative or preventive treatment of patients with drugs or vaccines depends on a long chain of factors: research and development of an appropriate pharmaceutical agent, production, quality control, distribution, inventory control, reliable information for health professionals and the general public, diagnosis, prescription, financial accessibility, drug dispensing, observance and pharmacovigilance. At each level, those involved may have conflicting interests, and poor populations turn out to be the first victims of frail links in this long chain. Today, entire populations lack access to essential quality drugs, and the situation appears to be deteriorating, further marginalizing much of the world’s population.

Essential drugs are the foundation for nearly every public health programme aimed at reducing morbidity and mortality in the developing world, and pharmaceutical expenditure can account for a high proportion of the total health expenditure of a country. It can vary from less than 10% of the total expenditure in the US to over 70% in a country such as Pakistan. Important health programmes that rely upon essential drugs include child survival programmes, antenatal care, treatment of enteric and respiratory pathogens, control of tuberculosis, and malaria. Other major public health issues like AIDS or african human trypanosomiasis have no effective, affordable and safe pharmaceutical treatment.

In spite of the progress made over the last twenty years, an estimated one third of the world’s population still lack access to essential drugs. In developing countries the proportion is much higher: in Bolivia 40% of the population do not have access to essential drugs; in Africa and many parts of Asia this number is over 50%. The revised drug strategy (WHO) and the essential drug concept are still key strategies to help improve access to essential drugs and contribute to improve health. The essential drugs concept is evidence based, it is simple, it promotes equity and is rooted in firm public health principles. WHO support to countries and advocacy work to promote the essential drugs concept and to support countries in the formulation and implementation of rational drug policies has resulted in change for the better. This strategy is a proven success but needs to be continued and strengthened, and given the changing context new ways of implementation must be explored.
In this new context, some major issues which are associated with the inaccessibility of drugs for populations in greatest need will be the key messages developed during the MSF campaign:

1. Insufficient Research and development (R&D) for new Drugs

Growing drug resistance, emerging and re-emerging diseases, unacceptable side-effects, and the lack of feasibility of current protocols strongly justify a need for greater research and development into new drugs. This need is greatest in the developing world. Between 1910 and 1970, the pharmaceutical industry’s contribution was crucial to the fight against endemic tropical diseases. Since then, pharmaceutical companies have adopted a completely different strategy.

Among the 1,223 new chemical entities commercialized between 1975 and 1997, 379 (30.9%) are considered as therapeutical innovations, but only 13 (1%) are specifically for tropical diseases. It can be concluded that pharmaceutical R&D is ignoring tropical diseases. There are four main reasons for this shift:

1. the costs and risks of R&D relative to the low purchasing power of consumers in developing countries;
2. a shift to more profitable production;
3. competition from counterfeit drugs;
4. the costs associated with adhering to quality standards.

There has been a general trend toward heavier regulations with which companies must comply in order to obtain approval before marketing a drug product, which raise the costs of clinical development. The necessity to minimize therapeutic risks voiced by consumers in the developed world leads to a reinforcement of various quality standards (good clinical, laboratory and manufacturing practices) but this is not adapted in terms of a risk: benefit perspective in the developing world.

In practice, when clinical development incidentally identifies a promising product (eflornithine used in the treatment of African trypanosomiasis) or a new indication (atovaquone for malaria, ivermectin for onchocerciasis, albendazole for lymphatic filariasis) for the treatment of tropical diseases, the manufacturer often decides not to market the drug, knowing it would be too expensive for the patients concerned. The company generally decides to either make exceptional arrangements (donations in the cases of albendazole, atovaquone and ivermectin) or takes negative action (discontinued production in the case of eflornithine).

2. Fluctuating Production of Essential Drugs

Drugs necessary for the treatment of certain tropical diseases have begun to disappear from the market because they are commercially unprofitable. Many of these drugs were discovered in the 1950s and 1960s, or earlier, and are seldom or never used in wealthy countries.

An example is seen in the effort to treat epidemic bacterial meningitis, which is caused by Neisseria meningitidis, and is rampant in sub-Saharan Africa. Efficacy of treatment with chloramphenicol in oily suspension (1 intramuscular injection repeated after 48 hours) for bacterial meningitis is comparable to the traditional treatment with ampicillin (4 times daily in intravenous injections over a period of 10 days).

