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Orphan Drug Laws in Europe and the US: Incentives for the Research and Development of Medicines for the Diseases of Poverty

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INTRODUCTION

According to the World Health Organization (WHO), more people have died in the last 50 years from malaria, tuberculosis (TB), and AIDS, than have died in all wars during the same period, combined. (Kapp 2001) The American Red Cross has noted that in 1999, 160 times more people died from diseases such as AIDS and malaria than from natural disasters. (Medical Industry Today 2000) These diseases, along with other diseases prevalent in the developing world, are collectively referred to as the "neglected diseases." Neglected diseases are seriously disabling or life-threatening diseases for which treatment options are inadequate or don't exist, and for which the drug-market potential is insufficient to readily attract a private sector response. (MSF 2001)

Less than 50% of the world's population have access to an adequate supply of safe and essential drugs capable of mitigating the morbidity and mortality of neglected diseases. (EDM 2000) Instead of being the focus of a worldwide marshalling of resources and international diplomacy, as might occur with wars or natural disasters of less magnitude, these diseases have been an object of neglect. 'Neglected' diseases cause 90% of the global burden of disease, yet they account for only 10% of global pharmaceutical research and development spending. (PIU 2001)

Joining the three major pandemics on the 'neglected' disease list are a number of predominantly tropical diseases with significant worldwide morbidity and mortality: human African trypanosomiasis (HAT), Chagas' disease, intestinal parasitic diseases, leishmaniasis, leprosy, lymphatic filariasis, and schistosomiasis. (Trouiller 1999) These diseases are sometimes also referred to as diseases of poverty, since they tend to be endemic among the populations of less industrialized countries or among impoverished sub-populations of countries with transitional economies. In the current report, these diseases will be referred to collectively as the neglected diseases.

In January 2000, the Commission on Macroeconmics and Health was convened by Dr. Gro Bruntland, Director-General of the World Health Organization (WHO), to produce a series of studies investigating the linkages between health and economic growth and development. Six working groups were organized to support the work of the Commission. The current report is a contribution to the mandate of Working Group 2 to investigate global public goods for health. Global public goods are understood in the health context to be ones that have the potential to benefit or harm the public health of the international community as a whole. Incentives that stimulate research and development (R&D) of medicines for neglected diseases affecting a large percentage of the world's population can be considered global public goods.

The purpose of this report is three-fold. Initially, we will describe the orphan drug laws of the United States and the European Community, including their impetus, history, scope, and utility for countervailing disincentives to R&D of neglected diseases. Next, we will discuss the impact of the orphan drug laws as incentives for R&D on medicines for the neglected diseases in the context of a categorization based on research needs, effect on global public health, and economic considerations (basically, there are three categories exemplified by: 1) AIDS; 2) malaria and tuberculosis; and 3) tropical diseases (e.g., sleeping sickness). Finally, we will present recommendations for possible modifications to the orphan drug laws, as well as options for implementation of these recommendations.

ORPHAN DRUG LAWS

In general, orphan drug laws were designed to encourage research, development, and marketing of products for rare diseases and conditions. Orphan drug laws were created because these products, for a variety of reasons, are often considered "uneconomical." For example, the products are often treatments for rare diseases, with few patients, making the expectation of achieving sufficient return on investment in the drug's development and marketing costs extremely unlikely. Alternatively, the products can be for patient populations that, although quite numerous and medically needy, may not be capable of supporting a sufficiently profitable market or sales profile for a drug. Lastly, regulatory burden may contribute to diminished returns. For example, even in developed countries, some essential drugs have become orphans

when the manufacturers decided that the costs of registration and distribution were too high to justify marketing the products. (Allerberger 2000)

While there are a number of countries that have orphan drug laws in various forms and stages of development, including well-recognized programs in Japan, Australia, and Singapore,[1] this report will confine its discussion to the orphan drug laws of the United States and the European Community (EC). The US and the EC together account for nearly three-quarters of R&D for pharmaceuticals and biologics (PhRMA 2001), and comprise two-thirds of the world pharmaceutical market. (Mann 2001) It is therefore not surprising that the primary incentive (i.e., market exclusivity) within each region's orphan drug laws is market-based. (Thamer 1998) This is especially true in the US. Historically, both the US and the EC have addressed the issue of the public health impact of uneconomical drugs for tropical diseases (a term now expanded to encompass the concept of neglected diseases) within the context of orphan drug laws.

The US Orphan Drug Act

The orphan drug law in the US was passed in December of 1982, and amended the Federal Food, Drug & Cosmetic Act (FFDCA) and the Public Health Service Act (PHS). The original impetus of the US Orphan Drug Act (ODA) was a heightened awareness of the need to develop therapeutic agents to treat diseases affecting small numbers of patients; these diseases are referred to as "rare disorders." The term orphan drug reflected the fact that no company would be interested in commercializing medicines for such small patient populations, due to the inability of the firm to achieve a reasonable return on investment. This became especially true in

[1] Japan has had an orphan drug program since 1993. Currently 132 orphan drug designations are listed on the website of Japan's Organization for Pharmaceutical Safety & Research (OPSR). Of these, approximately one-quarter are for neglected diseases: 25 for AIDS and AIDS-related diseases, 2 for malaria, 3 for parasitic diseases, and 6 for leprosy. However, orphan drug development is considered a social duty for large companies with the result that most orphan designations are for additional indications of existing drugs and over 40% of the applicants are foreign-affiliated companies. New orphan drug development in Japan is conducted by bioventure companies, a sector that is not well-developed there. (Shiragami 2000)

Australia has a robust but still incipient orphan drugs program with several features that could bode favorably for a future role as a source of drugs and vaccines for neglected diseases, such as its focus on anti-infectives for special conditions and its interagency agreement with the FDA for expedited approval of US orphan drugs.

Singapore's orphan drug law features expedited importation of orphan drugs approved by recognized foreign regulatory authorities, and could serve as a model for similar laws internationally.

the wake of the 1963 Kefauver-Harris amendments to the FFDCA, which raised the cost of drug development by requiring more rigorous safety and efficacy standards. (Haffner 2001)

The current eligibility requirements for orphan drug designation are that a drug must affect less than 200,000 people in the US, or if it affects more than 200,000 people, that there is no reasonable expectation that the costs of development and production will be recovered by sales. Whereas the ODA pertains primarily to drug and biological products, the orphan grants program has been expanded to include eligibility for medical foods and devices that meet the "orphan" criteria. (OOPD 2001)

The economic rationale for the ODA was to provide a mechanism to make the orphan drug market more attractive to drug developers. This was done by reducing the fixed costs of research, development, and approval of the orphan product, while increasing the expectation of profits, by providing monopoly market conditions. (Peabody 1995) There are five economic and regulatory incentives included in the ODA to accomplish these goals.

The first incentive is technical and administrative assistance with the identification and development of orphan products provided directly by the US Food and Drug Administration (FDA). Specific protocol assistance concerning what studies the sponsor needs to complete in order to obtain regulatory approval is available from the FDA reviewing divisions. The Office of Orphan Product Development (OOPD), which was specifically created within FDA by the Orphan Drug Act, monitors the review process and assists in resolving specific issues that may arise during the review process. The OOPD's mission also includes a directive to "assist and encourage the identification, development, and availability" of orphan drugs. (OOPD 2001) The OOPD has a staff of approximately 25 scientists and administrators. The ODA also created the Orphan Products Board (OPB) to facilitate the process of interagency communication. This process has progressed to the point that, in recent years, most of the responsibilities of the Orphan Products Board have been assumed by the OOPD. (Haffner 2001)

The second incentive of the ODA is the availability of FDA grants to cover clinical trial expenses. The FDA's FY2001 budget has $12.5 million available for these grants.[2] Typically, 18-24 new awards are funded annually. The grants are awarded for periods of 1-3 years, but multiple sequential grant awards have been made. Grants for direct costs are limited to $150,00 for Phase I studies, and $300,000 for Phase II or III studies. Additional funds for indirect costs are available; the rate is negotiable with the Department of Health and Human Services, but typically averages 50% of direct costs (occasionally as high as 100%). Thus, some single grant awards have exceeded $500,000, and sequential awards to the same grantee have resulted in multi-year funding of over a million dollars. No separate funds, however, have been appropriated by Congress for this purpose; funding for orphan drug research has been provided from a general grant program authorized under FFDCA. (Peabody 1995) Grant awards are not limited to domestic applicants. (65 Fed. Reg. 153) Studies may be conducted overseas by foreign or domestic grantees if certain prerequisites are met. (Whitley 2001)

The third incentive of the ODA is that user fees – i.e., registration fees paid to the FDA by a sponsor for review of a marketing application – are automatically waived. This waiver results in a current saving of approximately $300,000 per orphan product application. The FDA may also waive, upon request by the product sponsor, establishment and product maintenance fees, if proper justification is provided.

The fourth incentive is the availability of tax credits, which can be subtracted from the company's tax payment. These credits can be for as much as 50% of clinical development costs. The tax credits can be carried forward for 15 years or backward for 3 years. Even the costs of studies conducted overseas are eligible for credits, if the company can justify the need to do testing outside the US. (Mathieu 2000) To some critics of indirect government subsidies, tax credits are considered a more palatable incentive than market exclusivity. (Love 2000) However, because the amounts saved are still small relative to the fixed costs of R&D, they are not considered a strong incentive for industry. (Peabody 1995)

[2] A new bill is presently going through the legislative process that would double the funding available to the orphan grants program to $25 million for fiscal year 2002. (Pink Sheet 2001)

While the preceding four incentives help to reduce the R&D costs of product development, the fifth incentive of the ODA – market exclusivity – is consistently cited by pharmaceutical manufacturers and analysts as the most important incentive. (Peabody 1995, Arno 1995, Benzi 1997, Shulman 1997, Rohde 2000) For example, a health economist from Genentech, a leading US biotechnology firm, stated that his company's orphan drug successes were "... due to the certainty that stems from the [Orphan Drug] law's promise of market exclusivity." (Rich 1996)

The marketing exclusivity incentive ensures that FDA cannot approve a marketing application for the same orphan drug that treats the same orphan condition for seven years from the date of approval of the first orphan application, even in the absence of a patent. Although "same" is defined in the regulations, it is generally considered to mean a comparable or similar drug; the criteria differ for small molecule (i.e., drugs) and large molecule (i.e., biologics) products. (Shulman 1997)

There are two exceptions to the market exclusivity provision. One is that FDA can revoke exclusivity if the sponsor cannot produce enough of the drug to meet demand. The second is that the holder of the marketing exclusion can voluntarily consent in writing to the approval of another application. This exemption is an important mechanism for allowing two or more manufacturers to establish development or marketing agreements among themselves. For example, it could be used when two manufacturers are in a close race to bring similar products to market for the same orphan indication, or in cases where manufacturers wish to collaborate with each other. (Pulsinelli 1999)

There are several other ways that the market exclusivity can be circumvented. One is for a manufacturer to develop a clinically superior version of an already approved orphan drug. Another is for a firm to develop a different drug for the same orphan indication. Finally, a sponsor could gain approval of the same drug, but for a different, non-orphan indication, and

then take advantage of "off-label" use of the drug for the approved orphan indication, as permitted under current FDA policy. (Shulman 1997)

These five ODA incentives affect the various segments of the industry in different ways. Tax credits appeal to all segments of the industry, but especially to larger companies, which carry the majority of orphan products through to approval. From 1998-2000, large companies have garnered 56% of approvals, while designations have been more evenly spread over small, medium, and large companies. (Tufts CSDD 2001)

Grants and protocol assistance are especially useful to smaller companies. Through these incentives, FDA encourages smaller, less experienced pharmaceutical manufacturers to seek regulatory approval of orphan products. (Rohde 2000) This is evident from the fact that nearly 40% of orphan designations from 1998-2000 went to small companies. (Tufts CSDD 2001)

The market exclusivity provision is very attractive to sponsors of products that are not patentable (e.g., shelf chemicals, natural substances, and chemicals well described in the scientific or medical literature), or that have patents that have already expired. The economic rationale for the market exclusivity incentive is that, whereas large markets and patents are typically sufficient economic incentives for the development of non-orphan drugs, this is not the case for orphan products. (Pulsinelli 1999) Market exclusivity remedies the market failure in orphan products by ensuring a noncompetitive environment. Thus, a predictable revenue stream for the drug's sponsor is more likely. (Rohde 2000)

The market exclusivity provision is especially helpful to the biotechnology industry. One reason for this is that biotechnology R&D has been fueled by venture capitalists, who typically require some assurance of intellectual property protection once the product resulting from their investment reaches the marketplace. Orphan drug exclusivity has become a kind of patent substitute for many innovative products derived from biotechnology. This practice has arisen because of the uncertain state of patent protection for these inventions and the complexities of obtaining such protection. Patent prosecution requires a lengthy process of drafting and filing an

application that explains the invention, and then convincing the Patent and Trademark Office that the invention meets the statutory requirements for patentability. In contrast, requests for orphan drug designation are straightforward, involving only the compilation and submission of information to the FDA, as provided by regulations.

In absolute terms, an orphan drug exclusivity period of seven years is obviously shorter than a 20-year patent term. However, a biotechnology product's patent term begins when the patent application is filed, typically early in the development process. The time taken in patent prosecution and the time required to conduct preclinical and clinical studies to obtain regulatory approval eliminate a substantial portion of the 20-year term, leaving a relatively short period of effective patent life in which the sponsor can enjoy monopoly status for its product. Even though orphan drug exclusivity does not have the versatility of a patent, and the uncertain status of biotechnology patents is slowly being resolved in the courts, orphan exclusivity can serve as a powerful substitute for a patent. (Pulsinelli 1999)

The History of the US ODA and Tropical Medicines R&D

The early history of the initiative to develop an incentive program for R&D of rare diseases arose, in part, from civil defense concerns prevalent in the US during the early Cold War era of the 1950s and 1960s. In 1964, a Public Health Service (PHS) Task Force was convened to determine if the needs of the PHS hospitals were being met, regarding their capacity to treat rare and tropical diseases. The following year, the PHS undertook the first attempt to assess the actual availability of drugs for tropical and other rare diseases in the US. (Sarett 1984)

In the 1970s, as the civil defense urgency waned, the age of advocacy began to blossom with the emergence of patient groups for, among other things, rare diseases. These patient groups were later organized under the umbrella of the National Organization of Rare Disorders (NORD). The focus of concern shifted away from protecting the US against microbial invaders, towards providing drugs for indigenous rare diseases. The government contribution to this initiative was called the Interagency Committee on Drugs of Limited Commercial Value, which was convened by the FDA's Bureau of Drugs.

The committee identified several problem areas of drugs with high therapeutic but low economic value. These included drugs for rare diseases, single usage drugs (e.g., diagnostic and some vaccines), drugs that require lengthy development times (and thus are left with short effective patent lives), drugs with anticipated legal liability (e.g., birth control pills), drugs for use in *diseases endemic to third world countries* (i.e., countries with distribution and monetary resources issues), unpatentable drugs, and marketed drugs requiring FDA approval for use in new indications. (Asbury 1981)

Despite this legacy of considering rare and tropical diseases endemic in the "third world" as potential candidates for orphan drugs, the expression of legislative intent supporting the ODA as an incentive for R&D on treatments for diseases of developing countries comes only incidentally from the 1982 House Committee hearing on the ODA. These hearings concluded:

The term "rare in the States" is used to assure that the benefits of this bill apply to drugs for diseases or conditions which are rare here, even if prevalent in other countries. To the extent that this provision encourages the development of drugs for prevalent diseases in developing countries, the committee believes it is sound public policy. (Orphan Drug Act 1982)

Congress clarified its intent a few years later with more specific and stronger support to encourage R&D of medicines for tropical diseases. For example, the 1986 export amendments to the Federal Food, Drug, & Cosmetic Act authorized the export of unapproved drugs and unlicensed biologics to developing countries without sophisticated drug approval and health surveillance systems. The legislative history recognized that drugs to treat tropical diseases are seldom submitted for FDA review and approval, because it is usually uneconomical for firms to pursue the costly regulatory process in cases when the market is so small.

