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The World Health Organization and the Pharmaceutical Industry

Common Areas of Interest and Differing Views

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Contents

Abstract

No article published in the scientific press in the last 10 years reviews the various areas of interest common to the World Health Organization (WHO) and the pharmaceutical industry. Despite a vast amount of information in the public domain, the policies expound the views only of the bodies they represent rather than comparing differing views. An understanding of the factors which affect the interaction between these organisations as well as the organisational structures and the actual areas of intersecting interest, may help to find ways for the industry to assist the WHO in its endeavours in developing countries.

Modern drug development is performed initially in and for western society, leaving the areas of infectious or tropical diseases with relatively less industry investment than cancer and cardiovascular disorders. Aspects of the development of an ethical drug, regardless of its therapeutic class (selection of drug name, intellectual property rights, drug safety, marketing and pricing, quality assurance and counterfeiting, generic use, emerging drug donations) are influenced to varying degrees by the triad of money, politics and medical need and the perspectives (each defensible) placed thereon by the WHO and industry. Instead of simply defending their positions combining the best of these strategies to optimise drug development for the needs of developing countries appears logical. Similarly, via its philanthropic initiatives, industry will have donated over $US1 billion in drug and research aid in the period 1995 to 2005. These charitable projects should yield useful information for planning and organising future aid efforts.

Global warming, only recently given serious governmental consideration, is an area not yet addressed in drug development policy although along with geographical effects, it is likely to have an impact on the epidemiology of diseases e.g. malaria returning to the Mediterranean, worldwide. With changing disease patterns (and particularly if the western world is affected directly), a shift in emphasis on future medical needs and drug development can be anticipated. Furthermore, given the increased modern interest in herbal medicines and the fact that poorer countries rely heavily on traditional medicines, archiving of botanicals under threat would preserve plants for future medicinal testing or use. Coupled with the environmental and poverty issues that the WHO already attempts to address in developing countries, it is timely for both bodies to work towards certain agreed mutual aims. To work effectively, it is realistic that both bodies must benefit and also make concessions in this interactive process.

No recent article reviews the areas of interest common to both the World Health Organization (WHO) and the pharmaceutical industry and yet these areas and the different factors driving the interaction must form the basis of communication and decision-making for the two bodies. The vast amount of information in the press focuses on individual issues being addressed by the WHO or the pharmaceutical industry; this is informative but has limited scope. A review of all topics together could allow greater clarity in understanding communication and collaborations between the WHO and the industry. A broad understanding of the issues in drug development may bring possible benefits to ongoing projects in the developing world and exploration of new opportunities. Moreover, with global warming now being given serious consideration, there is a need to anticipate the consequences of climate change, decide strategies and put these into effect to minimise any negative impact on disease epidemiology.

1. Factors Which Influence the World Health Organization (WHO)/Pharmaceutical Industry Interaction

According to its Constitution, the WHO is defined as the directing and coordinating authority on international health work. Consequently, it is a considerable task to track all its activities. Only those individuals or groups with a specific public health interest or an interest that intersects an area of WHO work, despite regular press releases and communications from the WHO, are likely to have a working knowledge of the breadth of its work.

In contrast, general knowledge of the pharmaceutical industry is probably greater, presumably due to interest in self-health and also because of wider news coverage given to the industry and its products in the lay press and on television. Space is also provided in the media concerning the financial issues for an individual company and its share price movements, which generates a different type of interest in drug-related issues.

The WHO-pharmaceutical industry interface is affected by the factors of money, medical need and politics. These factors drive the interaction between the two bodies. These factors are interlinked and are beginning to cause contention to the areas where there is an intersection of the WHO and the pharmaceutical industry (hereinafter termed the 'industry') interests. They are already attracting considerable attention, analysis and commentary within the public domain.

Money is an obvious factor. Pharmaceutical companies are in a delicate position. They compete in an equity market in common with other business interests to retain the trust and allegiance of their shareholders. Huge amounts of high risk capital needs to be invested with the expectation that this will create products and returns that will assure the viability of the company and retain the confidence of shareholders.[1,2] To do this, they rely on a substantial period of patent protection for their marketed products.

Until a decade or so ago, this aroused little controversy. The fact was accepted by all parties that products under patent were, in general, beyond the reach of health services in developing countries. The WHO compiled a list of essential drugs addressed to developing countries that, as of principle, excluded newly developed products. However, in the late 1980s the organisation felt bound to publish a complementary list of antibiotics, many of which were under patent, as the only feasible way of contending with the increasing prevalence of multiple antibacterial resistance (Dunne J., personal communication). More recently, the catastrophe of HIV/AIDS within the developing world has forced a public discussion of antiretrovirals (ARVs) and other drugs needed by these patients within the context of the Essential Drugs programme.[3-5]

The same issues have been debated within the World Trade Organisation (WTO) in the context of Trade Related Aspects of Intellectual Property Rights. This has opened up the possibility of compulsory licences being issued in developing countries for local manufacture of patented ARVs and other compounds. The likelihood of these drugs

being manufactured beyond the control of the patent holder in countries with ineffective regulation must raise doubts within multinational companies about the complexities and uncertainties of investing in this area at a time when humanitarian need is pressing.

The moral dilemma for companies is that making cheap drugs available to Africa risks their reexport to developed nations, threatening prices and profits. Godson[6] stated that, long term, it is hard to see how the drug industry can protect its handsome margins of 30% or more and that charities, such as Oxfam, and hard-pressed health services will keep pressing for a better deal. The pharmaceutical industry is a product of the industrialised world, and its pricing structures reflect this. Only a small percent of its output, in financial terms, is shipped to, and hence consumed in, developing countries.[7]

The structure of the industry continues to evolve. Mergers between even the largest companies (e.g. Glaxo Wellcome-SmithKline Beecham) take place to optimise resources for the research, development and sale of medicines[1,8] which in turn, by strengthening the drug pipeline, permit a wider choice in the selection of therapeutic areas and goals for drug development plus a higher potential financial return. Decision making for a drug's development is influenced by the potential return on sales for the compound as well as the feasibility and cost of its development. Clearly, industry seeks the highest feasible price for a drug whereas public sector users search for the lowest.