The lower cost of the chloramphenicol in oily suspension - only one-tenth of the cost of ampicillin - and its simple administration makes it particularly suitable to the precarious working conditions in developing countries. This is particularly important during epidemics, which can affect thousands of patients in the same region at the same time (over 100,000 cases in Nigeria in 1996). However, production and availability of chloramphenicol in oily suspension are no longer guaranteed, Roussel-Uclaf Laboratory stopped production in 1995.

The circumstances described above also apply to other serious illnesses, such as Leishmaniasis and meglumine antimoniate, and African trypanosomiasis and melarsoprol.

3. Prohibitive costs of new drugs

The prohibitive cost of antiretrovirals for treatments of people with AIDS is well-known. There are many other examples of existing drugs that are simply not affordable, most of which have been recently marketed and are therefore still patent protected.

Shigellosis Sd1 dysentery is extremely contagious and without an effective treatment is lethal in 5-15% of cases. As mentioned before, Shigella Sd1 bacteria quickly became resistant to traditional treatments. The only effective antibiotics today are fluoroquinolones (ciprofloxacin, norfloxacin). However, treatment with these new drugs is ten-times more expensive than the traditional treatment using nalidixic acid ($20 vs. $2). A special agreement was reached between Bayer Pharma Laboratory and MSF to make available 50,000 treatments with ciprofloxacin for a unit price of $2 per treatment. This example shows that it is
possible to find an ad hoc solution with the pharmaceutical industry, yet no medium-term solution is anticipated.

At the level of African hospital, ceftriaxone is a vital antibiotics to reduce the mortality due to bacterial meningitis and to severe acute respiratory infection caused by *Streptococcus pneumoniae* but it is financially inaccessible to those populations that need it most of all.

Prohibitive pricing also extends to prevention when new vaccines are not available for the population most at risk. For example, Hepatitis B, Pneumococal conjugate and anti-Haemophilus vaccines, which help to prevent major public health problems are not accessible because of their steep price. Vaccines for Hepatitis B, a disease predominantly found in East Asia and sub-Saharan Africa are approximately ten-times more expensive than other vaccines included in the expanded programme on immunization (EPI) promoted by UNICEF.

4. Globalization and Drugs: Questions and Concerns

A snapshot of the current landscape in the area of drug availability would not be complete without a consideration of the increasing globalization of the pharmaceutical industry and the potential implications of recent and upcoming world trade agreements.

**Drugs: Another Industrial Product?**

The final GATT agreement was signed on April 15, 1994 that led to the creation of the WTO. This agreement ratifies the world-wide implementation of a free trade economy. Its enforcement with regard to the pharmaceutical sector raises certain doubts and concerns. Two types of provision seem particularly important for pharmaceutical companies in developing countries: those whose purpose is to put an end to protectionist measures and jeopardize some drug industries in developing countries; and those which define as mandatory the protection of patents on drugs and their respective manufacturing processes, i.e. the trade related aspects of intellectual property rights (TRIPS Agreement). This is particularly important, as many developing countries do not fully acknowledge patent protection rights in the area of pharmaceuticals for being able to locally produce low cost copies of innovative drugs.

**A Newly Invigorated Tropical Research?**

Pharmaceutical companies in the developed world have stated repeatedly that the reason for not conducting research on tropical diseases is the lack of protection for innovations in some developing countries, which would also explain their limited investments in the countries concerned. The moment the enforcement of patent protection becomes effective (in developing countries no later than January 1, 2006) tropical disease research should logically start again, funded by Western companies or by manufacturers in developing countries.

However, it is unlikely that Western manufacturers will devote much of their effort to non-solvent populations, with or without patents. Manufacturing companies in developing countries may actually be motivated to invest more in research for new drugs, but very few of them are in a position (financial and scientific) to do it. All things considered, it is to be feared that tropical research will not have a more promising future, even if patents are widely enforced.

**Increasingly Prohibitive Prices?**

A study financed by American pharmaceutical companies shows that granting drug patents does not tend to increase the price of drugs on the market. This study, however, does not examine the prices of new innovative drugs and declares that, logically, the price of these new drugs should be higher. Naturally, when the manufacturing company is assured that its product cannot be copied, it holds a stronger position to negotiate prices with public health authorities. Moreover, the liberalization of international pharmaceutical trade entails the development of parallel imports between countries where the same drug is sold at different prices. Pharmaceutical companies, which are consequently less and less inclined to grant significantly lower prices to less developed countries, may tend instead to set unique world-wide prices or delay marketing their drugs in developing countries. In either case, access to drugs is jeopardized.