The text of the law itself states that it was intended to promote worldwide public health by encouraging the development and availability of drugs to treat diseases or health conditions that were "rare in the United States," i.e., orphan drugs. Furthermore, the accompanying Senate

Report made it clear that the provision in the 1986 export amendments to modify the ODA by inserting the phrase, "including a disease or condition prevalent in a developing country," in the definition of orphan disease was intended to qualify drugs for tropical diseases for development assistance and marketing protection under the ODA. (Pharmaceutical Export Amendments of 1986)

In a 1990 regulatory review, FDA detailed the focus of the 1986 export amendments more specifically. The agency stated that they were intended to permit the export of drugs for the treatment of diseases or conditions that occur to a greater extent in the tropics, or that have significantly greater health implications there, such as *hookworm ascariasis, trypanosomiasis, leishmaniasis, schistosomiasis, malaria, amebiasis, filariasis, cholera and leprosy.* This FDA review also established the regulatory threshold that must be met in order to apply for expedited export; there must be credible scientific evidence, including clinical investigations, that the drug is safe and effective for its intended use in the country to which it is exported. Thus, the agency would expect the applicant to provide information regarding the needs of, and expected conditions for use within, the country to which the drug is to be exported. Studies reported in the scientific literature could, in some cases, provide support for this showing of credible scientific evidence, but FDA approval will ordinarily be based on data from at least two well-controlled clinical investigations. (FDA 1990)

The Success of the US ODA as an Incentive for Neglected Disease R&D

By most standards, the ODA has been an unqualified success as an incentive program for R&D on treatments for rare diseases. In the 17 years before the ODA took effect, only 58 new drugs were approved that would have qualified for orphan status. (Peabody 1995) In the 17 years since the ODA, 217 orphan products have been approved (Tufts CSDD 2001), providing treatments for 9 million people. (Haffner 2000) Moreover, the rate of orphan approvals has been increasing. Before the ODA was passed, two or three drugs that might have been eligible as orphans were approved annually. (FDA 1992) In the first ten years after the ODA was passed, there was an average of 8.5 approvals per year. After the first wave of FDA regulatory reform, i.e., passage of the Prescription Drug User Fee Act of 1992, the rate increased to 15.6 per year.

In the three years since passage of the FDA Modernization Act of 1997, an average of 18 orphan products have been approved annually. (Tufts CSDD 2001) The orphan program has been especially productive for biopharmaceuticals; nearly 70% of orphan designations are currently being granted to biotechnology companies. Moreover, from 1995 to 1999, 53% of biological products approved by FDA's Center for Biologics Evaluation and Research were orphans. (Tufts CSDD 2001)

The ODA has been particularly effective in encouraging R&D in certain therapeutic areas. For example, R&D related to AIDS and AIDS-related conditions has been notable – 77 designations resulting in 20 approvals as of the end of 2000. In the area of infectious diseases (excluding AIDS), there has also been considerable output – 80 designations with 19 approvals from 1983-2000. Overall, AIDS and infectious diseases have each comprised 9% of the total of 991 orphan designations and 8% each of the total of 217 approvals through the year 2000. (Tufts CSDD 2001) These are the highest percentages of orphan designations and approvals for any therapeutic areas, with the exception of cancer and genetic diseases, which are generally considered the mainstream therapeutic areas of orphan drug development. (Pulsinelli 1999)

Europe's Orphan Medicinal Products Regulation

Regulation (EC) No. 141/2000 of the European Parliament and the Council on Orphan Medicinal Products was published in January 2000, and implementing regulations entered into force in April of the same year. The main thrust of the legislation was to establish EC procedures for designating orphan products and to establish incentives for orphan product research, development, and marketing. The primary incentive is a 10-year period of market exclusivity, along with protocol assistance and the possibility of fee waivers. These waivers could amount to approximately $250,000 (US) for application, valuation, and maintenance fees associated with the centralized procedure for market approval, but are subject to fund availability. Tax credits, grants for R&D costs, and fee reductions for marketing approval through the mutual recognition procedure are being considered by the individual EC member states.

The basic criteria for orphan eligibility are (1) that the product is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the EC, and (2) that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment. (Commission 2000) Diseases prevalent in developing countries, but rare in Europe, can technically meet the letter of the law if there are a few documented cases of the disease occurring "…in the Community."

The European orphan product regulation grew out of EC Directive 91/507/EEC, which aimed to facilitate the registration process of drugs for rare conditions, a 1992 amendment to the French Public Health Code (article L601-2), and a 1994 National Institute of Health and Medical Research (INSERM) report on orphan drugs. This latter report specifically mentioned tropical diseases, particularly parasitic diseases, in the definition of orphan drugs. However, the final regulatory proposal only mentioned these products as benefiting indirectly:

...prevalence is established within the Community so that medicinal products intended for preventing or treating diseases which are very widespread in the Third World (tropical diseases, for example) but uncommon in Europe will benefit from the new system. (Trouiller 1999)

Similar to the course of events in the US, public health concerns in the EC, particularly concern regarding the potential risks of emerging infectious diseases, then considered rare in the EC, were an early impetus for the proposed orphan product regulations. (Trouiller 1999) In discussions leading up to the drafting of the orphan medicinal products regulation in Europe, it was proposed that tropical diseases should be an area of specific support and perhaps even specific language in the regulation itself. While several proposals in this vein seemed to receive broad support, the general direction ultimately taken emulated the US ODA, in which tropical disease R&D is considered eligible, but is not specifically mentioned. In fact, suggested amendments to the European regulation to create a special fund for this purpose or to include

language encouraging research in the third world were not supported by EC Commissioner Bangemann. (Cordis RTD-news 1999)

While neither the European nor the US orphan products laws have a specific provision that targets tropical disease R&D, the US has made a clear statutory commitment in the 1986 export amendments to the FFDCA. So far, the European legislation theoretically applies, because some tropical diseases imported into Europe, such as malaria, can fit the criteria. (Trouiller 1999)

European Community Interest in R&D of Neglected Disease Medicines

Historically, Europe has contributed to the current armamentarium of medicines for the neglected diseases (see TABLE 1). However, its recent contributions in this regard have slackened, in similar fashion to the US. From 1995 through the first quarter of 2001, some 160 products have been approved through the EC's centralized procedure. While 20 of those approvals have been for AIDS and AIDS-related conditions, none were for other neglected diseases. (Tufts CSDD 2001) Nonetheless, the current pipeline for investigational drugs and biologics for human African trypanosomiasis, malaria, and tuberculosis is equally divided between US and non-US developers, with the majority of the tuberculosis R&D located in Europe (see TABLE 2).

According to a summary of R&D activity for the neglected diseases, created by the European Federation of Pharmaceutical Industries and Associations (EFPIA), the following are the numbers of large pharmaceutical companies undertaking projects in this area: for AIDS/TB drugs, 15 companies; for malaria drugs, 3 companies; and for tropical disease (e.g., sleeping sickness) drugs, 2 companies. (Fournier 2001) While this summary is admittedly not exhaustive, it provides an indication of the apportionment of resources to the various categories of neglected diseases from available information.

This level of contribution is similar to the relative proportion of products already licensed for the same categories in European countries. This indicates that the degree of interest in these

categories of diseases has remained relatively constant over the years. For example, in the United Kingdom, there are 58 drugs, vaccines, and diagnostics licensed for tuberculosis and 41 for AIDS, whereas malaria has only 34, and leprosy, trypanosomiasis, pneumonia, and rotavirus combined account for only 13. (Medicines Control Agency 2001)

Some European countries have launched specific initiatives to address various problems associated with the neglected diseases. For example, France has shown particular concern about the impact of tropical diseases in Africa. The French humanitarian network ReMeD (Network for Medicines and Development) has set up a program to encourage the research, development, and distribution of treatments for tropical diseases. ReMeD will set up a working group on "indigenous medicines." The program will have three objectives: 1) to create a pharmaceutical development policy for tropical diseases, to set up a database of medicines already being used, and to establish a co-operative of companies and research groups in industrialized countries to foster pharmaceutical manufacturing in Africa; 2) to draw up regulatory, financial, and administrative measures to encourage R&D into tropical medicines; and 3) to promote local clinical trials in African centers with the collaboration of French teams, and galenical development. (Scrip 2000)

In May 2001, the UK proposed a global strategy developed by the Performance Innovation Unit (PIU), a special office reporting to the Cabinet secretary of the Prime Minister, to confront the neglected diseases. One of four main targets is to improve incentives for additional research into new more effective products. (PIU 2001)

Spain is taking a different tact, addressing tropical diseases that it believes are impacting the country directly due to the increasing number of immigrants, the adoption of children from other countries, and the increase in tourism. Spain notes that the number of cases of imported malaria went up 160% from 1986 to 1995. It proposes to create a national network of tropical medicine specialized units and a national reference center on tropical medicine for health care, research, and training activities. (Bosch 2001)

Current Status of the EC's Orphan Product Regulations as an Incentive for R&D on treatments for the Diseases of Poverty

Some European countries – France, Spain, Sweden, Denmark, the UK, and Germany - have been interested in orphan drug issues for several years (Euroabstracts 1999). Some of these same countries have expressed concern about the paucity of R&D on treatments for tropical diseases. Despite this concern, however, there have been few approved medicines for tropical diseases in the last few years, either within or outside of the orphan drug program context. The "uneconomic drug" initiatives in the member states have sometimes incorporated the concept of orphan drugs, but until recently these have been uncommon, and have certainly not led to any significant progress in research on rare diseases. (Commission 2000) Of 34 orphan designations granted so far by the EC, one was for leprosy, one was for hemorrhagic fever, and two were for AIDS-related complex, but no others were for the neglected diseases. (Community Register 2001)

At the outset, it was hoped that the European orphan legislation "…will benefit patients not only in Europe but also in developing countries as diseases such as malaria or sleeping sickness would be eligible." (Watson 2000) Similarly, soon after the adoption of the legislation, Fernand Sauer, Executive Director of the EMEA, commented that:

Pharmaceuticals intended to treat diseases, which may have high prevalence in some developing countries, but which are classified as rare in the European Union, such as malaria, may also be designated as orphan medicinal products. (Whyte 2000)

It is unclear at this point whether Europe will go the route of the early US efforts and include tropical medicine R&D under the rubric of orphan drugs. Although the French ReMeD network suggests looking at the orphan legislation as a model for the appropriate framework of regulatory and financial incentives, it wants to differentiate indigenous diseases from orphan diseases, and set up new incentives to promote investment in the development of tropical medicines. (Scrip 2000) More recently, however, there are reports of increasing interest among European manufacturers and legislators in an approach based on modifications of the EC Orphan Products Regulations. (Ronchi 2001)

Disincentives for R&D on Treatments for Neglected Diseases: Implications for the Orphan Drug Laws

There are a number of factors that act differentially as disincentives to R&D for the various categories of neglected diseases. These factors have been enumerated by various industry, public health, and government sources, and yet remain remarkably consistent from source to source. (Lang 1999, Trouiller 1999, Pécoul 1999, WHO-IFPMA 2001) Basically, there are five problem areas: lack of interest; cost-versus-risk ratio; impoverished markets; the North-South gap; and vaccine market concentration. These impediments can be addressed, in part, by modifications of the incentives in existing orphan drug laws.

Lack of interest

Lack of interest in developing drugs for tropical diseases is not a new phenomenon in the research-based industry. From 1910 to 1970, the pharmaceutical industry led the charge in the fight against microbial and parasitic diseases. (Pécoul 1999) Yet, from 1975 to 1997, only 13 of 1223 new chemical entities were developed specifically for tropical diseases. (Trouiller 1999) This lack of interest was already apparent as early as 1981, when Dr. Edmund de Maar, then Senior Program Officer for WHO's Tropical Disease Research (TDR) program, lamented:

Chemotherapy of tropical diseases is the prevention or cure by drugs of some major diseases, ... its application is a good example of protection of health through technology. Regretfully, this area of health technology has suffered from fluctuating interests, for a variety of scientific, economic and political reasons. (de Marr 1981)

The lack of interest by the drug industry in R&D on treatments for tropical diseases within the context of the US Orphan Drug Act was evident early on. An industry survey conducted at the time the ODA was passed queried companies as to what types of incentives would encourage them to develop orphan drugs. (Spilker 1985) The companies rated seven factors on a scale of one to ten. The lowest rated factor was inclusion of tropical or other diseases that are common diseases in the "third world" but not in the US, with an average score

of 2.5 out of 10. The subset of companies with the largest sales rated it even lower, at 1.5 out of 10. Not much has changed in this regard since the mid-1980s. Medecins Sans Frontieres (MSF) recently conducted a survey of the 20 top-grossing pharmaceutical companies on the scope of their drug development for neglected diseases (excluding AIDS). While malaria and tuberculosis are receiving some R&D attention, none of the 11 companies that responded had brought a drug to market in the last five years for any of the most neglected diseases, such as leishmaniasis or sleeping sickness. (MSF 2001)

By the early 1990s, $3800 was being spent on research per cancer-related death and $1,000 per heart disease death, but only $84 per malaria death, and that was the best funded of the tropical diseases. (Trouiller 1999) The insignificant level of corporate interest in R&D on treatment for diseases of poverty has worsened in the current atmosphere of mergers and acquisitions and competition for market share of a few profitable segments of the market.

While industry's lack of interest is responsible, in part, for the dearth of R&D on treatments for tropical diseases, consumer and patient advocacy has provided considerable motivation. Advocacy is defined in the dictionary as *active* support of a cause, idea or policy – a remedy to inaction. David Satcher, the Surgeon General of the US, proclaimed advocacy to be one of three prescriptions for eliminating global health disparity. There have recently been some notable successes in motivating the industry sector through advocacy. For example, GlaxoSmithKline (GSK), which has been the focus of a dedicated advocacy campaign by Oxfam to make essential medicines more available to developing countries, signed an agreement with WHO in March 2001 to develop a new oral treatment for malaria (LAPDAP - a combination of chlorproguanil and dapsone). This treatment will be developed primarily for use in sub-Saharan Africa, and will be made available at a preferential price for public health programs as early as 2002. (Pharma Marketletter 2001)

Advocacy can motivate government policy as well. For example, the growing acknowledgment within the US government of its responsibility to the global community to foster global health was used as justification for the fiscal year 1999 National Institute of Allergy

and Infectious Diseases budget before a US Congress House Appropriations Subcommittee. (Folkers 1998)

Implications for Modifications to the Orphan Drug Laws

The US ODA has a legacy of responsiveness to advocacy. The influence of the National Organization for Rare Disorders (NORD) on passage of the ODA is widely acknowledged. (ODA Amendments of 1992) When the ODA was passed, however, rare cancers, AIDS, and diseases affecting the elderly and other special populations were not contemplated. (Haffner 1994) Yet, the influence of the AIDS Action Council (acknowledged in the legislative record of the ODA Amendments of 1992) on orphan designations and approvals for AIDS and AIDS-related conditions has been remarkable - 100 designations and 24 approvals (see TABLE 3). The National Cancer Society and other cancer advocacy groups have had a similar impact; from 1983 to 1991, only 10 orphan drugs were approved for rare cancers, but from 1992 to 1999, that output nearly quadrupled, to 37. (Milne 2000) Recent advocacy efforts on behalf of special sub-populations have also had demonstrable effects in the last decade on orphan designation trends, as well as on the orphan program goals for the coming decade. (Haffner 1994, Henkel 1995)

The history of designations for neglected diseases also highlights the negative impact of limited or no advocacy on behalf of these indications. For example, there were 11 designations for neglected diseases (out of 213 total, or 5%) in the first full 5 years of the orphan drug program (1984 -1988), but only 8 designations (out of 778 total, or 1%) over the next 12 years (1989-2000). In the 1980s and early 1990s, the FDA and the OOPD espoused tacit support of the use of the ODA to encourage R&D for tropical disease medicines. (Norris 1986, Haffner 1993) Lack of industry interest, the competing R&D needs of other emerging diseases, and the lack of sustained advocacy efforts for neglected diseases may be responsible, in part, for the observed decline of orphan designations for neglected diseases.

The emergent role of patient advocacy had also been recognized by the drafters of the European regulation, when they included three patient representatives on the Committee for Orphan Medicinal Products, "underlining the increasing contribution of patients to the health

care debate." (Tambuyzer 2000) The European advocacy groups can play an important intermediary role by fostering the needs of the developing countries, not only in Europe but in the United States as well. Advocacy efforts must also be directed at other advocacy groups, so that there is unanimity of purpose. For example, the International Alliance of Patient Organizations (IAPO), which is based in Europe but includes member groups from developing countries, could jointly propose that NORD and IAPO support incentives for the developing countries. An argument for such a consensus approach could be based on global public health protection and the basic right of all human beings to enjoy living standards conducive to good health, as enshrined in Article 25 of the United Nations Universal Declaration of Human Rights. (Chintu 2000)

Cost vs. Risk Ratio

Costs and risks are greater for the neglected diseases than for diseases of the developed world. The fixed costs for R&D are high in these disease areas because they often present unique challenges in development. The variable costs are also high due to a number of factors: the immense resources required for production scale-up and distribution for multi-million patient populations in scores of countries; onerous packaging and formulation needs for tropical countries; the expense of multi-cultural, multi-lingual marketing and medical information programs; and the complexity of multi-country regulatory approval procedures. Similarly, risks are high, not only of clinical failure in development (e.g., see TABLE 4), but of market failure, due to low return-on-investment. A recent industry survey indicates that economics and market-related factors have become more prevalent in recent years as the primary reason for terminating compounds. (DiMasi 2001) Product liability, losses to unfair competition and counterfeiting, as well as lack of intellectual property protection, are other frequently cited problems.