The need for novel effective medicines is constantly evolving as a result of newly emerging diseases, acquired resistance to antibiotics and chemotherapy, advances in molecular biology and so forth. There are many diseases or conditions for which there is either no treatment (e.g. ebola virus) or inadequate treatment because of insufficient drug efficacy or tolerance in conditions such as malaria, cardiovascular diseases and the various cancers, in both the western and developing worlds. Moreover, for transmissible and communicable diseases, drug resistance provides a further complication for both drug development and health policy.

There is broad acceptance that many of these needs are most acute in developing countries. Treatments for HIV/AIDS are not available in many African countries at prices within reach of the majority of the affected population; drug resistance is posing problems for the use of affordable medicines for malaria treatment and the lack of available drugs to treat or prevent sleeping sickness and the haemorrhagic fevers means affected patients risk death. Several pharmaceutical companies have made gestures to help with the control of individual diseases by drug donations. But there is now widespread recognition that much more must be done through debt relief and intergovernmental aid before many countries, particularly in equatorial Africa, are to create self-sustaining economies. Meanwhile, the economic plight of many of these countries is aggravated by corruption, mismanagement, and civil unrest. Against this background, they are helplessly vulnerable to substandard, counterfeit, and spurious medicines. Health systems, where they exist, do not function optimally if at all, and because of a break up in government and society infrastructure and lack of funding, there can be a resultant inaccessibility to medicines for many.

Governments in industrialised countries with a national reimbursement scheme for medicines wish to contain drug costs, since this is the simplest and most immediate way of reducing the national healthcare budget without reducing services. Pressure is now being exerted on the research-based companies to provide essential drugs to developing countries at cost, or even less. More ominous for the companies is the prospect that increasing numbers of countries will issue compulsory licences under the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement thus allowing foreign manufacturers to market copies of newly developed drugs throughout the period of international patent protection. While the humanitarian intent of such judgements is not in question, such rulings could well dissuade many companies from involving themselves in the future development of drugs

for HIV/AIDS and other infectious diseases endemic throughout the developing world.

Politics also have become involved with the issue of patents. This is a two-edged sword. Governments may wish to see industry profit since there is the financial return via taxation. However, the pharmaceutical industry claims its profit is linked to the protection received from patents, which in turn protects the higher prices of ethical drugs still in-patent. Increasingly, this subject is the matter of media interest and in March 2001 a court case was brought by the industry against the South African government concerning national laws in force against patent protection in some cases of medical need (in this situation, exemplified by drugs to treat HIV). HIV and related illnesses receive global media attention and South Africa has a large, untreated population of several million. Although the court case was dropped, financial and political ramifications of this case can be expected both locally and in other countries.

Apart from the initial triad of issues, there are further 'complicating' factors. A fourth dynamic may be considered: image. The South African court case brought the pharmaceutical industry into a critical spotlight. Articles in the press presented both the position of industry and also that of industry's opponents or critics. Negative public opinion towards pharmaceutical companies, although not readily quantifiable as to how it could affect revenue, was portrayed in the media. It is probable that the perceived image of industry suffered as a consequence of this court case, despite press releases stating that industry and the South African government had reached an accord. Separately, industry is also under an image pressure via demonstrations from animal rights activists to not employ animals in research. Thus, in the ideal situation, the pharmaceutical industry has an equilibrium to find between satisfying the shareholders' profit and maintaining an optimal public image.

A fifth factor is emerging in drug development considerations; namely, public or consumer pressure from established groups. Due to its information-sharing role, consumer or patient groups may impact on the speed of new drug development. Regulatory websites have dedicated web pages for providing information to the public.[9] With regards to the South African court case, pressure was brought to bear on industry via public protest and by charitable organisations such as Oxfam and Medecins sans Frontieres (MsF), the latter organising a petition via the internet for industry to drop the court case.

Thus, from the press given to the activities of both the industry and of the WHO in pharmaceutical journals such as Scrip and particularly the daily newspapers, these factors can be anticipated to put increasing pressure on the issues discussed between the WHO and the industry. Furthermore, with the inclusion of more contributors such as MsF or consumer groups to health debates, there is an increasing emphasis on the politics of health issue and drug development decision-making and also an underlying need for good and effective communication between all parties concerned.

The industry sponsors philanthropic projects, many of which are coordinated by the WHO. Drugs are donated free of charge or sold at reduced prices. There is also support for education initiatives (e.g. in Africa). However, because of the extreme poverty, these efforts are not enough. Although not the individual responsibility of pharma, poorer nations continue to need help from outside sources, sponsored by the pharmaceutical (or other) industry. Just what action the industry can take to help developing countries and how much is reasonable, without compromising research strategy is currently an unanswerable question. External critics seem to expect the industry to undertake philanthropic activities and reduce drug prices without considering their impact on profit or drug development.

One other factor should be mentioned. With the recognition that global warming may well be a reality, climate change may affect both population spread and disease epidemiology. It is unclear whether there is any or sufficient planning for medical need to anticipate potential global climate change either by the WHO or industry. For exam-

ple, outbreaks of yellow fevers in Africa this year are ominous, while dengue fever is establishing itself widely, and is now poised to enter into northern Australia.[10] Consequently, this possibility should be factored into the future discussions and planning of public health organisations and also by the industry for drug development as a challenge, rather than be caught short because of not anticipating climate change or its effects.