5. Counterfeit and Substandard Products

Drug products must be manufactured according to strict Good Manufacturing Practices. Unfortunately, many developing countries do not have the technical, financial or human resources required for the application of such standards to their production. As for developed countries, they are sometimes less strict when the product being manufactured is destined for exportation. Today, the quality of drug products and therefore their effectiveness and safety is less and less certain, especially for the poorest populations who are attracted by lower priced drugs sold outside pharmacies.

Recent years have seen an increase in the prevalence of counterfeit and substandard drugs on the market. Counterfeit drugs are those that mimic authentic drugs; substandard drugs are those produced with little or no attention to good manufacturing practices.
During the meningitis epidemic in Niger from February to May 1995 (41,000 cases reported), the Niger authorities organized an extensive vaccination campaign. In March 1995, Niger received a donation of 88,000 Pasteur Mérieux and SmithKline Beecham vaccines from neighboring Nigeria. A Médecins Sans Frontières (MSF) team working with local health authorities noticed that the vaccines from Nigeria had an unusual appearance (difficult reconstitution, black filaments in the solution). Inquiries were made and Pasteur Mérieux laboratories confirmed that the batch numbers and the expiration dates did not correspond to their manufacturer records. The drugs supplied by these companies had been substituted with counterfeit drugs. Tests carried out found no traces of active product, confirming they were false. Bottles and labels were copied to perfection. Pasteur Mérieux subsequently filed a counterfeit suit.

Some of the false vaccines (approximately 28,000) were located by batch number and destroyed. According to estimates, around 60,000 persons were inoculated with false vaccines out of a total 5 million vaccinated during the campaign. Such a production would have necessitated an industrial-scale production facility, and it is probable that the 88,000 vaccines identified as false did not account for the entire fraudulent production.

MSF teams have encountered many similar field examples that lead to the following conclusions: organized illegal circuits seem more inclined to manufacture copies with the appearance of known trademark drugs (counterfeit), rather than comparatively less expensive generic products; whereas, non-organized illegal circuits (small production) increasingly manufacture drugs whose composition is substandard or inadequate, including generic drugs.

Poor quality may be accidental, with no intention to deceive, but oversights in manufacturing or neglected controls may sometimes have tragic consequences. Such was the case during recent decades with acetaminophen syrups which contained, by mistake, a lethal ingredient.

II - PHILOSOPHY OF THE CAMPAIGN - WHY MSF SHOULD BE INVOLVED IN THIS INITIATIVE?

The ultimate aim of the campaign is to reduce the gap between rich and poor people. It is a campaign against discrimination and for the application of the principles of equality with respect to access to quality drugs. Increasingly, our physicians in the field have to deal with a lack of effective drugs. Even if we are still strongly concerned with public health issues, during this campaign, we engage ourselves to defend the right of every individual to vital healthcare. However, it would serve no purpose to demand new public health rights or human rights in a manner that would make one believe that such rights will soon become a reality. In other words, we will not propose new slogan like 'Health for all in the year 2000'. Pragmatic solutions to respond to the need of individual patients are required.

First of all, we should try to demonstrate through field examples that feasible and original solutions can be developed. Subsequently, we will use examples to involve the different partners (governments, private sectors, international institutions, etc) in the definition of sustainable solutions.

With 400 health projects in the field, a permanent presence of more than 1000 volunteers on the side of the poorest, independence from governments and institutions, and an ability to speak out and to advocate for desperate situation, MSF is in a unique position to bring this campaign to a successful conclusion.

III - THE OBJECTIVES OF THE CAMPAIGN

Primary objectives

1. Restart R&D for tropical diseases and related areas:
   - define a legal and fiscal framework similar to those developed in the US, Japan and recently in Europe to motivate R&D for orphan drugs;
stimulate the public sector (large donors) to invest in R&D for tropical diseases;

stimulate WHO (mainly TDR), World Bank, UNDP, UNAIDS and UNICEF in playing a co-ordination role in R&D strategy;

motivate MSF or other NGOs to dedicate part of their activity to operational research for new drugs and vaccines, new form of drugs, and new treatment guidelines.

2. Make affordable new drugs and vaccines for disadvantaged populations

i. develop agreements between the pharmaceutical industry and international organizations to make affordable new existing drugs;

ii. create centralized purchase funds that would guarantee large sales volumes (financed by existing public and private circuits).