Implications for Orphan Drug Laws

While the problem of high costs and high risks plague the R&D environment for all neglected diseases similarly, it affects the various sectors of the industry differentially. Very few large companies do tropical disease R&D, because it takes away resources that could be allocated to more profitable lines; and small companies don't do it, because they don't have the

resources, know-how, or budget. (Olliario 1997) Yet both small and large companies are needed to meet the health needs of developing countries.

Industry has already recognized the potential of orphan drug laws in the US and Europe to be a part of this solution. (Anonymous 1997) The US ODA, for example, combines incentives that lower both the cost and risk of drug development, thus appealing to both small and large companies. While an incentive based on enhanced market protection may be sufficient for an established company with a product to market, small companies, such as start-up biotechnology firms or specialty pharmaceutical companies, also need incentives that lower the costs for entering this high-risk, low-return area of research. One way this can be accomplished is through grants and tax credits. While the US ODA already offers both options, the EC is in the process of developing tax credits and research grant mechanisms at the member state level.

Some believe, however, that tax credits and market exclusivity are not enough of an incentive. Another incentive element is needed in orphan drug laws – i.e., accelerated authorization procedures. (Olliario 1997) Accelerated procedures for final authorization and exemptions from all or part of the registration fee can reduce development costs, staffing requirements, and time to market, making the product a more attractive prospect to industry. (Lang 1999) Exemptions from regulatory fees are already available to a limited extent in both the US and EC. In addition, the US initiated a fast track product development program through the auspices of the FDA Modernization Act of 1997 (sec. 112). Although a review of fast track designated products indicates that at least 50% of these products are also orphan designated products (Tufts CSDD 2001), the two designations (fast track and orphan) are currently made independently. In Europe, the EC has recently adopted legislation for regulatory reform under which the EMEA may grant fast track review to drugs considered important to human health. (Maggos 2001)

Impoverished Markets

Whereas total public and private health spending on pharmaceuticals is less than 20% in most developed countries, it is 25-66% in developing countries. Moreover, while the per capita

income in developing and transitional economies is only 5-10% of the per capita income in developed countries, 50-90% of drugs in the developing countries are paid for out-of-pocket. (Schweitzer 1997; DAP 1999) The poor have no consumer power; the market has failed them. (McNeil 2001) Africa accounts for just 1 percent of drug industry sales. (Vick 1999) By contrast, North America, Japan, and Europe comprised 84% of the market in 1999. (IMS 2000)

At the same time, developing countries' share of world trade has increased from 20% to 25% over the past 15 years, and is expected to rise to 30% within the next decade. (Scrip 1999) In the year 2000, just under 20% of the world's population lived in "the marketplace" for modern medicines, comprised of Europe and North America. By 2050, that figure will drop to about 10%, with 97% of future population growth occurring in developing countries. (Raleigh 1999) Some multinational drug companies, such as GSK, acknowledge that a major portion of their sales growth over the next 10-20 years will come from developing countries. (Anonymous 1997)

The developing world may be a growth area for the pharmaceutical and vaccine industry in 10-20 years, but R&D is needed today. One market-based approach is for rich countries to sign a pledge to buy enough vaccine for developing countries at a guaranteed minimum purchase price, thereby galvanizing research in this area. (Sachs 1999) One study has suggested that the amount of the so-called 'purchase fund' for the neglected diseases would vary from $100-$500 million per product. (PIU 2001) However, a WHO study in 1998, on why new tuberculosis drugs were not being developed, determined that even though target sales vary by company, many would view the minimum target sales to be $200 million per annum, with priority given to drugs with annual sales potential of $1 billion or more. (McNeil 2001)

Nothing on the horizon can replace the role of big pharma in making R&D for these diseases a reality. But it must remembered that the research-based industry is a business, and R&D on medicines for neglected diseases bears scant returns compared to that for other potential markets. For example, in the year 2000, worldwide sales for six orphan drugs approved in the US for malaria and TB had combined total sales of only $75 million (see TABLE 5). In

comparison, the average return on commercial sales for one drug in today's mainstream market is about $265 million annually. (MSF 2001)

Implications for Orphan Drug Laws

The US ODA and European orphan regulations already rely on a market-oriented strategy for incentivizing orphan drug development, by permitting the successful developer to create its own market force through regulatory exclusivity. (Thamer 1998) The existing market exclusivity of seven years can provide a strong incentive to orphan drug sponsors by creating conditions for monopoly pricing. But market exclusivity as an incentive is linked with country-specific pricing and reimbursement policies. This monopoly status may not be sufficient when (1) the cost structure for an orphan drug is inconsistent with that of other pharmaceutical products (i.e., it is too expensive to develop compared to other competing R&D opportunities), or (2) if demand is sensitive to changes in price (i.e., it is so expensive, that too few can afford it, or third-party payers cannot reimburse).

Without the help of market forces, the options are few. The industrialized nations must carry the burden and either pay the manufacturers of medicines for neglected diseases directly, offer tax breaks, *provide longer patents on their most lucrative drugs*, or allow countries in crisis to declare health emergencies and to ignore Western patent law. (McNeil 2001) Industry representatives have spoken publicly in recent months about sustainable solutions that include legislation, which will genuinely affect R&D funding and agendas. (Scrip 1999)

Some have suggested that an incentive system is needed that transcends the market for unmarketable categories of drugs. This incentive system would provide a period of market exclusivity, not on the orphan product itself, for which even a guaranteed market may not be a sufficient incentive, but on another product, which the sponsor of the orphan drug feels would represent a sufficient incentive if its period of market exclusivity were extended. This variation of market exclusivity is called "transferable" or "roaming exclusivity." The period of market protection can take the form of a patent extension, enforceable in multiple countries through existing international treaties, or a period of market exclusivity provided by the regulatory agency of the country granting the orphan approval, enforceable only in that country or countries

with mutual recognition agreements. Thus, there would be the need to implement a system of multi-country mutual recognition of marketing exclusivity approval for a specific product to provide protection in the major global markets as well as to avoid undesirable competition for the same designation.

A precedent for this concept was provided in the US, to justify the addition of a pediatric studies provision to the FDA Modernization Act of 1997. Drug sponsors are awarded a 6-month extension of market exclusivity for all products they own that have the same active ingredient as the product for which the pediatric study was conducted. This provision recognized that the population directly benefiting from the clinical studies (i.e., children) did not constitute a sufficiently lucrative market. Currently, a transferable exclusivity has been proposed as an upgrade to the six-month pediatric studies exclusivity to encourage R&D for those products that remained unattractive to industry. (FDA 2001)

In the context of encouraging R&D on medicines for neglected diseases, a recent analysis of incentives by the Performance and Innovation Unit (PIU) within the British Cabinet proposes an international roaming exclusivity. This is described as a patent extension granted on an unrelated (revenue earning) product. (PIU 2001) A similar mechanism, called "patent exchange," has also been proposed in a recent analysis of neglected disease R&D conducted for a report by MSF. (MSF 2001) This approach is not without rough edges that would need to be ironed out, especially in Europe (i.e., agreement on the target product, agreement on the length of the transferable exclusivity in light of varying reimbursement and pricing practices across countries). The trade-off implied by a market approach has already been noted in the context of orphan drug laws several years ago in an editorial in the Lancet, which stated: Orphan drug development could turn out to be the acceptable face of disease-driven commerce. (Anonymous 1995)

North versus South: Bridging the Hemispheres

The means and ends of the developing and developed countries even for shared problems are often at odds. For example, the Director of UNICEF has commented that current efforts

directed towards developing an AIDS vaccine are focusing on variants affecting people in Europe and North America, rather than on those affecting people in Africa or Asia. (Birmingham 1998) The traditional model for global access to immunization has meant that the developing countries get new vaccines 10-15 years after they are available in the rest of the world. (Anonymous 2000) Several compounds with prolific trypanocidal activity and potential as treatments for African sleeping sickness have been identified, but because they are Ames-test positive, they are unlikely to be developed in the US, since they are considered potentially carcinogenic. (Barrett 1999)

Even when an orphan drug is developed with potential use in tropical diseases, the indication targeted is often a more lucrative disease, such as AIDS or cancer. As a result, the medicine is often priced too high for people in developing countries to afford. For example, atovaquone when combined with proguanil, can be used for malaria, but it is also used for AIDS-related P. carinii pneumonia. (Olliario 1997) The positive side of this phenomenon is that orphan drugs approved for one indication have sometimes ended up as treatments for other indications, by virtue of science or serendipity (See TABLE 6).

In the long term, the developing world will have to develop its own R&D infrastructure to achieve a sustainable solution for addressing indigenous health concerns. One positive trend is the emergence of the Multilateral Initiative on Malaria (MIM), which aims to develop linkage between scientists in the developed and developing world to tailor disease control to local needs. (Ridley 2001) The US National Institute of Allergy and Infectious Diseases is striving to improve the competency of African scientists working on malaria prevention and control, and is investing in drug development, vaccine research, and a minority training program. (Newman 2001)

In the short term, R&D for many neglected diseases will not occur, simply because it is not commercially viable. If it is a poor investment for "big pharma," then it is also likely to be an unattractive investment for local companies as well, since they must produce investment yields consistent with worldwide rates, unless they obtain outside subsidies. (Schweitzer 1997)

This is where charitable foundations, corporate sponsors, and government can bridge the gap. Prioritization of grants by the US and EC orphan drug programs could provide a feasible starting point for early stage R&D. If the results are positive, then these efforts could later be continued with industry or private/public partnership funding.

Implications for Orphan Drug Laws

How could such a prioritization scheme be justified? The globalization of public health is part of the problem presented by the neglected diseases, but it can also be part of the solution. (Fidler 1997) Two million people each day cross national borders. (Satcher 1999) With international travel increasing by 50% each decade, the prospects of containing new outbreaks of disease are diminishing. (Kapp 2001) Infectious diseases are the leading cause of death worldwide, but they are also the third leading cause in the US. (Binder 1999) At least 30 newly recognized diseases and syndromes have been identified since 1980, including AIDS. (Folkers 1998) A report from the US National Intelligence Council has outlined the worldwide threat presented by infectious disease to military capacity, socioeconomic development, international trade and travel, and global stability. (Folkers 2001) Similarly, the Security Council of the United Nations (UN) discussed a health issue – HIV/AIDS in Africa – for the first time as a threat to world stability. (Gopal 2000)

A *prioritization* scheme has already been suggested in the context of amendments to the US ODA. The scheme would have placed the demand for an orphan product in the developing world among the factors considered when prioritizing orphan diseases. According to this proposal, such high-priority projects would receive targeted grant funding, greater tax incentives, and longer periods of market exclusivity. (Peabody 1995) Some industry executives as well have stated that public health consequences for the developing world are important to them, as is goodwill, and could be addressed by developing a list of priority orphan vaccines. (Lang 1999)

Vaccine Market Concentration

In many respects, the challenges for encouraging R&D on vaccines for neglected diseases are more significant than those for encouraging R&D on drugs. A spokeswoman for Genzyme put it bluntly: "it would be disingenuous to claim that pharmaceutical companies historically had

some interest in developing vaccines against diseases that affect people in third-world countries." (Dove 1998)

By any measure, vaccines are the most cost-effective health product for addressing the neglected diseases, compared to drugs and vector control measures. (PIU 2001) Therefore, it is critical to find incentives that are appealing to industry. Industry has shown a willingness to re-enter the field, but this interest has been tempered by the reality of what vaccine development entails. For example, Merck disappeared from the field of AIDS vaccine R&D after the failure of its 6-year effort based on an antibody approach. Merck has recently begun small human studies using a new approach, but the company admits that it will take at least five years before it will be able to determine whether this approach is going to work or not. (Cohen 2001)

The Director of the International Vaccine Institute, a private/public partnership created to provide assistance in the developing world, emphasizes that certain realities must be taken into account in order to address the problem of producing vaccines for the developing world. The first is that vaccine development today is 'high tech,' requiring expertise in multiple scientific disciplines, large numbers of skilled staff, and costly investment in research and manufacturing facilities. For example, GSK received $6.7 million from the Malaria Vaccine Initiative to step up development of a malaria vaccine candidate in progress since 1983. A GSK spokesperson said that the company welcomed the funding, but added that it takes around $500 million to develop a vaccine. (Pharma Marketletter 2001)

A second reality is that globalization of international commerce, forcing those wishing to stay competitive to consolidate, has resulted in the domination of the global vaccine industry by a few large multinational companies. (Shin 1998) IMF missions or World Bank health-sector loans alone cannot produce a malaria vaccine. Monsanto, a life-science MNC, has an R&D budget that is more than twice the R&D budget of the entire worldwide network of public sector tropical research institutes. (Sachs 1999)

The third factor is that although vaccine development has become primarily the purview of large industrial laboratories, it is often augmented in key segments by specialized biotechnology companies funded by venture capital. The involvement of venture capitalists necessitates that their investment be protected through internationally enforced patents. (Shin 1998)

The fourth factor is that increasingly stringent international product safety standards required of vaccines has particular implications for the supply of vaccines to developing countries. (Shin 1998) Several of the larger developing nations are significant producers of vaccines, but few of these vaccines can be exported because they can't meet the international standards for safety. Since their facilities are older, significant investment would be required to bring them up to speed. At the same time, new candidate vaccines for HIV, tuberculosis, and malaria, need to be evaluated in the populations affected in the developing world. (Shin 1998) So, while the needs are great in many poor and transitional economies, their capacity to meet those needs is limited in the near-term.

Implications for Orphan Drug Laws

Throughout most of the history of the US ODA, these realities have acted as barriers to the participation of vaccine manufacturers in the orphan drug program. In addition, there were concerns early on related to the inadequacy of orphan grant amounts and the capacity of vaccines to meet the eligibility requirements for orphan designation. (Lasagna 1984) Not surprisingly, a review by two industry analysts of the FDA's orphan designation web site revealed that as of the end of 1997, only 8 orphan designations were for vaccines. (Lang 1999) In a follow-up to that report, two commentators from the Centers for Disease Control (CDC) and the US National Institutes of Health (NIH) further noted that none of the 194 orphan drugs then approved were vaccines. (Schwartz 1999)

Nonetheless, the horizon is brightening for smaller companies searching for a pathway into the field of vaccine R&D. Although the "…huge costs associated with developing and manufacturing vaccines…", as well as development times of 15-17 years, ensure the domination of large manufacturers, circumstances have changed somewhat in the last few years. (Siwolop

2001) Four companies still dominate the vaccine market, but there are now some 50-60 smaller and mid-sized vaccine companies operating in the US alone. (Siwolop 2001, Reichert 2001)

Analysts point to several factors as responsible for engendering this expansion in the number of vaccine sponsors. One is the success of a federally mandated vaccine injury liability fund. Another is the attention-grabbing philanthropic efforts of the Bill and Melinda Gates Foundation, the recent opening of NIH's vaccine research center, and the existence of several private-public partnerships focused on vaccine development. Lastly, advances in immunology and biotechnology have made approaches available that were not even contemplated 10-20 years ago. (Siwolop 2001)

As a likely consequence of this incipient evolution in the vaccine R&D environment, which appears to be especially favorable to smaller companies, the US orphan drug program is experiencing an upsurge in activity related to vaccines. Whereas only eight vaccines were designated as orphans in the first 15 years of the program, four vaccines have received orphan designations in the last three years. All of these products have been sponsored by smaller specialty drug and biotechnology companies. (Tufts CSDD 2001) Moreover, biotechnology companies are increasingly turning to the US government for funding now that private capital is scarce. (Healthline 2001)

Both small and large companies have a role to play in vaccine R&D for neglected diseases. For example, in AIDS vaccine research, the emphasis of Phase I clinical trials[3] must be to reject poor performers early, thereby avoiding the costly commitment of precious resources on a product that will eventually fail in development. This is a challenge to the corporate practice of large companies, and beyond the financial capacity of smaller companies, which is why alternative funding mechanisms must be developed. (Burton 1998)

There are various approaches that could work as sources of alternate funding for smaller companies. The World Bank, or similar institutions (also private/public consortia) could

[3] Vaccine and drug research and development is typically described as comprised of a number of periods encompassing discovery, preclinical research (animal and laboratory testing), clinical testing (on humans) which consists of Phases I, II, and III, culminating in regulatory agency review and approval for marketing.

subsidize the early stages of drug and vaccine discovery to spread the financial risk. (Anonymous 1997) Alternatively, investigational treatments could be developed up to the patent stage and then sold to governments or producers in foreign countries interested in pursuing further development and marketing of promising products. (Reich 2000) Once a promising candidate has reached Phase II, the corporate experience and expertise of large companies in vaccine development will be essential. (Burton 1998)