This article examines the stages in the life cycle of a compound where both the industry and the WHO have common interests and which can be used to investigate the impact of factors that influence the WHO-pharmaceutical industry interface. Various contemporary challenges face both the WHO and the industry, and swift action to address these challenges would give the greatest chance of their optimal outcome.

A literature search was performed to assess whether an overview of WHO activities and those of the pharmaceutical industry had been published. A publication search via the Internet on the Pubmed (Medline) database held at the National Library of Medicine, at the National Institute of Health, USA was conducted (search cut-off date of 30 April 2001). The search terms 'World Health Organization' (760 publications), 'Drug Industry' (13990 publications) and 'Pharmaceutical Industry' (14751 publications) with no search restrictions were used separately. The search using the 'common' set produced either five (using 'WHO and pharmaceutical industry') or six (using 'WHO and drug industry') publications, which resulted in seven from pooling the 'common set' searches.[11-17] The most relevant publication providing a succinct description of the International Federation of Pharmaceutical Manufacturers Association (IFPMA) activities at that time appeared in press in 1991.[16] No article, which gave a comprehensive description or assessment of the pharmaceutical industry and its intersecting interests with the WHO, was identified.

2. The Players and Their Policies

2.1 The WHO

The WHO was created after the Second World War as a result of a United Nations conference in San Francisco, USA, approving establishment of an independent health body. It was formed from a fusion of the Office International d'Hygiene Publique situated in Paris and the Health Organisation of the League of Nations based in Geneva. Its constitution, approved in 1946 by a quorum of United Nations (UN) Member States, came into force on 7 April, 1948 (World Health Day, celebrated with a changing theme annually).[18]

2.1.1 The WHO Constitution

The objectives and functions of the WHO, summarised from its Constitution,[19] address the external or environmental factors which affect health as well as disease management. This is reflected in the breadth of its programmes. The summarised objectives and functions are to:

- assist governments, upon request, in strengthening health services
- establish and maintain such administrative and technical services as may be required, including epidemiological and statistical services
- provide information, counsel, and assistance in the field of health, to stimulate the eradication of epidemic, endemic and other diseases
- promote improved nutrition, housing, sanitation, working conditions and other aspects of environmental hygiene
- promote cooperation among scientific and professional groups which contribute to the enhancement of health
- propose international conventions and agreements on health matters
- promote and conduct research in the field of health
- develop international standards for food, biological and pharmaceutical products
- assist in developing an informed public opinion among all peoples on matters of health.

In essence, the self-defined role of the WHO is to promote and foster technical research and work

and establish standards to support healthcare in all parts of the world. WHO policies result from initiatives at individual Member State level and also at the Headquarters level. In becoming a WHO Member State, a country agrees to abide by the WHO decisions and regulations unless stating in writing its reservations about, or rejection of, an individual proposal. Although established to perform technical tasks, increasingly the WHO has been called on to fulfil a mediating or political role to obtain its objectives which is in line with its Constitution.

Since its inception, the WHO has aimed to improve quality, safety and efficacy of medicinal products on a worldwide basis. Its mission (published on the website www.who.int.medicines) with regards to medicines 'is to provide global guidance on essential drugs and medicines, and to work with the countries in the implementation of national drug policies which ensure equity of access to essential drugs, drug quality and safety, and rational use of drugs'.[20] The WHO claims that irrational drug use has a medical (sub-optimal, ineffective or even dangerous) outcome, which often leads to higher cost. It aims to make available safe, effective and high quality medicines at the lowest possible price. According to the WHO, 3.8 billion of the world's population in 1997 had access to essential drugs, leaving one-third still without this basic right[21] and for whom WHO works to redress this balance. The objective of general drug accessibility for all patients is defined by the WHO as comprising: therapeutic access (i.e. there are drugs developed and marketed for the disease); physical access (availability within 1 hour's travelling) and financial access (the drugs should be affordable).

In 1981, the WHO Assembly unanimously adopted a Global Strategy of 'Health for All' (HFA) by the Year 2000. This strategy aimed for health resources to be evenly distributed and for all to have accessibility to essential healthcare. By extension, it encourages not only healthcare professionals but also the general public to be involved in health issues. The strategy, which embraces health at school, work and home, is still promoted by the WHO in its updated HFA policy for the twenty-first century. The objectives and functions of the WHO are compatible with its definition of health, i.e. 'health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity'. This definition is cited in the Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19 to 22 June, 1946. It was signed on 22 July 1946 by the representatives of 61 States (official records of the WHO) and entered into force on 7 April 1948. This definition has not been modified.

2.1.2 The WHO Structure

The WHO structure comprises three groups: (i) the World Health Assembly (WHA); (ii) the Executive Board; and (iii) The Secretariat.

The WHA, meets annually in Geneva and is attended by delegates from each Member State. Its tasks are to approve the biennial programme budget and to decide on major policy matters.

The Executive Board of 32 members, comprises delegates designated by a Member State elected to do so by the WHA. The Board's role is to enable the decisions and policies taken by the WHA, to advise the WHA and to aid its work. Regional Committees, composed of both Member and Associate Member States, meet annually and concentrate on the areas of specific interest to the Region.