3. Ensure the production and commercialization of orphan drugs

i. on a case by case approach and in collaboration with different partners look for ways of providing sustainable solutions for orphan drugs for tropical diseases.

4. Humanize the WTO and TRIPS agreements

i. develop an exception in commercial agreements for drugs: drugs should not be considered just as another industrial product;

ii. promote the use of 'compulsory licenses' to deal with major public health issues in poor countries;

iii. reinforce the role of WHO in advocating the right to health care in the resolution of trade disputes.

Secondary objectives

These objectives are very important. However, other partners already have a leading role to play in the development of such actions. MSF will therefore act in supporting these initiatives.

1. Support the policy of rationale use of essential drugs

i. continue and even strengthen our effort to produce relevant guidelines and particularly the 'therapeutic guideline' and the 'essential drugs guideline';

ii. support the national programmes of rational use of essential drugs where they exist and promote the development of such programmes where they do not.

2. Surveillance of the quality of drugs

i. adopt an irreproachable procurement policy of drugs;

ii. assist in the maintenance of a permanent ‘observatory of drug quality’. This should be established under the co-ordination of WHO.

3. Improve the policy of drugs donations

i. apply and reinforce the WHO guidelines;

ii. advocate in rich countries the adherence to such guidelines.

IV - A SELECTION OF PRIORITY DISEASES

To support this campaign we propose to choose a list of 10 priority diseases according to two criteria:

i. public health importance (see table)

ii. field experience of MSF

Suggestions:

- Tuberculosis*
- Malaria*
- Acute respiratory infections
- Diarrheal diseases (Shigellosis*, Cholera)
- AIDS*
- Visceral leishmaniasis (Kala Azar)*
- African human trypanosomiasis*
- Bacterial meningitis*
- STDs
- preventable diseases
For each disease, we will develop a file combining the field experience of MSF and the independent opinion of experts on: description of epidemiological context, description of current preventive and curative strategies, identification of problems, listing of potential solutions, actions to be developed...
We already have several examples (see Annex). These files should be regularly updated.

V - TARGET AUDIENCE OF THE CAMPAIGN AND STRATEGY

The campaign should be directed to different target audiences:
1. The world-wide general public. Sensitization of the public through the media and fund-raising material by MSF and in collaboration with other national and international medical NGOs and consumer organizations.
2. Institutional organizations. Sensitization, solution finding, financial investment and definition of responsibilities. The main targets will be WHO, the World Bank, and Unicef.
   The new WHO should particularly hold our attention. The campaign director should try to be intesnively focus on developing a partnership with this institution. An attitude of critical support to WHO has to be endorsed by the whole MSF movement.
3. The governements. idem 2.
5. The medical and the scientific community. idem 2.

The probable strategy will be a combination of:
- a 'target campaign' with realistic objectives (such as to ensure the production and commercialization of a specific drug) using stategic consideration and probably strategic alliance with specific partners;
- a 'journey campaign' tactically driven and based on the defense of principles.

That part of the project will be further developed after the recruitment of a campaigner (see Job Profile in Annex).

VI - CONSEQUENCES FOR THE MSF MOVEMENT

1. Operational
   - develop projects with strong components of operational research (20 projects for the year 1999);
   - permanent revision of guidelines;
   - rigourously sustained procurement policy of drugs.

20 projects with a strong component of operational research
The experience of MSF is a key issue for the success of the campaign. Among our 400 health projects, it will not be difficult to select 5% that include this component. But, today, we are still far from this objective.
Some examples currently developed:

- Kala Azar in South Sudan (MSF H)
- AHT in Uganda (MSF F and Epicentre)
- Malaria in Thailand (MSF F and Mahidol institute)
- Bacterial Meningitis in Mali (Epicentre)
- Tuberculosis in Russia (MSF B and IMT Anvers)
- AIDS in Thailand, Cambodia and perhaps Kenya
- STD in Kirgistan

It will be fundamental for the campaign to define the 20 projects before the finalization of the 1999 operational project in the different sections. These projects can be as diverse as: identification of a problem (antibiotic resistance, pharmacovigilance), clinical trial (new drugs or new treatment guidelines), feasability studies, etc.

2. The Image of MSF
   - medicalization of the image: that objective was clearly defined at Chantilly in 1995. The campaign will be a great opportunity to improve our medical image;
   - political image: humanization of the liberal policy. We have to be conscious that during this campaign we will be illustrating the current political debate of the negative consequences of globalization;
   - long-term campaigning: this is a new challenge for MSF.