Additional orphan program incentives may be necessary to encourage vaccine R&D for the neglected diseases. Of 14 products currently with orphan designations for neglected diseases (one for malaria, two for TB, and 11 for AIDS), none are vaccines. Some remedies suggested by vaccine manufacturers include: increase the period of market exclusivity; facilitate national/regional product approval procedures; seek funding for orphan projects from private bodies looking to capitalize on an ethical business image; advance the concept that world public health concerns support measures to produce affordable orphan vaccines; expand and harmonize orphan drug policies as part of the ICH process[4]; and, strengthen political and public health collaboration between orphan programs and other countries by creating a supranational office dedicated to orphan vaccines. (Lang 1999)

Along the same lines, commentators from the CDC and NIH point out that lowering the risks or costs of orphan vaccine development may be much less important than increasing the potential for profit. If large manufacturers shift vaccine development priorities on the basis of incentives and other measures so that the total number of products brought to market is not increased, but instead one set of priorities is substituted for another, the overall impact on disease prevention may not be the desired change. The greatest increase in disease prevention and in the development of orphan vaccines would occur by increasing the total number of vaccines produced. Thus incentives that draw new companies to invest in vaccine development may be extremely useful for the development of orphan vaccines. (Schwartz 1999) These statements by

[4] The International Conference on Harmonization (ICH) was established in 1990 as a joint regulatory agency/industry project. The founding objective was to improve, through harmonization, the efficiency of the process for developing and registering new medicinal products in Europe, Japan, and the United States (other countries and international organizations have a presence in the process as observers) to minimize delay and make these products available to patients.

industry, CDC, and NIH would appear to support modifications of the orphan drug laws such as a *transferable exclusivity*, product *prioritization* based on global public health criteria, *fast-track regulatory review*, and *international cooperative agreements.*

CATEGORIZATION OF THE NEGLECTED DISEASES AND THE IMPACT OF MODIFIED ORPHAN DRUG LAWS

Whether the ODA has been a success as an incentive program for R&D of neglected diseases depends on expectations and perspective. In the 20 years before the ODA came into force in 1983, there were 13 new drugs approved for neglected diseases in the US (including TB, malaria and tropical diseases, but excluding AIDS). In the nearly 20 years since the ODA, only ten new drugs for these same diseases have been approved, but eight of those were orphan designated drugs (see TABLE 7). For malaria, tuberculosis, and sleeping sickness in particular, there have been 16 orphan designations granted so far, and eight have resulted in product approvals (see TABLE 7). In addition, another five orphan drugs approved for other indications are being used off-label for malaria and sleeping sickness (as well as leishmaniasis and leprosy). Taken together with the 20 orphan approvals for AIDS treatments, the US ODA has contributed significantly to the current medical armamentarium for the neglected diseases.

Clearly, however, more is needed. The existing range of products to tackle HIV/AIDS, TB, and malaria are not effective enough – especially against new drug-resistant strains. (PIU 2001) Effective population-based vaccines against HIV, TB, and malaria are years away. Products for human African trypanosomiasis and other tropical diseases have these same problems, as well as often being unaffordable or unavailable in developing countries (see TABLE 1).

The neglected diseases have particular research needs, global public health implications, and market dynamics, such that modifications to the orphan drug laws may impact R&D for neglected diseases in a differential manner. To facilitate a discussion on this issue, the neglected diseases have been divided into three categories, and representative diseases are selected to serve as examples.

The first category consists of neglected diseases with global public health impact and a global market (e.g., HIV/AIDS, pneumonia, and diarrheal diseases). AIDS has been chosen as a representative of this category based on its worldwide public health consequences and the fact that it represents a newly emergent pandemic. AIDS is not a neglected disease in terms of the magnitude of either private or public sector investment in R&D, but in terms of the types of products that have ultimately resulted from that investment.

The second category encompasses neglected, predominantly tropical diseases (e.g., tuberculosis, malaria, intestinal parasites and leprosy) that have public health importance for the developing world as well as the developed world, but in less significant global markets. Tuberculosis and malaria were both selected as examples for this category. These two diseases represent somewhat different ends of the spectrum for this category; tuberculosis has greater public health implications for the developed world, but is a less attractive R&D investment; whereas, malaria has less significance in the developed world, but is considered a better R&D investment.

The third category is comprised of neglected, exclusively tropical diseases of public health importance in the developing world, but of little public health and economic significance in the developed world (e.g., African sleeping sickness, Chagas' disease, schistosomiasis, trachoma, lymphatic filariasis, onchocerciasis, and leishmaniasis). African sleeping sickness, also known as human African trypanosomiasis (HAT), was selected as a representative disease for this category because it exhibits many characteristics typical of the other tropical neglected diseases. These characteristics include significant morbidity and mortality confined to the developing world, vector-born transmission, and a history of re-emergence as a public health threat.

AIDS

Acquired immunodeficiency syndrome (AIDS) is caused by an infection with the human immunodeficiency virus (HIV), transmitted through sexual contact, blood or blood products, or

mother-to-fetus. As of 1999, more than 18.8 million people worldwide have died of AIDS, and 34.3 million are infected with HIV. (Letvin 2001) In sub-Saharan Africa, only an estimated 10% of the predicted illness and death has occurred; the full impact on people, communities, and economies is still to come. (Logie 1999) In developing countries, AIDS is inextricably tied to the other diseases of poverty; it contributes to the morbidity and mortality of malaria and tuberculosis, and takes away resources that would be dedicated to the treatment of other tropical diseases.

There are a number of drugs marketed for AIDS and AIDS-related conditions (See TABLE 1). However, resistance is on the increase in the developed countries. In San Francisco, for example, researchers found that 14% of all new cases of HIV infection are already resistant to at least one anti-AIDS drug, while studies in France and Switzerland showed the rate to be up to 10%. (MSNBC Online 2001) The multi-drug cocktails (Highly Active Anti-Retroviral Therapy, or HAART) are reaching the limit of their capacity to stem the tide of AIDS symptoms. A recent study of patients in the US who began HAART in 1996 showed that almost 20% have developed AIDS again or died over the past 5 years. Moreover, administering HAART to patients newly infected with resistant viruses only exacerbates the problem. (Sternberg 2001) Toxicity and side effects of the drugs are still problematic. For example, stavudine and didanosine may increase the risk of fatal lactic acidosis in pregnant women, especially when combined with other medications. (CNN Online 2001)

Current Status

The Pharmaceuticals Research and Manufacturers of America (PhRMA), listed 103 drugs in development for AIDS and AIDS-related conditions in 2001. (PhRMA 2001) This is encouraging, as new treatments are desperately needed. It is worth noting, however, that only one significant breakthrough in HIV/AIDS treatment – the so-called "fusion" inhibitors currently in late-stage clinical trials – has been identified, since the protease inhibitors were first approved in 1996. Whereas part of the reason for the slow pace of new AIDS drugs introductions is the difficulty of treating the virus, another major factor is commercial. Creating different versions of

existing drugs guarantees that there will be at least some measure of therapeutic, and hence, commercial success. This approach has had benefits; sometimes these drugs have found therapeutic applications against other diseases, such as hepatitis. (amfAR 2001)

Development of an AIDS vaccine will be difficult but essential to controlling the epidemic. (Shann 1999) Ten major genetic subtypes of HIV-1 (or clades) have been identified, each with a distinct geographical spread. While initial efforts have focused on matching vaccine strains with those in the trial population, future efficacy testing will be required to pursue cross-protection between different subtypes. (Esparza 2000)

At the time the anti-retrovirals emerged in the mid-1990s, only 1% of AIDS spending was on vaccines. The International AIDS Vaccine Initiative (IAVI), a nonprofit consortium, has doubled spending on vaccine research to $350 million. (Vick 1999) The history of the development of an AIDS vaccine is littered with the carnage of formerly "promising" vaccine candidates. To date, more than 30 have been tested, primarily in the US and Thailand, and eventually proved to be ineffective or only partially effective. (Vick 2001) Currently, there are around 30 candidates for HIV vaccines, but IAVI says only one is in phase III and two are in phase II. One vaccine manufacturer says a viable vaccine is still 8-10 years from reaching the market. And there are other problems – the vaccines may be effective on only 40% of inoculated individuals, and they are likely to need tailoring for different parts of the world. (Anonymous 2000)

In a promising new development for AIDS control in developing countries, scientists in England and Kenya have developed the first experimental vaccine expressly intended for Africa. The research is based on the observation that prostitutes in Nairobi have developed a natural resistance to the disease. Early phase trials are now under way and show promise for stimulating killer T-cells. (Vick 2001) But the enthusiasm must be tempered by the fact that while the vaccine, at best, will make it more difficult to become infected, it will not provide absolute immunity against the virus. Also, its utility for the developing world will likely be limited to Africa, and it is still years away. (Vick 2001)

The Impact of Modified Orphan Drug Laws on AIDS R&D[5]

The market dynamics for AIDS as a neglected disease bears some similarity to malaria, in that much of the R&D is focused on products for the developed world market. It also bears some similarity to TB in that resistance, toxicity, cost, and compliance will pose significant challenges to the creation of a vaccine. Unlike TB, the neglect is not so much the level of total funding, but where and how the money is spent, i.e., not on new approaches to therapeutic advances and not on medicines tailored to the developing countries.

AIDS advocacy has been a potent force, and has even given rise to a new term to describe the phenomenon – AIDS exceptionalism. (Casarett 1998) The impact of this phenomenon becomes apparent when the relative levels of research funding for the three major neglected diseases are compared. Health research funding worldwide for malaria totaled $60 million; for tuberculosis, it was $19-$33 million; while for AIDS, it was $919-$985 million. (Michaud 2001) Funding from the US National Institutes of Health (NIH) for TB and malaria is $6.5 million and $25 million, respectively; this is compared to $250 million for AIDS. (Enserink 2000)

AIDS not only commands a disproportionate share of R&D funding, it dominates the marketplace as well. Drugs developed for other diseases can become unavailable for that indication if an AIDS indication is discovered (e.g., see *infra* discussion of pentamidine for African sleeping sickness). However, AIDS R&D can benefit the other neglected diseases as well. For example, atovaquone was developed to treat an AIDS-related condition, but is now being used in combination with proguanil for malaria. Most importantly, controlling AIDS is crucial to achieving control of the other neglected diseases, especially TB and malaria. At the same time, unless pre-existing diseases endemic to developing countries, such as helminthiasis,

[5] While AIDS exemplifies the relevance of orphan drug laws as an incentive for R&D of category 1 diseases, there is concern regarding other category 1 diseases, in particular diarrheal diseases and pneumonia, as to whether or not they meet the prevalence threshold for orphan designation in the US. The most significant global public health impact from these diseases is childhood mortality. The five agents most consistently identified as the cause of life-threatening diarrhea worldwide are: rotavirus, E.coli, Shigella, Camphylobacter jejuni, and cryptosporidium. While highly prevalent globally, only Camphylobacter is questionable for meeting the prevalence threshold for orphan designation in the US (i.e., >1 but <200,000). The majority of childhood pneumonia worldwide is caused by S. pneumoniae and H. influenzae, both of which would meet the prevalence criteria for orphan disease designation in the US. (CDC 1999, WHO 1999, Gorbach 2001)

are brought under control, the efficacy of certain types of AIDS vaccines is likely to be compromised. (Markus 2001) These complex dynamics underscore the need for statutory incentives that equalize access to R&D funding for all the neglected diseases, without diminishing current levels of investment in AIDS R&D.

Historically, the ODA has been a productive avenue for AIDS and AIDS-related conditions, resulting in 77 orphan designations and 20 orphan approvals. Currently, there are eight orphan designated products in development (five active and three inactive; none of these products is a vaccine). (Pharmaprojects 2001) This highlights the fact that the ODA is still a useful avenue for AIDS research. Moreover, the ODA now has a built-in mechanism that will permit other neglected diseases to compete for funding with AIDS.

As of 1993, reclassification by the CDC of the definition of AIDS has resulted in a lack of eligibility of some AIDS treatments for orphan designation, due to the prevalence threshold. Nonetheless, the ODA prevalence limitation is not particularly relevant as an obstacle to R&D of an AIDS vaccine intended for use in developing countries, which would likely involve a different strain than the one prevalent in the US (as long as there was at least one case in the US). Also, drugs for many AIDS-related conditions continue to be granted orphan designations. Some of these have already found utility as treatments for other neglected diseases (see TABLE 6). Increased orphan grants could be useful to incentivize R&D efforts in foreign countries, in which AIDS vaccine funding may still need a boost and where modest amounts may be enough to have an impact on building an R&D infrastructure, especially if discovery and pre-clinical testing expenditures become eligible. Similarly, a transferable exclusivity award could provide the necessary incentive to vaccine companies in developed countries interested in developing an AIDS vaccine designed for use in developing countries. This incentive would have the additional benefit of allowing such companies to derive their guaranteed profit stream from the market in countries with greater wealth, rather than in poorer countries.

Tuberculosis

Tuberculosis is a chronic bacterial infection, typically transmitted by inhalation of airborne droplets inoculated with Mycobacterium tuberculosis, and less typically with M. bovis or M. africanum. TB kills 2 million people annually. (Letvin 2001) The two most populous countries, China and India, account for an estimated 3.1 million of the world's 8 million incident cases in 1997. (Espinal 2001) The worldwide incidence of TB increased 5% in the period 1997 to 1999. (WHO 2001) The emergence of multidrug-resistant tuberculosis (MDRTB) and co-infection with immune suppressing HIV are believed to be responsible for the dramatic increase in the incidence of disease. (Letvin 2001) The co-infection rate of TB cases with HIV was 8% worldwide in 1997, but 32% in sub-Saharan Africa. (Dye 1999)

The accepted regimen for treating TB is a cocktail of drugs, which needs to be administered over a period of months with supervision to ensure compliance. This process is referred to as directly-observed-treatment-short-course (DOTS). Only 21% of patients received DOTS worldwide in 1998. (Stokstad 2000) The DOTS treatment failure rate for MDRTB ranges from 15% to 77%. (Heymann 1999)

TB is very much a global public health problem. For example, London is currently dealing with a significant outbreak of TB. (Scrip 1999) In Europe, drug resistance has risen by 50% in Germany and Denmark since 1996, to rates of 10% and 13% respectively. In New Zealand, drug resistance has doubled to 12%. Worldwide, there are 200,000 to 300,000 new MDRTB cases. (Gupta 2001) In the US, a recent outbreak in New York City had a MDRTB rate of 9% (resistance to two or more drugs) and took several years and $1 billion to get under control. (Stokstad 2000) WHO has expressed particular concern about the spread of tuberculosis worldwide by airline travel of over 8 hours, and has issued guidelines to address this threat to public health. (Scrip 1999)

Current Status

With one-third of the world infected with TB, 10% of which will develop active disease, the present DOTS approach is limited in its potential to address the TB pandemic. (Pym 1999) WHO and the International Union against Tuberculosis and Lung Diseases want to encourage

greater use of fixed-dose combination products (FDCs), which contain two or more of the essential antituberculosis drugs used in DOTS: rifampicin, isoniazid, pyrazinamide, ethambutol, and thiacetazone. FDCs can cut the number of tablets that must be taken, from 16 to three or four, eliminate disruption of treatment caused by supply problems with single dose products, and avoid monotherapy, which is the leading cause of drug resistance. (Scrip 2001)

Resistance, toxicity, availability, expense, and compliance are the major challenges to pharmacotherapy of TB (see TABLE 1). In the US, as a result of the TB crisis in several inner cities, the FDA urged Pfizer back into production of streptomycin, which the company had stopped producing due to lack of commercial viability. There are no new drugs for the treatment of MDRTB in clinical trials and effective new drugs for TB are at least a decade away. (Scrip 2000) MDRTB treatment costs can range from $800 to $10,000 in a developing country. (Heymann 1999)

The only currently available vaccine is BCG, which has wide variability in its effectiveness. (Letvin 2001, Das 2001) While there are over 40 potential vaccine candidates, the cost and complexity of advancing even one of them into Phase III trials is enormous. (Pym 1999) There are four basic populations that have to be tested for vaccine efficacy: infants at high risk for early infection; tuberculin-positive healthy adults; uninfected individuals; and the general population. Because a major cause of post-primary tuberculosis is exogenous re-infection (as opposed to endogenous reactivation), some crucial questions have emerged. These questions relate to determining appropriate strategies for chemoprophylaxis of different exposed populations, designing trials that accurately measure an agent's efficacy, and ascertaining the difficulty of developing effective vaccines if natural infection does not confer protective immunity (van Rie 1999)

The Impact of Modified Orphan Drug Laws on Tuberculosis R&D

The pipeline for TB drugs is much less active than that of malaria or AIDS, with just one product recently launched and only two in late stage development (see TABLE 2). One reason for the stagnant pipeline is that TB was nearly eradicated in the developed world, and research

priorities were refocused on other disease areas. (PIU 2001) Tuberculosis suffers from this stigma as an "old" disease. One of the most active areas of TB research currently is in the "new" field of diagnostics to identify drug resistant strains and to determine the chemotherapeutic susceptibility of resistant isolates. (Ronchi 2001) This is an important area of R&D, but it needs to be coupled with a reinvigoration of interest in traditional R&D for new chemotherapeutic agents. However, potential developers of R&D drugs and vaccines still face high costs of development, and the perception that the potential global market is insufficient to guarantee return on investment. (Scrip 2001) In one respect, the market dynamics for TB are analogous to malaria, in that there is a lucrative market for drugs for the developed countries, but not for the developing countries. Developers of TB drugs, vaccines, and diagnostics, however, have greater R&D complexities and costs to overcome.