The Secretariat, headed by the Director General, and appointed by the WHA, is staffed by around 3500 persons in both professional and general service categories, 30% of whom work at the headquarters in Geneva, 40% at the six regional offices (located in Harare for the African Region; Alexandria for the Eastern Mediterranean Region; Copenhagen for Europe; New Delhi for South-East Asia; Manila for the Western Pacific; and Washington, DC, for the Americas/Pan America) and 30% in the member countries. There are other WHO offices with more specific functions such as the International Agency for Research on Cancer in Lyon, France, where there is also an office to

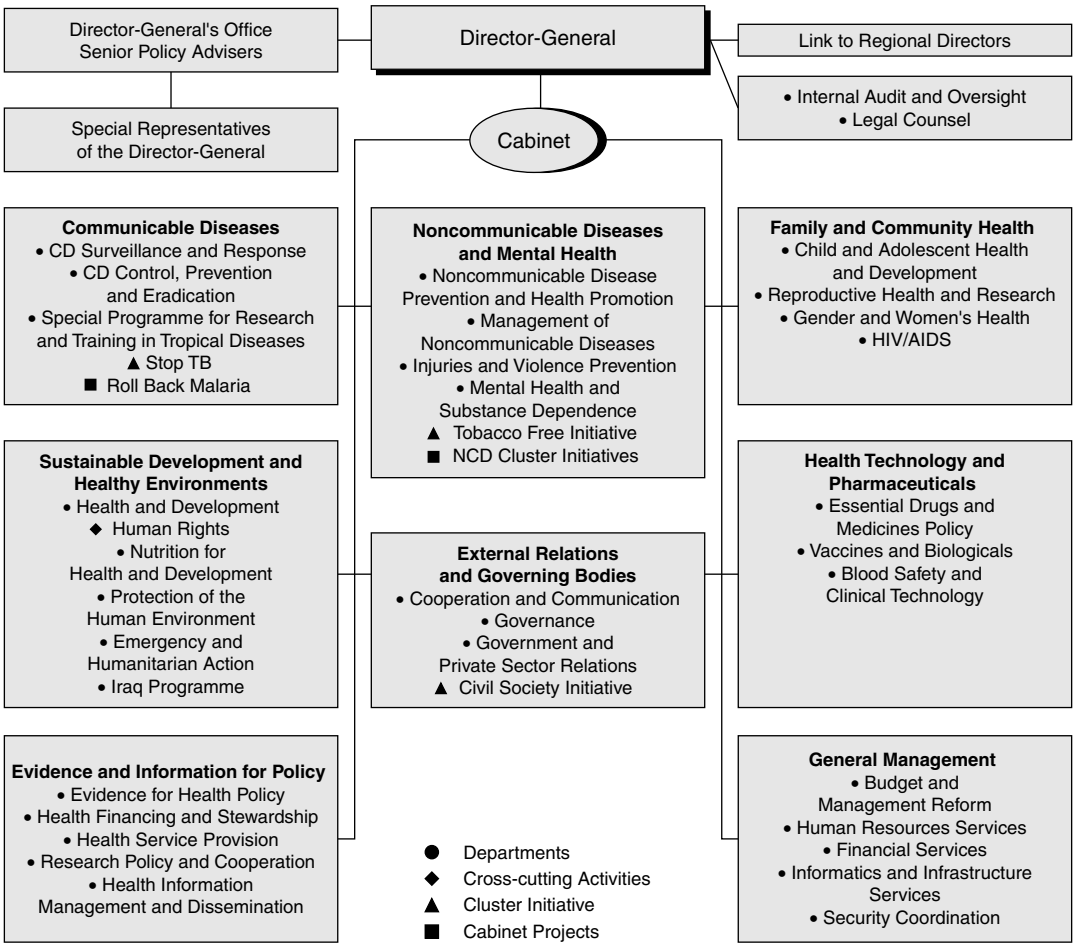

Fig. 1. The structure of the World Health Organization headquarters, April 2002 (reproduced from the World Health Organization,[22] with permission). **CD** = communicable diseases; **NCD** = noncommunicable diseases; **TB** = tuberculosis.

help developing countries detect and control epidemics and emerging diseases, including drug resistance. The management of the current Secretariat structure is presented in figure 1.

The WHO activities most relevant to the industry are mainly those under the aegis of the Essential Drugs and Other Medicines Department (EDM) [figure 2]. EDM comprises four teams:[22] the Drug Action Programme team, the Policy, Access and Rational Drug Use team, the Quality Assurance and Safety of Medicines team (QSM), and the Traditional Medicine team.

2.1.3 The WHO Budget

The WHO budget is derived from assessed contributions from Member States and Associate members (the regular budget) plus voluntary contributions from Member States and other sources (extra budgetary contributions).

An example to aid perception of the scale of work and costs managed by the WHO is the regular budget adopted by the fiftieth WHA for 1998 to 1999 which was $US842 million with an additional extra budgetary sum for the same period of $US956 million (a total of $US1.8 billion).[23] The reparti-

tion of this combined budget was 12% for Africa, 17% for the Americas, 6% for South-East Asia, 5% for Europe, 5% for the Eastern Mediterranean, 5% for the Western Pacific and 49% for Global/Interregional spending. This seemingly large budget needs additional funds to make further inroads to improve health and healthcare in developing countries.

2.1.4 Links with Bodies External to the WHO

The WHO carries out its functions in concert with other organisations. Examples of some of the partnerships entered into by the WHO are described in the following paragraph.[18] The number and variety of these partners demonstrates the broad area of health issues covered by the WHO around the globe.

The WHO has a formal arrangement with the UN covering reciprocal representation at meetings, establishment of joint committees for special purposes, exchange of information and coordination of statistical services. It has a complementary role within the UN framework of emergency management coordination.

There are close collaborations with, for example, UNICEF, UNESCO, UNHCR for emergency relief, disaster preparedness and disaster management, and co-sponsorship of UNAIDS, to address the problems of HIV/AIDS. Other links peripheral to ethical pharmaceuticals include those with the International Civil Aviation Authority concerning disinfection of aircraft, quarantine, hygiene and sanitation at airports; the International Telecommunications Union regarding notification of epidemiological radio bulletins, and the Universal Postal Union for transport of goods such as biological specimens.