While the availability of R&D funds for tuberculosis is growing commensurate with the increase in global public health concerns, the market for TB drugs in the rich countries does not approach that for AIDS. In fact, the current worldwide market for TB drugs is approximately $455 million; 60% of this represents sales to private doctors and hospitals, and the remainder to public programs. (Scrip 2001) Even if a purchase fund for a TB vaccine or breakthrough drug was amassed at the maximum projected figure of $500 million, the worldwide market falls short of supporting a blockbuster product, i.e., on with $1 billion in sales. Moreover, research needs for tuberculosis are expansive and expensive. Transferable exclusivity could rectify the market shortfall. Prioritized and increased orphan grant funding could contribute to early stage R&D for efforts to produce TB vaccines tailored to the specific needs of the developing world.

Malaria

Malaria is a protozoal infection typically transmitted by the bite of the male anopheline mosquito. The disease is caused by four species of Plasmodium (P. falciparum, P. vivax, P. malariae, and P. ovale), of which the falciparum (malignant tertian) malaria is the most serious form. Malaria kills 1-3 million people annually and accounts for 300-500 million new infections every year. In many parts of the world, malaria is more common today than 25 years ago.

(Letvin 2001) HIV-1 infection leads to increased frequency of symptomatic and symptomless malaria. (Verhoef 2001)

Malaria is a major public health problem in more than 100 countries, inhabited by some 2.4 billion people. (Persidis 2000) Over the last 30 years, there have been 87 cases of "Airport malaria," i.e., malaria infection in people living near airports, in 12 countries. Non-indigenous mosquito species have been established in countries solely through introduction by foreign visitors. (Nation's Health 2000) More than 7 million US citizens, including business travelers, military personnel, airline employees, vacationers, and missionaries, travel to malaria-endemic areas each year in sub-Saharan Africa, Southeast Asia, the Amazon Basin, and the islands of the South Pacific. More than 1,000 cases of acute malaria are reported each year from this type of exposure. (R&D Directions 2000)

Although several new drugs have been developed over the past 20 years – atovaquone, malarone, halofantrine, mefloquine, proguanil, artemisinin derivatives, co-artemeter, and tafenoquine – few of the currently available drugs are totally free of problems (see TABLE 1). One problem is that some of the current agents have serious side effects. For example, halofantrine can occasionally cause serious cardiac complications. (CDC 2001) Another significant problem is resistance. Of 100 countries with P. falciparum malaria, only Central America and Egypt have not recorded cases of chloroquine resistance, as well as resistance to fansidar and mefloquine. (Folkers 1998)

The ongoing malaria epidemic in Burundi, affecting some 700,000 people, highlights the significant global impact of resistance. Whereas the national policy in Burundi calls for the use of chloroquine to treat malaria, resistant to that agent is widespread. As a result, WHO recently advised the government of Burundi to switch to sulphadoxine-pyrimethamine. Unfortunately, there are now growing reports of resistance to that agent as well. (Etchegorry 2001)

Current Status

Malaria control in Africa has been complicated by both drug resistance of the parasites and insecticide resistance of the *Anopheles* mosquito. Other complications arise from the deterioration of political and health care infrastructure, movement of non-immune refugee populations into malaria-endemic areas, and the population explosion in the sub-Saharan region. (Letvin 2001) Successful malaria eradication requires the cure of every infected host by anti-malarial agents and complete interruption of transmission. (Fang 2001) New and affordable drugs are needed in better formulations in the developing world. Even so, there is still concern that wide-scale chemoprophylaxis could substantially increase the growth of drug resistance. (Goodman 1999) Vaccines are clearly crucial to achieving some measure of long-term control.

It has proven difficult to produce an effective malaria vaccine. For example, several types of malaria vaccines are needed: one for nonimmune travelers; another for young children in sub-Saharan Africa limiting virulence without preventing infection; and a third directed at the sexual phase of the parasite to reduce transmission within the community. (Letvin 2001) Parasite proteins exposed to the immune system have many polymorphisms and can force a non-protective immune response, or induce apoptosis of immune T-cells. (Shann 1999)

Promising developments in malaria vaccine research, however, have occurred. Persons living in hyperendemic areas develop a high degree of immunity, and protection has been provided experimentally by immunization with irradiated sporozoites. (Shann 1999) DNA-based vaccine technology holds the promise of being especially suited for tropical use, because the vaccine comes in a dry form that remains stable until reconstitution just prior to use. (Kumar 2000) Completion of the assembly of the P. falciparum genome within the next two years should allow researchers to identify potential antigenic targets. (Kumar 2000)

The Impact of Modified Orphan Drug Laws on Malaria R&D

Malaria elicits attention from industrialized countries because it represents both a marketing opportunity and a public health concern, especially to the US military and their

families. The US Navy, for example, has had a malaria program for 12 years, with a focus on vaccines for the past five years. (Signals 2001) The Walter Reed Army Institute of Research is also involved in evaluating several new applications of existing agents in the war against malaria – tafenoquine for use in children and to block transmission of the parasite, as well as azithromycin for use in anti-malarial combination treatment, especially for children and pregnant women. (NIAID News Sept. 2000)

Malaria as an endemic tropical disease, however, is the object of neglect. While the prospect for a short-term vaccine for temporary residents and tourists in tropical countries is expected in the near future (Newman 2001), prospects for a long-term vaccine providing protection to inhabitants of an endemic area is still 7-15 years away. (Persidis 2000)

The malaria product development pipeline is currently active. The developers are diverse geographically (e.g., Australia, UK, Switzerland, USA, India) and involve a variety of sectors, including big pharma, biotech, academia, government, and private/public consortia (See TABLE 8). Interest in malaria R&D is due, primarily, to the growing competition for the lucrative traveler chemoprophylaxis market. Even as various drugs and combinations are being tested in comparative studies and cost-effectiveness issues are emerging in the developed countries (Croft 2001), the developing world is anxiously awaiting the discovery of a truly safe, effective, and affordable malaria treatment.

The amount of the purchase fund needed for a course of malaria treatment in sub-Saharan African children would be approximately $250 million annually. (Scrip 1999) The anti-malarial market is currently about $200 million, for the most part limited to the traveler market. (Ridley 2001) Even if the purchase fund were expanded to cover all children in all poor countries with endemic malaria, the current worldwide market for malaria treatments may not rise to the level of blockbuster status. Thus, even though there is a lucrative market for travelers and the military, a transferable exclusivity would be needed as an incentive for vaccines designed for patients in the developing world, and to keep ahead of the wave of resistance to currently available drugs.

African Sleeping Sickness

African sleeping sickness is caused by a protozoal infection with Trypanosoma brucei gambiense or rhodesiense, transmitted by the bite of the tsetse fly. Infection is generally confined to tropical Africa, but another form of trypanosomiasis (Chagas' disease) affects South America. The death toll from human African trypanosomiasis (HAT) in 1996 was 150,000, and there were 200,000 new infections. (Pécoul 1999) It is believed that 450,000 people may be currently infected and 60 million are at-risk. The disease had almost vanished from Africa by the 1960s, but surveillance, reservoir control, and vector eradication waned, and wars obliterated national health programs and displaced infected individuals who migrated with their parasites. (Barrett 1999)

There are some public health implications of this disease for the industrialized nations, but they are not considered significant. The vector of African trypanosomiasis, the tsetse fly, has been found in aircraft completing international flights. (Scrip 2000) Travelers, foreign workers, and immigrants returning to their home countries for extended visits are at risk for infection. Aside from these concerns, however, trypanosomiasis represents little threat to spread outside its endemic region.

There are only four drugs generally recognized as treatments for this disease: melarsoprol; eflornithine; suramin; and pentamidine (See TABLE 1). Melarsoprol, eflornithine, and pentamidine are all owned by Aventis, while suramin is owned by Bayer. (McNeil 2001) Suramin and pentamidine can be used only to treat the early hemolymphatic stage of the disease, before there is CNS involvement. WHO had to intervene to keep suramin in production by Bayer, and it had to negotiate a special contract for pentamidine after Rhone-Poulenc-Rorer (now Aventis) found it more lucrative to pursue an AIDS-related indication for the drug. (Barrett 1999)

Melarsoprol is the first-line treatment for the late meningo-encephalitic stage of the disease, but it induces a fatal reactive encephalopathy in about 5% of patients. (McNeil 2001)

Up to 25-30% of patients in epidemics are not responding to melarsoprol. (Pécoul 1999) Melarsoprol is likely to remain the drug of choice for second-stage trypanosomiasis during the next decade, despite the fact that it is "far from being an excellent drug." (Burri 2000)

Eflornithine is useful at either stage of the disease, but its availability has been illustrative of the problems with R&D of medicines for tropical diseases in the current environment. Two senior scientists working for the Merrell Dow Research Institute in the 1980s were encouraged to pursue research on African sleeping sickness, involving investigations in sub-Saharan Africa. Eflornithine was the result, and in 1990 FDA approved it as an orphan drug. (Sjoerdsma 1999) Marion Merrell Dow (later Hoechst Marion Roussel, now Aventis) announced that it would manufacture eflornithine under the tradename Ornidyl as the first new medicine in 40 years for African sleeping sickness. It was later discontinued due to poor sales. (Silverstein 1999)

The license for eflornithine was then offered to WHO, but WHO was not able to find a manufacturer for the drug at a low enough cost. Eflornithine was licensed to Ilex Oncology, who wanted to pursue the compound as a cancer drug and was willing to produce it for WHO, but at a prohibitive cost. (Sjoerdsma 1999) In late 1999, MSF stated that it would be willing to guarantee purchase of the drug for 2-3 years, and assist with distribution, registration, and pharmacovigilance. At that time, Aventis planned to produce a batch of 10,000 vials as an interim measure. (Pécoul 1999) In February 2001, only 1,000 doses of eflornithine remained, however, because early hopes that it would be a new cancer drug were dashed. Aventis then decided to no longer produce the drug. (McNeil 2001)

Current Status

Only about 10% of individuals with HAT are believed to be receiving proper treatment. (Scrip 2001) The currently available therapeutic agents all are problematic (See TABLE 1), and the pipeline is nearly empty (See TABLE 4). One area of research is on new treatment regimens for melarsoprol, offering economic and practical advantages over the current regimen (10 days instead of 26). (Burri 2000) Also, eflornithine was reborn as an ingredient of a cream to remove facial hair. An interim deal is being negotiated to produce eflornithine as a therapy for HAT for

3 years, while a long-term solution is sought. A program against African trypanosomiasis has been established to bring various organizations with an interest in the disease under one umbrella. (Barrett 1999)

There are some recent promising developments. MSF, an independent medical humanitarian organization, has recently secured a deal to ensure the long-term production of four sleeping sickness drugs. (MSF 2001) Also, the Bill and Melinda Gates Foundation has provided a grant for the development of new drugs for African sleeping sickness (and leishmaniasis) of $15.1 million over five years to an international consortium from the public and private sectors. The consortium will concentrate on DB 289, a drug currently in clinical trials in Germany for Pneumocystis carinii pneumonia. (Scrip 2001) Another promising area of research is the antibiotic thiolactomycin, which inhibits myristate synthesis, a process that does not occur in mammals, but whose disruption in insects kills trypanosomes. (Morita 2000)

The Impact of Modified Orphan Drug Laws on Human African Trypanosomiasis R&D

Market-based incentives can work well for some neglected diseases, but not in others. For example, while malaria may be a break-even economic prospect for drug companies, because it could be sold at higher prices as prophylaxis to travelers from industrialized countries, treatments for African sleeping sickness is less likely to warrant private-sector investment, with only 25-50 thousand new clinical cases a year in 36 African countries. (Olliario 1997)

Neither global public health nor global economic considerations are particularly compelling reasons for conducting R&D on treatments for Category 3 diseases. As a result, HAT and similar diseases are the most obvious examples of neglect by a marketplace and R&D establishment dominated by the industrialized world. Even with a guaranteed purchaser, eflornithine, for several years, was a product in search of a manufacturer. The prospects for eflornithine have improved only because it has found another use important to the market in the developed world. The reverse situation exists for pentamidine. Its existence in the developing world marketplace as a treatment for HAT was put in jeopardy by the discovery of its utility in the developed world marketplace as a treatment for an AIDS-related condition. Advocacy by

WHO and MSF have temporarily salvaged both products, but their continued availability is tenuous and new treatments to replace them are unlikely to reach the market any time soon.

Whereas several private-public partnerships have been functioning over the past few years to address the research needs for malaria and TB, partnerships to address the needs of Category 3 diseases are still in their infancy. Moreover, while the public sector is beginning to dedicate significant funding to malaria, tuberculosis, and several other emergent infectious diseases, this has not been the case for Category 3 neglected diseases. For example, in September of 2000, NIH announced its Challenge Grants program, which made $20 million available for research for malaria and TB therapeutic agents and vaccines. Other categories eligible for these monies are vaccines and therapeutics for emerging and resistant infections, including dengue, West Nile Virus, and multi-drug resistant Staphylococcal infections. (NIAID 2000) HAT is not included.

Industry reluctance to undertake R&D for Category 3 diseases is likely to persist, without a notable incentive such as transferable exclusivity. By the same token, orphan grant monies may have more of an effect for incentivizing R&D for these neglected diseases, because so little funding is available from other sources. Also, grants that may seem insignificant when directed toward diseases such as TB or malaria, may go a long way toward providing treatments for HAT and other Category 3 diseases.

RECOMMENDATIONS FOR MODIFYING THE ORPHAN DRUG LAWS OF THE US AND EUROPE

Providing medicines to the developing world requires a two-fold solution: making currently available essential drugs accessible, and encouraging the development of "new essential drugs." (Reich 2000) Modified orphan drug laws can directly impact the latter, and indirectly affect the former. Incentives for R&D of the neglected diseases have been categorized as "push" measures to stimulate R&D at an early stage, "pull" measures to strengthen the prospective market for the product, and regulatory measures to speed up approval and licensing of the product making them available to patients more quickly. (PIU 2001) The push measures

are especially needed by small companies, such as start-up biotechnology and specialty drug companies, as well as the public sector. The pull and regulatory measures are particularly attractive to larger companies. Each of these sectors is an important contributor to the R&D environment for the neglected diseases (see TABLE 2). Modified orphan drug laws could provide a panoply of push-pull and regulatory incentives.

Recommendations for Modifications to the US Orphan Drug Act

The US private sector alone accounts for half of the worldwide investment in health R&D. (MSF 2001) Therefore, creating a favorable environment in the US for neglected disease R&D is critical.

The following is a list of incentives, based on the US ODA, that are needed to encourage R&D for neglected diseases:

- Prioritization or identification of diseases considered neglected;
- Designation of neglected disease products as fast track products for expedited regulatory review;
- Priority consideration for orphan grant funding, and extension of eligibility to the pre-clinical phase of R&D;
- Harmonization of orphan product regulations through the ICH process; and
- Transferable market exclusivity for the development of new molecular entities, and expanded market exclusivity for new indications of existing products.

<u>Priority List of Neglected Diseases – Advantages and Disadvantages</u>

Advantages: Publication of a list of priority diseases will alert potential sponsors that products for listed diseases are eligible for R&D incentives. The list would both identify and limit candidate diseases. Criteria for prioritizing the neglected diseases could be determined by a special task force comprised of experts from the CDC, WHO, and the OOPD.

Disadvantages: There is a strong likelihood that there will be concern among advocates for other rare diseases that the ODA is being co-opted for diseases of the developing world, to the

detriment of making resources available for addressing the unmet R&D needs of patients with rare disorders in the US.

The arguments to counteract criticism from advocates of rare diseases not on the priority list could be based on global public health and national security impact of the priority diseases. Furthermore, there exist indicia of prior intent by Congress to facilitate R&D for certain neglected diseases through the ODA and the 1986 export amendments. Although orphan designations for the neglected diseases have been awarded historically, throughout the existence of the ODA, the current orphan program incentives are "insufficient to attract serious attention from companies for R&D in neglected diseases." (WHO-IFPMA 2001)

Moreover, there is the likelihood that R&D needs for the neglected diseases, which are essentially infectious and parasitic diseases, may not affect the capacity already focused on the more typical targets of orphan drug R&D – metabolic conditions, genetic disorders, and rare cancers. While there may be an initial drawing away of resources from rare disease R&D to neglected disease R&D, if the incentive is sufficiently attractive, additional capacity will develop to meet the demand in the near-term.

Fast Track Designation – Advantages and Disadvantages

Advantages: Automatic designation of priority list diseases as fast track products with priority review status will save the sponsor the time and manpower necessary to go through the designation application process. If designated, the development program becomes eligible for enhanced access to FDA/sponsor consultations, submission of portions of the marketing application on a rolling basis, and the likelihood of receiving priority review. Priority review limits FDA to a six-month time frame for first action during the approval process for a marketing application.

Disadvantages: None – except that it may be irrelevant to request a formal legislative provision for automatic fast track designation, since orphan drugs typically meet the eligibility requirements and often receive the fast track designation already. (Haffner 2001)

Grant Prioritization – Advantage and Disadvantages

Advantage: Prioritizing grants for the neglected diseases will be important for bringing in new players to this field of R&D. This will be especially helpful for public sector institutions, private/public partnerships and start-up companies, both foreign and domestic. The current level of funding may be sufficient to contribute significantly to out-of-pocket clinical costs, especially in developing countries where R&D dollars may go farther. However, for these grants to be useful for invigorating an R&D infrastructure for neglected diseases, they may have to be extended to pre-clinical and discovery expenses, which are currently ineligible.

Disadvantages: Advocates for rare diseases not on the priority list will view prioritized grants as prejudicial to their interests. In addition, R&D for some neglected diseases, such as Category 3 diseases, needs orphan grants more than others do. Prioritization of grant awards among the categories of neglected diseases may be necessary. Lastly, at present, only clinical testing projects are eligible for orphan grants. Eligibility for grant funding would have to be expanded to pre-clinical testing projects.

Harmonization of Orphan Product Regulations

Advantages: Since similar orphan product programs now exist in the three major global markets for pharmaceutical and biotechnology R&D, these programs could be harmonized through the ICH process, or through a cooperative agreement, such as exists between the US and Australia. The benefit would be to avoid duplicative efforts and to facilitate global registration of orphan products that meet global public health needs.

Disadvantages: Risk-benefit decisions for orphan drugs could be more regionally idiosyncratic than with mainstream drugs. Harmonization procedures would have to be crafted such that rejection by one regulatory authority does not necessitate rejection by the other authorities. Nonetheless, discordant reviewing decisions may undermine the utility of the process.

Transferable Exclusivity and Market Exclusivity Extension

Advantage: There is a precedent in US law for a market exclusivity extension – the pediatric studies provision of the FDA Modernization Act of 1997 (section 111) awards an additional six months of market exclusivity to all of the sponsor's products that have the same active moiety as the product for which that sponsor submits an acceptable pediatric study. This incentive is granted for a new indication of an already approved product (i.e., use in a new sub-population – children).

A similar type of incentive program could be adapted to R&D on the neglected diseases. Sponsors would be eligible for a six-month exclusivity for a new indication of an existing drug (e.g., use in a new disease – trypanosomiasis).

There is also precedent for consideration of a one-year transferable exclusivity. FDA suggested a transferable exclusivity (without specifying a specific time period) as a possible modification to the pediatric exclusivity provision. The transferable exclusivity would be for products for which the 6-month market exclusivity extension was an insufficient inducement for conducting the needed studies. (FDA 2001) As is the case for pursuing pediatric indications, significant disincentives exist for R&D on most neglected diseases. Only a very attractive financial incentive, such as transferable market exclusivity, will be sufficient inducement.

There are other advantages to offering a transferable exclusivity incentive. First, because of industry's familiarity with the pediatric exclusivity program, transferable exclusivity is likely to be viewed as a credible, and therefore attractive, benefit. Next, there will not be an economic barrier to access by developing countries, since the medicines for the neglected diseases will have no additional market protection beyond whatever patent term remains after approval. Moreover, patent protection will very likely be limited by the availability of compulsory licenses under TRIPS. Also, the program would be highly sustainable, since it would not depend on creating a market in poor countries. Instead, it would take advantage of existing markets in wealthier countries. Finally, the program could be implemented in a relatively brief amount of time, it would not require additional bureaucracy, and it would involve only minimal oversight. For example, the pediatric exclusivity program has been highly productive in a short period of

time with nearly 30 pediatric studies completed in 3 years, about half of which have already been labeled for the new indications. (FDA 2001) Similar to what the pediatric exclusivity program has accomplished for pediatric medicines R&D, a transferable exclusivity would likely serve to expand capacity for tropical medicine R&D.[6]

As with pediatric exclusivity, the availability of the reward just in the US is likely to be a sufficient economic incentive. The US represents 43% of the global market for pharmaceuticals and is growing at a rate of 15%. Moreover, 60% of global profits came from the US market. (Scrip Magazine 2001) The possibility of harmonization of orphan regulations in the three major markets – Japan, US and Europe – through the ongoing ICH process, serves to increase the potential benefit of this program.

Disadvantages: It is likely that some critics will raise the question of whether the economic cost to society is justified by the granting of transferable exclusivity. It is worth noting, however, that the cost of granting a six-month pediatric exclusivity to 119 products in the US has been estimated by FDA to be $700 million per year for the next 20 years. (FDA 2001) This amounts to a penny per person/per day in the US.

Another concern is, Who would really end up paying for the transferable exclusivity? The answer is that it will be the average US citizen (and perhaps those of other developed countries depending on the form of the market exclusivity) as a consumer and to a lesser extent as a taxpayer. According to a study by the Global Health Council, however, US consumers are concerned about the spread of infectious diseases, and they recognize that the best place to stop their spread is in the developing countries themselves. (Nation's Health 1999) It is also important to consider that the costs of some of the other suggested incentives for increasing R&D for neglected diseases medicines, such as global purchase funds supported by government

[6] In fact, the importance placed by industry on an incentive based on market exclusivity compared to one based on other incentives, such as tax credits, was recently illustrated during the debate concerning the reauthorization of the pediatric exclusivity program. In response to a legislative proposal to replace the pediatric exclusivity provision with tax credits, a representative from a major pharmaceutical firm pointed out that while tax credits provide some recoupment of clinical trial costs, they provide no support for projected returns or for developing an infrastructure for sustained pediatric research. (Pink Sheet 2001)

aid or corporate contributions, and private-public partnerships, would ultimately come out of the pockets of US consumers and/or taxpayers, as well.

The length of the transferable exclusivity would certainly be controversial. As discussed above, there is a precedent for the six-month length of market exclusivity attaching to the development of a new indication for an approved drug. The justification for calls for a one-year term derives from the deliberations on the reauthorization of the pediatric exclusivity. FDA has estimated that a hypothetical innovator drug makes $500 million to $1 billion in peak year sales. (FDA 2001) Taking these figures and reducing the profit by 60% for production, administrative, and marketing costs (OTA 1993), that drug would earn $200-$400 million. This $200-$400 million profit range resulting from the one-year transferable exclusivity must be viewed in comparison to the magnitude of a hypothetical R&D program for a neglected disease, lasting 7-11 years and requiring an incentive of $100-$500 million per product. (PIU 2001)

The value of any particular transferable exclusivity period on a hypothetical product ten years in the future cannot be calculated with enough exactness to ensure accuracy. The eventual length of the exclusivity awarded may be too long or too short to adequately counterbalance the R&D investment.

One scenario for an inequitable result has already been espoused in relation to the so-called "blockbuster orphan." A few orphan products have been sold at what some have viewed as very high prices, portrayed as out-of-sync with the magnitude of the R&D investment. Even though there are actually very few blockbuster orphans (Grabowski 2000), the circumstances creating this imbalance are less likely to be caused by inelastic demand and consequent price insensitivity (i.e., exorbitantly priced life-or-death drug), than to off-label use and foreign markets. (Peabody 1995) With the transferable exclusivity, those circumstances are not as likely to arise, since few widely selling, breakthrough products are life-or-death medicines without alternatives on the market.

The possibility cannot be discounted, however, that a transferable exclusivity may accrue to a future breakthrough drug for a common form of cancer. In which case it would delay the availability of lower cost alternatives for no more than a year, since the transferable exclusivity will only be added to whatever existing patent term or market exclusivity period the selected product already has. In these circumstances, the additional costs born by patients in rich countries would be counterbalanced by the additional lives saved in poor countries as a result of the availability of treatment or prophylaxis for neglected diseases. Congress acknowledged the possibility of such a trade-off when it passed the ODA:

In debating the need for orphan drug exclusive marketing, Congress weighed the potential dangers of granting orphan drug exclusive marketing, which would limit competition, against the benefits to be gained by encouraging sponsors to develop drugs of marginal commercial value. In passing the law, Congress determined that the benefits exceeded the dangers. Any form of exclusive marketing may have negative consequences, such as noncompetitive pricing. (Orphan Drug Regulations Preamble Dec. 1992)

Options for Modifying the US Orphan Drug Act

There are three approaches that could be taken to utilize the US ODA as an incentive for R&D of neglected diseases. The first approach would entail the legislative promulgation of a formal amendment to the ODA (actually to the FFDCA and the Public Health Service Act). A second approach would involve increasing the amount of orphan grant funds from the ODA's yearly appropriation and earmarking these funds for neglected diseases. The third approach would consist of passing a Neglected Disease Act, based on the ODA.

<u>Amending the ODA</u>

A formal amendment to the Orphan Drug Act containing language similar to that suggested below could be proposed.

- The Secretary of the Department of Health and Human Services (i.e., FDA) shall develop, prioritize and publish a list of diseases affecting global public health, after

consultation with such experts in global public health (e.g., CDC, WHO) as deemed necessary by the Secretary.

- A sponsor may submit a request for orphan drug designation of a drug intended to treat indications of listed diseases. Inclusion on the list together with a rationale for the use of the drug or biological product as a treatment for the listed disease shall be considered sufficient documentation that the drug is eligible for orphan designation.
- Sponsors of such orphan designated drugs shall be eligible for priority consideration for orphan grants.
- Sponsors of such orphan designated drugs shall be designated fast track products consistent with current statutory authority.
- Upon approval of a sponsor's marketing application for a new molecular entity as an orphan drug or biological product for treatment of a listed disease, a sponsor will be awarded a period of market exclusivity of one-year for new molecular entities transferable to another product for which the sponsor is the holder of the approved application before the expiration of that product's current period of market exclusivity or patent.
- Upon approval of a sponsor's marketing application for a new indication of an already approved product as an orphan drug or biological product for treatment of a listed disease, a sponsor will be awarded a six-month extension of the existing patent or period of marker exclusivity for all products with the same active moiety as the orphan approved product for which the sponsor is the holder of the approved application.
- Alternatively, after approval of a sponsor's marketing application for a designated orphan drug product for treatment of a listed disease, a sponsor may elect an award of seven years of market exclusivity in a manner consistent with current regulations.
- The provision will sunset ten years from the effective date of this amendment unless reauthorized.

Because the ODA has been the subject of proposed amendments in the past – some successful, some not – the above approach has some viability. Politically, it may be unpalatable

to congressional sponsors and the administration unless the backing of NORD can be assured or significant advocacy from other sources can be mustered in its support. While there are benefits to amending existing legislation, in lieu of promulgating new legislation, and being able to take advantage of a standing administrative unit for implementation (OOPD), there are risks as well. For example, a proposed amendment is likely to be delayed and possibly defeated during the legislative process, in the absence of support from a broad-based coalition representing all affected parties.

Appropriation for Neglected Disease R&D

The amount of funding available in any fiscal year for orphan grants is determined by the amount appropriated in the budget under the authority of the Federal Food, Drug & Cosmetic Act each year. With advocacy efforts targeted toward garnering executive office and legislative backing, the FFDCA budget could include an increased amount of funding for the orphan grants program earmarked for pre-clinical and clinical expenses for the R&D of listed orphan designated neglected diseases.

While this approach may avoid some of the criticisms from advocates of rare diseases that would occur with a prioritization scheme under a formally amended ODA, it may still be viewed as drawing away resources (both funding and FDA personnel) that should be available equally to all rare diseases eligible under the ODA. In addition, it is not a mechanism for providing enhanced market exclusivity protection. Thus, unless the available grant amounts were very large, it would only be an incentive for smaller companies. It is also likely that any sizeable amount of funding would have to be appropriated on an annual or biennial basis, rather than as a lump sum in any one fiscal year budget. Nonetheless, this approach has the advantage that specific diseases could be identified along with the appropriation, and that if sufficient funding is provided with the capacity to use the grant funds for pre-clinical and clinical expenses, it could have a significant impact on Category 3 neglected diseases.

Neglected Disease Act

The ODA is generally considered to have the type of legal and fiscal framework that is most likely to contribute to the creation of the "optimum environment" for providing medicines to combat the diseases of poverty. (Trouiller 1999, Pécoul 1999) An alternative to modifying the existing ODA is passage of a "Neglected Disease Act" (Consumer Project on Technology 1999) modeled on the ODA. (Pulsinelli 1999) This, approach, however, carries the impediment of not having a standing administrative unit to implement it (such as the OOPD for orphan drugs). If it were passed without its own funding, to avoid a more protracted and complex legislative route through the appropriations committee process, implementation would be delayed and erratic.

Alternatively, this approach could rely on the model of another piece of US legislation – the Safe Medical Devices Act of 1990. This law, which exempts qualifying devices from effectiveness requirements, was passed to provide an incentive program for the development of devices to treat or diagnose diseases affecting small populations. Although the Safe Medical Devices Act was passed as a freestanding bill and not as an amendment to the ODA, the OOPD was designated as the implementing office within FDA. (Haffner 2001)

Recommendations for Modifications to Europe's Orphan Medicinal Products Regulation

There is some disparity among the member states of the EC as to the level of interest in providing incentives for tropical medicine R&D. Yet, some European pharmaceutical companies have developed anti-malarials without any government incentive at all, while others have developed tropical medicines as spin-offs from drugs intended for the developed world market, such as atovaquone and liposomal amphotericin B. (Olliario 1997)

Even among those countries with a high level of interest, individual approaches are being pursued – for example the ReMeD proposal in France and the PIU proposal in the United Kingdom. At the same time, as a concerted action, the EC has proposed that a European Clinical Trials Platform be established to accelerate development of new products against the neglected diseases for use in developing countries. (PIU 2001) Given these conditions, and the fact that the

orphan product regulation in the EC is still dealing with a backlog of issues related to its recent passage, it may be more advantageous for incentive programs for tropical medicines R&D to be developed within the context of legislation passed by the individual member states. These incentive programs could be either freestanding versions based on orphan drug laws or framed within the scope of the existing EC orphan product regulation. The advantage would be to allow countries with greater interest and readiness to move ahead rapidly, while the EC as a whole works on the clinical trials platform.

CONCLUSION

The challenges of developing new medicines to treat and prevent the neglected diseases are formidable. Over a decade ago, a letter from a well-known health economist to *Lancet* identified the dire medical needs of developing countries, and lamented that less than one cent per exposed person was being spent on tropical disease R&D. (Garattini 1988) In the late 1980s, private-public partnerships between WHO and industry were hailed as the dawn of a new era. The approach of having the World Bank and WHO guarantee large-volume purchasing of new drugs for tropical diseases was extolled as a very promising approach. But as we begin the third millennium, little progress has been made on any of these fronts.

For 30 years after the colonial period ended in 1960, infant and childhood mortality rates declined steadily in sub-Saharan Africa. Among the reasons for this decline in mortality were the widespread availability of antibiotics and anti-malarial drugs, and an increase in vaccinations. (Müller 1999) Unfortunately, that salutary period came to an abrupt end in the early 1990s with the rapid spread and devastating consequences of AIDS. It is now time, once again, to recognize the enormous impact that effective drugs and vaccines can have on the health and well-being of people in the developing world. The next step is finding the right incentives to encourage the development and marketing of these life-saving medicines.

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WHO-IFPMA. WHO/Industry Drug Development Working Group. Incentivising new medicines for 'neglected' diseases. April 2001.

Table 1: Marketed Medicines for Neglected Diseases (WHO = currently appears on World Health Organization Essential Drugs List, 11th Edition 1999; CDC = recommendation for use by US Centers for Disease Control)
(Sources: PhRMA; Martindale, 31st Edition; Pécoul 1999; American Drug Index, Billups, 43rd Edition, 1999; Offices of Drug Evaluation Statistical Report, FDA, 1993.)