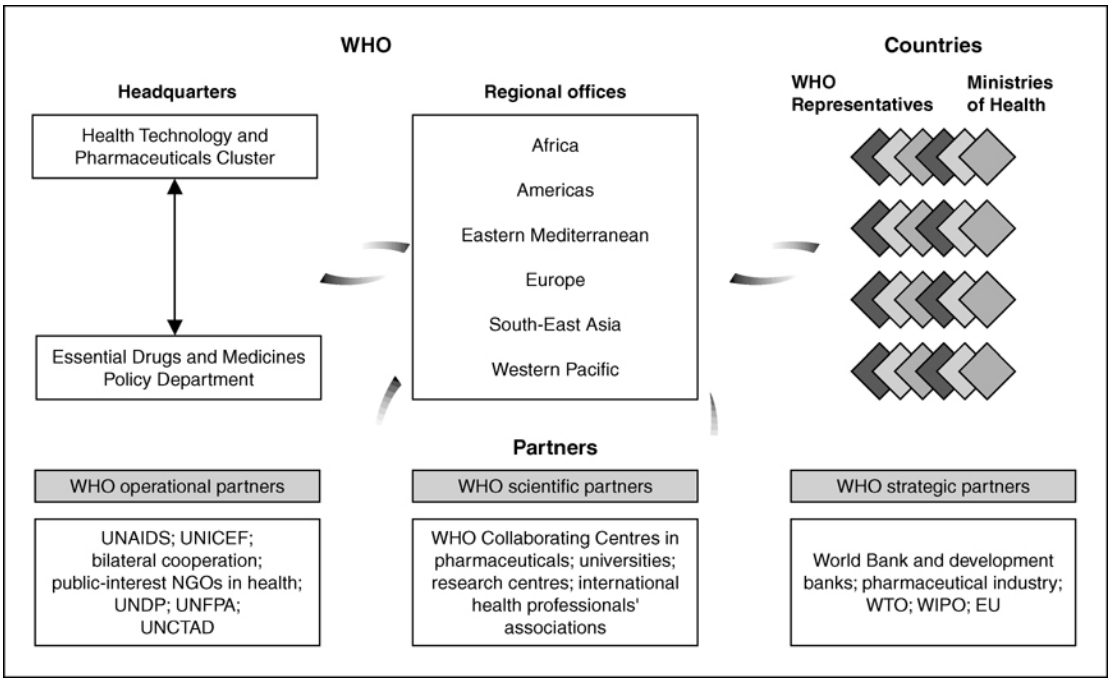

Fig. 2. Functioning of the Essential Drugs and Other Medicines Department, April 2002 (reproduced from the World Health Organization,[22] with permission). **EU** = European Union; **NGOs** = nongovernmental organisations; **UNAIDS** = United Nations on HIV/AIDS; **UNCTAD** = United Nations Conference of Trade and Development; **UNDP** = United Nations Development Programme; **UNFPA** = United Nations Fund for Population Activities; **UNICEF** = United Nations Children's Fund; **WHO** = World Health Organization; **WIPO** = World Intellectual Property Organisation; **WTO** = World Trade Organisation.

Important partnerships exist with financial institutions such as the International Monetary Fund and World Bank, key players in the need to match the economic aspects of work with the agendas for the Member States. The WHO also works with regional development banks.

The WHO has established links with more than 180 nongovernmental organisations (NGOs) using given published principles based on common grounds of interest and that the pursuit of these health interests conforms to the principles in the WHO Constitution. These collaborative activities and the list of NGOs are reviewed and updated on a regular basis. Also, the WHO systematically uses existing national centres or institutions whose services are made available by the responsible national authorities, with the consequence, either direct or indirect, of gathering information and increasing knowledge.

International representation of the pharmaceutical industry, including interaction with the WHO, occurs via the IFPMA for ethical (prescribable) drugs and the World Self-Medication Industry (WSMI) for non-prescription medicines. The majority of company personnel involved in the IFPMA and WSMI are at company (or company group) president or board member level.

2.2 The Pharmaceutical Industry

The pharmaceutical industry has a circa $US210 billion turnover[24,25] employing many thousands of persons to synthesise, test, select and develop therapeutic compounds for product registration and subsequent prescription by doctors for use by patients. The industry is a business; it was not established as a philanthropic body, although it does conduct such activities.

As a whole, the industry annually invests 15 to 20% of its total sales[26] in the research and development (R&D) of new medicines, although some may invest more to ultimately reap the benefit from an increased investment e.g. Serono which plans to increase R&D expenditure over the coming years to 40% from its current level of 18%.[27] For a new chemical entity (NCE), the discovery and development phases will typically take between 6 to 12 years to arrive at registration. It has been estimated that around 1 in 10 000 new compounds synthesised actually reach the point of drug registration.[28] Taking into account this high failure rate of compounds to reach the market plus the development time for an individual drug to achieve registered status, there is clearly considerable pressure on the industry to optimise the discovery/development process. This is possible, depending on the therapeutic area and the funding available, the latter probably being a function of the pharmaceutical company size because of good resource availability.

In recent years in the western world, NCEs have usually been chemically synthesised (but less commonly, may be extracted from animals or plants).[29] Current mainstream western medical practice is directed towards treatment of a diagnosed medical problem with a single 'purified' chemical substance in preference to a natural but less pure (i.e. possibly containing other pharmacologically active or toxic substances) treatment form such as herbs. Regulations from health authorities in the western world for the development of NCEs reflect this approach and development guidelines are oriented towards requirements for a single active therapeutic principle.