Trade/Generic Name	Developer/Manufacturer	Comment
TUBERCULOSIS		
BCG	***PowderJect (UK)***	***Vaccine***
isoniazid	**Merrell Dow**	WHO. Poor compliance w/ therapy & outbreaks of drug-resistant strains. First-line drug. ***Can induce beta-hydroxybutyric (BHB) acidosis***
rifampicin	***Dow***	WHO. Poor compliance w/ therapy & outbreaks of drug-resistant strains. Dangerous side effects. First-line drug
pyrazinamide	**Merck Sharp & Dohme**	WHO. First-line drug
ethambutol	**Lederle**	WHO. First-line drug
streptomycin	Pfizer	WHO. Production halted due to lack of commercial viability, recently restarted. First-line drug
thiacetazone		
Aminosalicylic acid and salts, e.g. sodium aminosalicylate, PAS	Jacobus (US)	Production not secured, toxic effects of drugs. Second-line drugs
cycloserine	***Lilly (US)***	
ethionamide/prothionamide		
capreomycin sulfate	***Lilly (US)***	
rifapentine (Priftin®)	Aventis (France)	Limited use because of high prices
BCG vaccine	BioChem Pharma (Canada)	Effectiveness disputed
tobramycin (TOBI)	Chiron (USA)	
isoniazid & ethambutol		WHO
rifampicin & isoniazid		WHO
rifampicin & isoniazid & pyrazinamide		WHO
rifampicin & isoniazid & pyrazinamide & ethambutol		WHO
thioacetazone & isoniazid		WHO
kanamycin	***Bristol-Myers Squibb; Smith Kline Beecham***	
amikacin	**Bristol**	**Second-line drugs**
ofloxacin	**RW Johnson**	
ciprofloxacin	***Bayer***	
Malaria		
Riamet/Co-Artem (artemether & lumefantrine)	**Novartis (Switzerland)**	***Not approved for children under 12. Not approved for standby treatment for travelers. Safe. Fast-acting. Cure rates above 95%. High dose administered for a short period promising for compliance. Supplied to WHO at cost for use in Africa***

tafenoquine	**Smith Kline Beecham**	**Prevention**
artemether (Paluther)	Public/private collaboration (WHO TDR/RPR); Aventis (France)	Available but production not secured for substandard products. Resistance.
atovaquone & proguanil (Malarone)	Glaxo Wellcome (UK)	Available but limited use. Too expensive for poor countries. Currently partial drug donation program. CDC:treatment, prevention. Resistance. ***Recommended in areas with chloroquine or multidrug resistance. Tolerated by travelers better than chloroquine & proguanil***
halofantrine (Halfan)	WRAIR (Walter Reed Army Institute of Research (USA) Public/private collaboration (WHO/WRAIR/SmithKline Beecham).; GSK (UK)	Expensive producer price. Used for multi-drug-resistant P. falciparum malaria. Resistance. Toxicity
mefloquine (Lariam)	WRAIR discovery (US). Public/private collaboration (WHO/WRAIR/Hoffmann La Roche (Switz)	Expensive but cheaper products exist (eg, Mephaquin). CDC: prevention. Resistance.
doxycycline	Pfizer (USA)	WHO. CDC: prevention. Resistance
doxycyline & quinine	WHO	WHO if used with quinine
tetracycline	***Bristol-Myers Squibb***	Used in combination w/ quinine
sulfadoxine & pyrimethamine (Fansidar)	Treatment of P falciparum malaria, including infection acquired in areas w/ chloroquine-resistant or multi-drug-resistant strains.	WHO. CDC: treatment. **Resistance** ***Possible cross-resistance for those also receiving trimethoprim-sulfamethoxazole for HIV***
atovaquone & proguanil	GSK (UK)	Limited use because of high price
dapsone with pyrimethamine (Malarone)		
clindamycin	**Upjohn**	
primaqine phosphate	Non-Industrial Source (University of Cardiff, UK)	Used for radical treatment of P. vivax and P. ovale malaria
chloroquine	**Sanofi Winthrop**	WHO. Resistance.
artemether & lumefantrine (Riamet)	Novartis (Switz)	
dapsone	**Ayerst**	
artemotil (Artecet)	Brocacef (Netherlands)	
hydroxichloroquine		
amodiaquine		
primaquine	**Sanofi Winthrop**	WHO
chloroquine & proguanil		WHO. Resistance.
quinine	**Hoechst Marion Roussel**	WHO. Resistance.

artesunate (Arsumax)	Atlantic, (Thailand)	WHO
HUMAN AFRICAN TRYPANSOSMIASIS (HAT)		
Suramin sodium	Bayer (South Africa)	WHO. Production not yet secured (no commercial interest). Poor penetration of blood-brain barrier.
pentamidine isethionate (Pentacarinat, formerly Lomidine)	Galenic re-formulation (from mesylate to isethionate of pentamidine) by Rhone Poulenc Rorer (France), Aventis (France)	WHO. Production not yet secured (no commercial interest). Drug donation for HAT indications through WHO. Has more lucrative use as AIDS drug. **Treatment for early stages of the infection**
Melarsoprol		WHO. Resistance Production not yet secured (no commercial interest). Highly toxic. ***5 to 25% of patients die from side effects***
Nifurtimox	Veterinary R&D originally Bayer (Germany)	Producer price
eflornithine (Ornidyl) – DFMO	Merion Merrell Dow (US)	WHO. Limited use because of high price & cumbersome dosing schedule. Interim 3-year deal for production starts in 2001.
tryparsamide & suramin	US	Tryparsamide is associated w/ increased risk of toxicity
difluoromethylornithine (DFMO)		**Treatment for late stages of the infection.** **Possible resistance**
HIV/AIDS		
antiretroviral drugs; see following list.		Available but limited use. Prohibitive price.
amprenavir (Agenerase)	Glaxo Wellcome (US), Vertex Pharmaceuticals (US)	HIV infection. ***Toxicity: rash, nausea, diarrhea***
Lamivudine/zidovudine tablets (Combivir)	Glaxo Wellcome (US)	HIV infection
Indinivir Sulfate (Crixivan)	Merck (US)	HIV infection. ***Toxicity: hyperbilirubinaemia, nephrolithiasis, nail changes, dry skin***
Lamivudine (3TC) (Epivir)	Glaxo Wellcome (US), BioChem Pharma (Canada)	HIV infection. ***Few side effects***
Saquinavir (Fortovase)	Hoffmann-La Roche (US)	Combination treatment for adults w/ HIV infection. ***Few side effects***
Immune globulin intravenous (human), (Gamimune-N)	Bayer (US)	Pediatric HIV infection
Zalcitabine (HIVID)	Hoffmann-La Roche (US)	Combination treatment for HIV infection. **Toxicity: peripheral neuropathy, mouth ulcers**
Saquinavir mesylate (Invirase)	Hoffman-La Roche (US)	Combination treatment for HIV infection
Lopinavir/ritonavir (Kaletra)	Abbott Laboratories (US)	HIV infection (pediatric & adult). ***Toxicity (lopinavir): diarrhea***

Ritonavir (Norvir)	Abbott Laboratories (US)	HIV infection (pediatric & adult). ***Toxicity: perioral dysathesia, flushing, hepatitis, diarrhea, nausea, vomiting***
Delvaridine (Rescriptor)	Agouron Pharmaceuticals, US)	HIV infection
Zidovudine (AZT), (Retrovir)	Glaxo Wellcome (US)	HIV infection (pediatric & adult). Prevention of maternal/fetal transmission of HIV infection. WHO. ***Toxicity: bone marrow suppression, nausea, vomiting, myopathy***
Efavirenz (Sustiva)	Du Pont Pharmaceuticals (US)	HIV infection. ***Toxicity: rash, dysphoria, mood changes, vivid dreams, hypercholesterolaemia***
VIDEX	Bristol-Myers Squibb (US)	HIV infection (pediatric & adult). Once-daily dosing
Didanosine (ddl) (VIDEX EC)	Bristol-Myers Squibb (US)	HIV infection. ***Toxicity: pancreatitis, dry mouth, peripheral neuropathy***
Nelfinavir mesylate (Viracept)	Agouron Pharmaceuticals, US)	HIV infection, AIDS (pediatric & Adult). ***Toxicity (nelfinavir): diarrhea, rash***
Nevirapine (Viramune)	Boehringer Ingelheim Pharmaceuticals, (US)	Combination treatment for HIV infection. WHO. ***Toxicity: rash, hepatitis, Steven-Johnson syndrome***
Stavudine (d4T), (Zerit)	Bristol-Myers Squibb, (US)	HIV infection (pediatric & adult). First-line in combination treatment. **Toxicity: peripheral neuropathy, hepatitis**
Abacavir (Ziagen)	Glaxo Wellcome (US)	HIV infection. ***Toxicity: hypersensitivity reaction, nausea***
AIDS-RELATED CONDITIONS		
Amphotericin B lipid complex (ABELCET)	The Liposome Company (US)	Treatment of severe systemic fungal infections in patients refractory to or intolerant of amphotericin B therapy
Docosanol 10% cream (Abreva)	Avanir Pharmaceuticals (US), SmithKLine Beecham (US)	Topical treatment for recurrent oral-facial herpes simplex infections
Interferon alfa-n3 (Alferon N Injection)	Interferon Sciences (US)	Genital warts (condyloma acuminata)
Liposomal amphotericin B (AmBisome)	Fujisawa Pharmaceutical (US), Gilead Sciences (US)	Primary treatment for fever of unknown origin in neutropenic patients and visceral leishmaniasis. Secondary treatment for certain systemic fungal infections, cryptococcal meningitis, histoplasmosis.
Amphotericin B cholesteryl sulfate lipid for injection (Amphocil)	ALZA Corporation (US)	Apergillosis. Opportunistic systemic fungal infections.
Trimethoprim and sulfamethoxazole (Bactrim)	Hoffmann-La Roche (US)	PCP prophylaxis and treatment
Clarithromycin (Biaxin)	Abbott Laboratores (US)	Mycobacterium avium complex (MAC) prophylaxis and treatment
Ganciclovir (IV), (Cytovene)	Hoffmann-La Roche (US)	CMV retinitis treatment
Ganciclovir (oral), (Cytovene)	Hoffman-La Roche (US)	CMV retinitis maintenance treatment. CMV retinitis prophylaxis in AIDS patients.
Pyrimethamine (Daraprim)	Glaxo Wellcome (US)	Toxoplasmosis treatment
Daunorubicin citrate liposome injection (DaunoXome)	Gilead Sciences (US)	Advanced AIDS-related Kaposi's sarcoma
Cytarabine liposome injection (DepoCyt)	SkyePharma (US)	Neoplastic meningitis

Fluconazole (Diflucan)	Pfizer (US)	Cryptococcal meningitis. Candidiasis. Pediatric use for candidiasis fungal infection prophylaxis and treatment.
Doxorubicin HCl liposome injection (DOXIL)	ALZA corportation (US)	AIDS-related Kaposi's sarcoma
Famciclovir (Famvir)	SmithKline Beecham (US)	Recurrent herpes simplex
Injection foscarnet sodium (Foscavir)	Astra USA (US)	CMV retinitis in AIDS paitients. Acyclovir-resistant herpes simplex virus (HSV) in immunocompromised patients.
Interferon alfa-2b (recombinant), (Intron A)	Schering-Plough (US)	Kaposi's sarcoma
Dronabinol (Marinol)	Unimed Pharmaceuticals (US)	Treatment of anorexia associated weight-loss in AIDS patients
Megestrol acetate (oral suspension), (Megace)	Bristol-Myers Squibb (US)	Treatment of anorexia and cachexia associated w/ AIDS
Atovaquone (Mepron)	Glaxo Wellcome (US)	Treatment of mild to moderate PCP in individuals intolerant to TMP/SMX. PCP prophylaxis.
Rifabutin (Mycobutin)	Pharmacia (US)	MAC prophylaxis in patients w/ advanced HIV infection.
aerosol pentamidine isethionate (NebuPent)	Fujisawa Healthcare (US)	PCP prophylaxis
Trimetrexate glucuronate for injection (Neutrexin)	MedImmune Oncology (US)	Treatment of moderate-to-severe PCP in immunocompromised patients, including patients w/ AIDS, who are intolerant of or are refractory to TMP/SMX or for whom TMP/SMX is contraindicated.
Ketoconazole (Nizoral 2% Shampoo)	Janssen Pharmaceutica (US)	Tinea versicolor (fungal infection)
Ketoconazole (Nizoral tablets)	Janssen Pharmaceutica (US)	Systemic fungal infections (blastomycosis, candidiasis, chronic mucocutaneous candidiasis, chromomycosis, coccidioidomycosis, histoplasmosis, oral thrush, paracoccidioidomycosis).
Alitretinoin (Panretin Gel)	Ligand Pharmaceuticals (US)	AIDS-related Kaposi's sarcoma
para-aminosalicylic acid 4-aminosalicylic acid (PAS), (PASER extended release granules)	Jacobus Pharmaceutical (US)	Tuberculosis treatment
300 pentamidine isethionate (IM & IV), (Pentam)	Fujisawa Healthcare (US)	PCP treatment
Rifapentine (Priftin)	Aventis Pharmaceuticals (US)	Tuberculosis
epoetin alfa (PROCRIT)	Ortho Biotech (US)	Anemia in Retrovir-treated HIV-infected patients
protein A immunoadsorption (Prosorba Column)	Cypress Bioscience (US)	Immune thrombocytopenia purpura
Interferon alfa-2a, recombinant, (Roferon A)	Hoffmann-La Roche, (US)	Kaposi's sarcoma in adult patients
Trimethoprim and sulfamethoxazole (Septra)	Monarch Pharmaceuticals (US)	PCP prophylaxis and treatment
Somatropin (rDNA origin) for injection (Serostim)	Serono (US)	Treatment of AIDS-associated cachexia
Itraconazole (Sporanox Capsules)	Janssen Pharmaceutica (US)	Histoplasmosis, blastomycosis. Second-line aspergillosis.
Itraconazole (Sporanox injection)	Janssen Pharmaceutica (US)	Systemic mycoses
Itraconazole (Sporanox Oral	Janssen Pharmaceutica (US)	Esophageal and oropharyngeal candidiasis

Solution)		
Paclitaxel (Taxol)	Bristol-Myers Squibb (US)	AIDS-related Kaposi's sarcoma
Trovafloxacin (Trovan)	Pfizer (US)	Nosocomial pneumonia
Valacyclovir (Valtrex)	Glaxo Wellcome (US)	Episodic treatment of recurrent genital herpes and herpes zoster in immunocompetent adults. Suppression of genital herpes simplex virus (HSV).
Cidofovir injection (Vistide)	Gilead Sciences (US)	CMV retinitis in AIDS patients
Fomivirsen (Vitravene)	Isis Pharmaceuticals (US)	CMV retinitis in AIDS patients
Rh_0(D) immune globulin intravenous (human)	Nabi (US)	Immune thrombocytopenic purpura (ITP) secondary to HIV infection
Azithromycin (Zithromax)	Pfizer (US)	Mycobacterium avium intracellulare (MAI) infections (prophylaxis)
Acyclovir (Zovirax)	Glaxo Wellcome (US)	Herpes zoster/simplex. Treatment of initial episodes and management of recurrent episodes of genital herpes. Treatment of chicken pox and shingles

Table 2: Development Sources for Malaria, TB, and Sleeping Sickness Pipeline (Source: Pharmaprojects)

Development Sector / Source	United States	Non-US	Unidentified
Pharmaceutical, N=37	16	21	0
Biopharmaceutical N=30	18	11	1
Other (Universities, NIH, and other Non-Industrial sources, including 3 for which development company information is unknown), N=33	33		

Table 3: Orphan Products for AIDS and AIDS-Related Conditions (Source: Tufts CSDD)