More recently, therapeutics research has also been directed towards other approaches for managing disease via genomics and proteomics. The benefits of these two different approaches cannot be expected to yield proven therapies for several years although ultimately, they may allow medicine selection to be 'individualised' to enable a higher percentage of patients to respond to contemporary treatment.[30-32] In the meantime, new medicines coming to the ethical market will be chemical or biotechnology products.

2.2.1 Decision Making for Drug Development: Clinical and Marketing Considerations

Decision making for drug development involves both an assessment of medical need and also anticipation of the market.[33] The choice of a therapeutic area or condition is greatly affected by the

recent developments in scientific understanding resulting from the publication of fundamental scientific and medical research including epidemiological research programmes occurring around the world. Particular credence is given to results emanating from the western world because the knowledge and techniques are available to conduct good quality studies as well as the funding for such influential and beneficial work.

To develop an NCE, a medical need is to be demonstrated; this medical need can be identified because there is no drug available to treat the target disease, or because the degree of efficacy (judged, for example, as the percentage of patients who respond positively or the degree of disease response/control) or safety (type and incidence of adverse events) observed with current treatments could be improved. In some disease areas (e.g. asthma or cardiovascular illness such as acute myocardial infarction and congestive heart failure) in addition to an innovative approach to treatment, trials may need to be performed in a very large patient population. Taking this with the considerable cost and time taken for drug development, a substantial commercial return for the long-term financial investment made by the company is sought.

Market influences are also involved in the decision to develop drugs and in the design of the development programme. Factors such as how the market is defined (e.g. target patient populations and whether treatment is on an outpatient or inpatient basis) and how it can be can be broken into the following sub-analyses: an audit of these markets to evaluate their attractiveness; environmental factors which will affect the target market(s); market needs (e.g. an anti-emetic drug can prevent anticipatory vomiting for patients undergoing chemotherapy) and segmentation (to identify common needs); and experience and ability of the company to develop and market the drug plus positioning of the product all can affect the decision to enter a particular market.[34]

It is no coincidence that the majority of NCEs have been developed by major companies in industrialised countries. The consequences of the successful NCE development are not only good sales to give the company an adequate or preferably, a high sales turnover from the drug but also to support or increase the share price of the company on the stock exchange.[1]

2.2.2 The Pharmaceutical Bodies Representing the Industry

The International Federation of Pharmaceutical Manufacturers Association

The IFPMA is central to the exchange of information within the international ethical pharmaceutical industry and is pivotal in the development of position statements on industry policy issues. IFPMA is the main communication channel for industry exchanges with the WHO, World Bank, WTO, and World Intellectual Property Organisation (WIPO). Founded in 1968 as a non-profit, non-governmental organisation, IFPMA has more than 60 countries represented through national or regional associations (at 31 May 2001). Conditions of membership include commitments by each association, on behalf of its members, to good manufacturing practices and acceptance of the provisions of the IFPMA Code of Pharmaceutical Marketing Practices.

Admitted into official relations with the WHO in 1971, there are also relationships with WHO and non-governmental organisation status with the Council of Europe, UNCTAD, ECOSOC, UNICEF, UNIDO, and WIPO. The IFPMA produces Health Horizons (a journal printed 3 times a year) and the Compendium of International Requirements for Drug Registration.

Its objectives and principles[35] are to:

- deal with all questions of common interest (e.g. health legislation, science, research) in order to contribute to the advancement of health and welfare of the peoples of the world
- promote and support continuous development throughout the pharmaceutical industry of ethical principles and practices
- contribute expertise to and cooperate with national and international organisations having the same aims

- coordinate its members efforts to meet these objectives.

Established committees exist for intellectual property coordination, biologicals, public affairs, an advisory committee on health economics and various sub-committees. Scientific advice for matters outside the remit of the permanent committees are referred to a panel of scientific coordinators within the IFPMA Member Associations.

The World Self-Medication Industry

Although the emphasis in this article is on ethical pharmaceuticals, there is increasing emphasis placed on the primary care [over the counter (OTC)] sector for patient management and hence, the representative body for the self-medication industry, the WSMI, requires description. Founded in 1970, with a membership of 54 associations (at 31 May 2001), the WSMI has regional representatives appointed to each of the WHO regions. There are links also with WIPO, IFPMA, Fedération Internationale Pharmaceutique, and the World Medical Association. Links with the WHO were officially established in 1977. The self-defined mission of the WSMI is 'to further the acceptance, understanding, trust, availability and responsible use of self-medication products as safe and effective treatment of conditions which are suitable for self-care and for maintenance and well-being'.

Given the spread of non-prescription products to non-pharmacy outlets (e.g. supermarkets, mail order and the internet) consumer choice is widening. This also raises the question of consumer responsibility in self-care, an area which could benefit from more research. WSMI advocates industry doing more to emphasise the cost-savings available from increased personal responsibility in healthcare. The consequences are that public healthcare services could benefit financially as well as operating more effectively (presumably via a lower case load on medical services). However, personal responsibility can only operate effectively and safely when consumers are educated about medicines.

WSMI also has created a database detailing the prescription status of ethical pharmaceuticals in Europe and globally.[36] An equivalent database could also usefully be constructed for herbal medicines. Because of wider public access to self-medication products with the consequent need for more available information on both ethical and complementary medicines, the role of the WSMI is likely to expand.

2.2.3 Third Parties: Consumer and Charitable Organisations

Increasingly, consumer and charitable organisations are becoming involved in healthcare issues. Patient groups for a large variety of conditions (HIV/AIDS groups are a strong and vocal example) have evolved worldwide to support, inform and educate their patient members about their specific disease, drugs and the drug choices that can affect patient care. The strength of these groups is aided by the fact that patients have first-hand knowledge of their illnesses.

Charitable bodies such as Oxfam and MsF, originally established to aid the world's needy are at the forefront of some of the interventionist or operational activities coordinated or supported by the WHO. Workers from these organisations in developing countries are able to observe at first hand where treatment and drug access inequities lie. Consequently, these groups are able to question the effectiveness and efficiency of specific programmes or basis of a treatment policy, and they are becoming more outspoken and critical of the WHO policies and work, of the industry and how they work together.[37]

Consumer groups, such as the European Health Forum Gastein, Health Action International (HAI) and the International Alliance of Patient's Organisations, have links not only with patient organisations but also medical and para-medical individuals and professional groups, scientific and research groups among others. Via internet discussion groups, individuals and organisations communicate easily with others worldwide, permitting an open and critical discussion of current or new issues. Although without formal legal standing currently, by efficiently networking, these large, informed consumer groups interact with and influence decisions of policy-making bodies either locally or region-

ally.[38] Some organisations have established official relations with the WHO and have the right of audience at meetings of WHO governing bodies; some work with the WHO on specific projects (e.g. MsF) is a joint author with the WHO and other parties on a drug pricing document.[39] Thus, MsF has both the information and the opportunity to voice criticism of the WHO, industry or any other healthcare organisation about drug pricing issues and the ramifications for drug access for patients in developing countries.[40,41] This is another reason for the WHO needing to fulfil a more political role in managing these issues and partners than originally intended.

3. Issues Addressed by the WHO

3.1 Current and Future Health Issues

Ongoing WHO projects concern communicable/infectious diseases; tropical diseases; vaccine preventable diseases; non-communicable diseases; the environment; family and reproductive health; health policies, statistics and systems; health technology and lifestyle issues. In parallel, the WHO has also had to concern itself with environmental issues and lifestyle factors. The problems associated with smoking, a lifestyle factor affecting health in all nations, developing and industrialised, have been highlighted. In developing countries, the WHO operates in the face of the fundamental problems of poverty; lack of clean water, nutritional deprivation, safe childbirth, family planning as well as communicable and transmissible disease.

The WHO can access epidemiological data of its target diseases via collaborative centres, allowing it to survey their management and institute interventions. The organisation is in a unique position to also predict the pattern and nature of the health problems of the future and could advise where public and private, including the pharmaceutical industry, research programmes could be focussed to address medical need.

In its 1999 World Health Report, the WHO predicted that non-communicable diseases such as heart disease and stroke, cancer (lung) and depression may replace infectious diseases as the leading cause of premature disabilities and deaths by 2020. HIV was still expected to be a significant weight on healthcare systems and resources. These predictions applied to developing regions as well as industrialised nations. Driving factors for this prediction were the ageing population, increasing numbers of persons exposed to tobacco and other risk factors such as obesity, physical inactivity and heavy alcohol consumption. Thus, it is logical that drug development efforts are targeted at these conditions. Even so, there are still conditions for which drug treatments are lacking or where new alternatives are needed.[42]

3.2 WHO Achievements

The WHO remit involves too many projects for adequate description. A few examples of work it has conducted or coordinated are provided to indicate that successes have been and can be achieved with the right collaboration and approach.

The global campaigns for eradication of smallpox and polio requiring vast expenditure have been successful. Smallpox was endemic in 31 countries in 1967. A fearsome disease, the last known case was detected in October 1977 in Somalia. In 1980, the WHO declared the disease eradicated. Widely endemic on five continents in 1988, polio is now found only in the Indian sub-continent and parts of sub-Saharan Africa. As well as vaccination, WHO has negotiated via the UN immunisation days and even in war-torn areas, to continue its polio eradication project. The target of the Global Polio Eradication Initiative, which is a coalition of WHO, governmental and non-governmental bodies including the pharmaceutical industry, is certification of the world as polio-free by 2005.

Yaws was successfully treated with injectable penicillin; by 1965, 46 million yaws patients had been successfully treated in 49 countries.

The successful treatment of onchocerciasis has been achieved by a vector control programme (Onchocerciasis Control programme) and also via the donation for as long as needed by Merck & Co.,

Inc. of ivermectin (Mectizan®[1] Donation Programme). Moreover, this approach permitted people to settle and cultivate land which was previously uninhabited because of fears of onchocerciasis.

Childhood mortality, in part due to global immunisation programmes, has been reduced from 134 per 1000 live births in 1970 to about 80 in 1995. The global infant mortality rate has fallen by more than 37% since 1970.

These achievements are remarkable given the conditions and difficulties under which the work has been conducted.

3.3 WHO Information Management and Communication

3.3.1 General Issues and Provision of Information

The WHO is a prolific producer of documents to function as reference material. To exchange information, the WHO has established systems to standardise data collection, classification and coding so that resultant statistics were interpretable. To ensure the widest utility of and audience for its documents, many are published in its six official languages.

Member States are required to inform the WHO promptly of important laws, regulations, official reports and statistics pertaining to health and to provide statistical and epidemiological data in the format requested by the WHO. This information is then published in one of the WHO journals or on its internet site (www.who.org). For the use of the general public, the WHO via the Internet, permits access to its library database, abstracts from the WHO journals, and text from many newsletters and documents (also in the form of CD-ROMs).

Up to date, independent and comparative information with a focus on (essential) drugs is developed via consultation with the WHO Expert Advisory Panel on Drug Evaluation and with governments, NGOs, the pharmaceutical industry, WHO Regional Offices and other technical programmes within the WHO.