Orphan Designations Year	Generic Name	Company	Orphan Approval	Disease Indication
1984	Pentamidine isethionate	Rhone-Poulenc Rorer		Pneumacystis carnii pneumonia
1984	Pentamidine isethionate (Pentam 300)	Fujisawa	Y (1984)	Pneumacystis carnii pneumonia
1985	Ganciclovir sodium (Cytovene)	Syntex	Y (1989)	Cytomegalovirus retinitis in immunocompromised patients with AIDS
1985	Zidovudine (Retrovir)	Burroughs Wellcome	Y (1987)	AIDS
1986	Diethyldithiocarbamate	Connaught		AIDS
1986	Interferon Alfa -NL	Burroughs Wellcome		Karposi's Sarcoma
1986	Trimetrexate g lucoronate (Neutrexin)	U.S. Bioscience	Y (1993)	Pneumocystis carinii pneumonia
1986	Zalcitibine (DDC)	NCI		AIDS
1987	AS-101	Wyeth Ayerst		AIDS
1987	Dextran sulfate sodium	Ueno Fine Chemicals		AIDS
1987	Interferon alfa 2A recombinant (Roferon-A)	Hoffman-La Roche	Y (1988)	Karposi's Sarcoma
1987	Interferon alfa 2B (recombinant) (Intron-A)	Schering Corp.	Y (1988)	Karposi's Sarcoma
1987	Pentamidine Isethionate	Fisons Corp.		Prevention of Pneumocystis carinii pneumonia high risk patients
1987	Zidovudine (Retrovir)	Burroughs Wellcome	Y (1987)	AIDS Related Complex (ARC)
1988	Clindamycin	Upjohn		Prevention of pneumocystis carinii pneuomia in AIDS patients
1988	Clindamycin	Upjohn		Pneumocystis carinii pneumonia
1988	Megestrol acetate (Megace)	Bristol-Myers Squibb	Y (1993)	AIDS anorexia
1988	Pentamidine isethionate (Pentam 300)	Fujisawa	Y (1989)	Prevention: Pneumocystis carinii pneumonia high risk patients
1988	Piritrexim isethionate	Burroughs Wellcome		AIDS PCP infections
1988	Poly I: Poly C12U	Hem Pharmaceuticals		AIDS
1988	Zalcitabine (DDC) (Hivid)	Hoffman-La Roche	Y (1992)	AIDS
1989	Carbovir	Glaxo		AIDS
1989	Erythropoietin	R.W. Johnson Research Institute		Anemia associated w/ HIV infection or treatment
1989	HIV Immune globulin	North American Biologicals		AIDS
1989	Human T-Lymphotrophic virus type III GP160 antigens (Vaxsyn HIV-1)	Micro Genesys		AIDS
1989	Molgramostim	Schering		AIDS w/ neutropenia due to disease, AZT, or ganciclovir
1989	Recombinant soluble human CD4 (RCD4)	Genentech		AIDS
1989	Recombinant soluble	Biogen		AIDS

	human CD4 (RCD4)			
1989	Rifabutin (Mycobutin)	Adria Labs	Y (1992)	Prevention: Mycobacterium avium complex in advanced HIV
1989	Rifabutin	Adria Labs		Treatment: Mycobacterium avium complex in advanced HIV
1990	Epoetin alfa (Epogen)	Amgen	Y (1990)	Anemia associated w/ HIV infection
1990	Bovine colostrum	Dr. Donald Hastings		AIDS related diarrhea
1990	Gentamicin liposome inj.	The Liposome Company		Mycobacterium avium-intracellulare infection
1990	Lactobin	Roxane Laboratories		AIDS assoc diarrhea unresponsive to antidiarrhea therapy
1990	PR-225 Redox acyclovir	Pharmatec, Inc.		AIDS herpes simplex encephalitis
1990	PR-239 Redox penicillin	Pharmatec, Inc.		AIDS associated neurosyphilis
1990	Recombinant human CD4 immunoglobulin G	Genentech		AIDS
1991	Amphotericin B lipid comples	The Liposome Company		Cryptococcal meningitis
1991	Atovaquone (Mepron)	Burroughs Wellcome	Y (1990)	Prevention: Pnuemo carinii pneumonia in HIV patients who had PCP in past
1991	Cryptosporidium hyperimmune bovine colostrum	Immucell Corp.		AIDS diarrhea caused by infection with Cryptosporidium parvum
1991	Dapsone USP	Jacobus Pharmaceutical		Prevention: Pneumocystis carinii pneumonia
1991	Dronabinol (Marinol)	Unimed	Y (1992)	AIDS stimulate appetite
1991	Epoetin alfa	Amgen		Anemia associated w/ HIV infection
1991	Filgrastim	Amgen		AIDS patients with CMV retinitis & use ganciclovir
1991	Interferon beta (recombinant)	Biogen		Karposi's sarcoma
1991	Monoclonal antibody to CMV	Protein Design Labs		CMV retinitis in AIDS
1991	Oxandrolone	Gynex		HIV wasting syndrome
1991	Poloxamer 331	Cytrx		AIDS toxoplasmosis
1991	Sermorelin acetate	Serono Labs		AIDS associated catabolism/weight loss
1991	Somatropin for injection (Serostim)	Serono Labs	Y (1996)	AIDS associated catabolism/weight loss
1992	Dapsone USP	Jacobus Pharmaceutical		AIDS PCP comb treatment in conjunction w/ trimethoprim
1992	HIV neutralizing antibodies	Hemacare		AIDS
1992	HIV immune globulin	North American Biologicals		AIDS in pregnant women
1992	Interferon Beta (recombinant)	Biogen		AIDS symptomatic w/ CD4 counts <200 cells per mm3
1992	Primaquine phosphate	Sterling Winthrop		Pneumocystis carinii pneumonia

1993	5A8, monoclonal antibody to CD4	Biogen		Prevention: Post-expos prophylax for occ expos to HIV virus
1993	Aminosidine	Dr. Thomas Kanyok		Mycobacterium avium complex
1993	Atovaquone	Burroughs Wellcome		Prevention: Toxoplasma gondii encephal in HIV+ high risk
1993	Atovaquone	Burroughs Wellcome		Toxoplasma gondii encephalitis treatment and suppression
1993	Immune globulin intravenous (Gamimune N)	Miles	Y (1993)	Prevention: Infection in pediatric HIV patients
1993	Somatropin	Bio-Technology General		AIDS cachexia
1993	Tumor necrosis factor-binding protein I	Serono		AIDS
1993	Tumor necrosis factor-binding protein II	Serono		AIDS
1994	Aminosidine	Dr. Thomas Kanyok		Visceral Leishmaniasis (Kala-azar)
1994	Bovine immunoglobulin concentrate	Galagen		Crypto Parvum infect in GI tract of immunosuppressed patients
1994	Dapsone	Jacobus Pharmaceutical		Toxoplasmosis in immunocompromised patients
1994	Reduced L-glutathione	Telluride Pharmaceutical		AIDS cachexia
1994	Sulfadiazine	Eon Labs	Y (1994)	Toxoplasma gondii encephalitis
1995	Ganciclovir intravitreal implant (Vitrasert implant)	Chiron	Y (1996)	Cytomegalovirus retinitis
1995	HIV immune globulin	North American Biologics		HIV pediatric patients
1995	Mycobacterium avium sensitin RS-10	Statens Serum Institute		Diagnosis: Mycobacterium avium disease
1995	Rifapentine	Marion Merrell Dow		Mycobacterium complex
1995	Sorivudine	Bristol-Myers Squibb		Herpes zoster in immunocompromised patients
1996	Daunorubicin citrate liposome injection (DaunoXome)	NeXstar Pharmaceuticals	Y (1996)	Karposi's Sarcoma
1996	Amphotericin B lipid complex	The Liposome Company		Invasive Zygomycosis
1996	Amphotericin B lipid complex	The Liposome Company		Invasive Coccidioidomycosis
1996	Amphotericin B lipid complex	The Liposome Company		Invasive Candidiasis
1996	Amphotericin B lipid complex	The Liposome Company		Invasive Protothecosis
1996	Amphotericin B lipid complex (Abelcet)	The Liposome Company	Y (1996)	Invasive Fungal infections
1996	Amphotericin B lipid complex	The Liposome Company		Invasive Sporotrichosis
1996	Dihydrotestosterone	Unimed		Weight loss in AIDS patients

		Pharmaceuticals		w/ HIV associated wasting
1996	Liposomal Amphotericin B	Fujisawa USA		Histoplasmosis
1996	Liposomal Amphotericin B (AmBisome)	Fujisawa USA	Y (1997)	Cryptococcal Meningitis
1996	Methionine/L-methionine	Fujisawa USA		AIDS Myelopathy
1996	Nitazoxanide	Unimed Pharmaceuticals		Immunocompromised patients w/ cryptosporidiosis1
1996	Rifapentine	Marion Merrell Dow		Prevention: Mycobacterium avium complex in patients w/ AIDS and CD4+ count < or = to 75/mm3.
1996	Somatropin for injection	Serono Labs		Failure to thrive in children w/ AIDS associated wasting
1996	Testosterone	Unimed Pharmaceuticals		Weight loss in AIDS patients w/ HIV associated wasting
1996	Thalidomide	Celgene		HIV-associated wasting syndrome
1997	Liposomal amphotericin B (AmBisome)	Fujisawa	Y (1997)	Visceral leishmaniasis
1997	Paclitaxel (Taxol)	Bristol-Myers	Y (1997)	AIDS-related Kaposi's Sarcoma
1997	Paclitaxel	Baker Norton Pharmaceuticals		AIDS-related Kaposi's Sarcoma
1998	3-(3,5-dimethyl-1h-2ylmethylene)-1,3-dihydro-indol-2-one	Sugen		Kaposi's Sarcoma
1998	Alitretinoin, aliperetinate (Panretin)	Ligand	Y (1999)	Topical treatment of cutaneous lesions in AIDS-related Kaposi's sarcoma
1998	Recombinant bactericidal/permeability-increasing protein (Neuprex)	Xoma Corp.		Severe meningococcal disease
1998	S-adenosylmethionine	Dr. Alessandro Di Rocco		AIDS-myelopathy
1999	L-glutamyl-l-tryptophan	Cytran Inc.		Treatment: AIDS-related Kaposi's sarcoma
1999	Marijuana	Multidisciplinary Assoc for PS		HIV-associated wasting syndrome
1999	Recombinant Human nerve growth factor	Genentech		HIV-associated sensory neuropathy
2000	Liposomal nystatin (Nyotran)	Aronex Pharmaceuticals		Invasive fungal infections

Table 4: Summary of Status of Investigational Products for Neglected Diseases (Source: Pharmaprojects)

Disease Indication	Total Number of Investigational Products in Development	Early Development	Late Development	Development Halted or No Progress Reported
Malaria as Primary indication	63	23	12 (4 launched)	28
	(26 prophylaxis, 17 vaccines)			
Human African Trypanosomiasis (HAT) as Primary indication	1	0	0	1
Tuberculosis as Primary Indication	26	13	3 (1 launched)	10
	(8 prophylaxis, all vaccines)			
Secondary Indications for Malaria, TB, or HAT	10	4	5 (1 launched)	1
	(5 malaria, 4 TB, 1 TB & HAT)			

Table 5: Worldwide Sales for Orphan Approved Drugs for Neglected Diseases (Tuberculosis, Malaria, & Sleeping Sickness) in Thousands ($). (Source: IMS)

Product Name	Year 1996	Year 1997	Year 1998	Year 1999	Year 2000
Lariam (malaria)	58519	54665	51711	52988	54175
Rifater (TB)	7157	9695	11326	11889	9323
Rifadin IV (TB)	6986	6983	8536	9973	7078
Halfan (malaria)	5464	4678	4278	4653	3998
Mephaquin (malaria)	867	1019	1126	1014	1041
Priftin (TB)	0	0	1	8	12
*Ornidyl (HAT)	---	---	---	---	---
*Paser (TB)	---	---	---	---	---

(*No IMS data for these products)

Table 6: Orphans Helping Orphans (Source: Tufts CSDD, Trouiller 1999)

Aminosidine	1993 (US) Orphan designation For: Mycobacterium avium complex in patients w/ AIDS.
	Also designated for tuberculosis (1993) & visceral leishmaniasis (kala-azar) (1994).
Rifapentine	1995 (US) Orphan designation For: Mycobacterium avium complex in patients w/ AIDS.
	Also designated for treatment of pulmonary TB
Atovaquone	1990 Orphan designation For: AIDS associated Pneumocystis carinii pneumonia & prevention in high risk HIV-infected patients
	Also used w/ proquanil in treatment of malaria from P.falciparum
Dapsone	1994 Orphan designation For prophylaxis of toxoplasmosis of severly immunocompromised patients and prevention of P.carinii pneumonia in high risk HIV-infected patients
	Now used for leprosy and in combination w/ pyrimethamine for malaria prophylaxis
Primaquine phosphate	1993 Orphan designation For: P.carinii pneumonia in AIDS patients in combination w/ cindamycin
	Also used for radical treatment of P.vivax & P.ovale malaria
Suramin sodium	1997 Orphan designation For treatment of metastatic hormone-refractory prostate cancer
	Also used for treatment of early-stage infection by T.b. gambiense and T.b. rhodesiense
Pentamidine isethiomate	1984 Orphan designation For: prevention & treatment of P. carinii pneumonia
	Also used for treatment of early-stage T.b. gambiense & Leishmaniasis
Eflorinithine	1986 Orphan designation For HAT.
	Also designated in 1986 for treatment of PCP in AIDS patients, which was withdrawn in 1993.

Table 7: Orphan Products for TB, Malaria, and African Sleeping Sickness (Source: Tufts CSDD)

Orphan Designation Year	Generic Name	Company	Orphan Approval	Orphan Designated Disease Indication
1985	rifampicin (Rifadin IV)	Marion Merrell Dow; HMR, Aventis	Y (1989)	Tuberculosis treatment where oral form is unfeasible
1985	rifampicin, isoniazid, prazinamide (Rifater)	Marion Merrell Dow; HMR; Aventis	Y (1984)	Tuberculosis short course treatment
1986	eflornithine hcl/DFMO (Ornidyl)	Marion Merrell Dow; HMR; Aventis	Y (1990)	Trypanosoma brucei gambiense infection (sleeping sickness)
1987	mefloquine hcl (Mephaquin)	Mepha AG(Switz)		Prevention: Malaria falciparum chloroquine-resistant
1987	mefloquine hcl, (Mephaquin)	Mepha AG (Switz)		Treatment: Chloroquine-resistant falciparum Malaria
1988	aconiazide	Lincoln Diagnostics (USA)		Tuberculosis
1988	mefloquine hcl (Lariam)	Hoffman-La Roche (USA)	Y (1989)	Prevention: Plasmodium falciparum malaria resistant to other drugs
1988	mefloquine hcl (Lariam)	Hoffman-La Roche (USA)	Y (1989)	Treatment: Acute malaria due to Plasmodium falciparum & Vivax
1991	halofantrine (Halfan)	SmithKline Beecham (USA); GSK	Y (1992)	Malaria acute mild to mod due p. falciparum/p.vivax
1992	aminosalicylic acid	Jacobus Pharmaceutical (USA)	Y (1994)	Tuberculosis infections
1993	aminosidine	Dr. Thomas Kanyok (USA)		Tuberculosis
1993	thalidomide	Celgene Corporation (USA)		Mycobacterial infections due to mycobacterium TB & non-tuberculous mycobacterium
1994	sodium dichloroacetate	University of Florida (USA)		Malaria caused lactic acidosis
1995	rifapentine (Priftin)	HMR; Aventis	Y (1998)	Tuberculosis pulmonary
1999	artesunate	World Health Organization (Switz.)		Malaria
1999	Rifalazil	Pathogenesis Corp. (USA)		Pulmonary Tuberculosis

Table 8: Medicines in Development for Malaria
(Source: PharmaProjects, Persidis 2000, BioCentury)

Product Type and/or Name	Developer/Country	Comment
p.falciparum & P. vivax detection kit	Amrad Corp. (Australia)	
Synthetic peptide vaccine (Quilimmune)	Aquila Biopharmaceuticals, (USA) & SmithKline Beecham (UK)	Phase I/II
needle-free injection device for vaccine injection	Bioject Medical Technologies (USA)	
peptide vaccine	CEL-SCI, USNMRC	Preclinical
Protease inhibitors for prevention and treatment	Corvas International (USA)	
Acute cerebral malaria	CytRx (USA)	
Vaccine	Epimmune (USA)	
Vaccine	Hollis-Eden Pharmaceuticals (USA)	
Malarex against Malaria	Millenia Hope (USA)	
Vaccine	Novartis (Switzerland)	
Vaccine	Pasteur Merieux (USA)	
DNA vaccine	PowderJect Pharmaceuticals (England)	
Vaccine adjuvant technology	RIBI ImmunoChem (aquired by Corixa, USA)	
Cerebral malaria (CytoTAb)	Therapeutics Antibodies (now Protherics, UK)	
DNA vaccine	Vical (USA), Aventis (US) USNMRC	Phase II
DNA vaccine	Imperial College Innovations & Oxxon Pharmaccines	Phase I
Peptide vaccine	Aquila & U of Hawaii	Preclinical
Peptide vaccine	Genzyme (USA)	Preclinical
Peptide vaccine	Institut Pasteur & SmithKline Beecham (UK)	Preclinical
Prophylaxis (Tafenoquine)		Estimated filing: 2002 EC & US
Pyronaridine		Phase III
Coartemether		Phase 2, 3
Antimalarial vaccine (preerythrocytic)		Phase 2, 3
Antimalaria vaccine (asexual erythrocytic stage)		Phase 2
Antimalarial (Triclosan)	Centre for Advanced Scientific Research (India)	Commonly found in mouthwashes and deodorants