1 The use of trade names is for product identification only and does not imply endorsement.

3.4 WHO Communication

Since the arrival of Gro Harlem Brundtland, the need for more effective cooperation between industry, governments, WHO and other NGOs has been emphasised as the way forward to tackle the health needs of developing countries.[43,44] Whilst confrontation is rarely an optimal way for progress to be made, this spirit of partnership with NGOs such as the industry, places the WHO in a sensitive position with regards to taking a stand on some issues where industry has a diametrically opposite view, such as the one for patenting rights in developing countries. The degree to which the WHO may push the limits of an argument may be tempered by the potential souring of the sought after partnership. Ironically, the arrival of charities and consumer groups on the political scene for healthcare issues may ultimately give the WHO a more diplomatic and conciliatory role between these groups and industry in order to find the middle ground on which to formulate policies for the developing world.

4. Intersecting Areas of Interest: Positions of the Pharmaceutical Industry and the WHO

4.1 Basic Drug Development and Marketing: Pre-Marketing 'Costs' to Industry

The areas of common interest between the WHO and the industry cover both the development of drugs and also their marketing. The processes of ethical drug development are presented schematically in figure 3. The focus of this article is on aspects where there is an intersection between drug development and the WHO role and functions in healthcare. Since various texts[28,29,33,45] describe the drug development process in detail, only an overview is given. The areas causing most controversy between the WHO and industry concern the human (clinical) aspects of a drug's life cycle where health policy or medical need may conflict with the marketing or pricing of a drug.

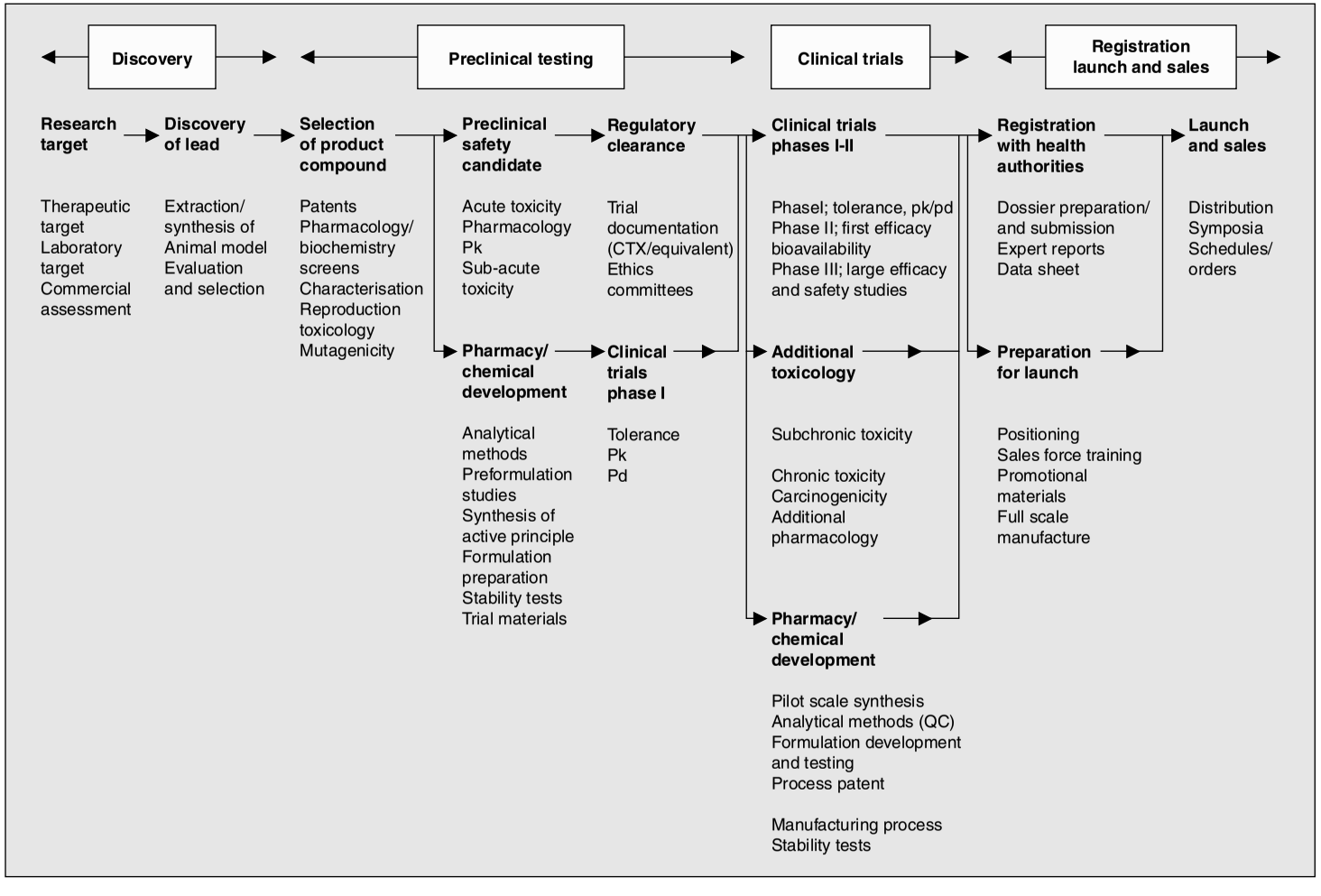

Fig. 3. The discovery and development of a new chemical entity (redrawn after Langford[46] with permission of the Editors of the Textbook of Pharmaceutical Medicine from its first edition, 1993, by publisher, The Queen's University of Belfast). **CTX** = Clinical Trials Exemption; **Pd** = pharmacodynamics; **Pk** = pharmacokinetics; **QC** = quality control.

4.1.1 Discovery, Preclinical Research and Development

NCEs are synthesised daily by pharmaceutical companies, with characterisation of their molecular properties and screening for biological activity and possible structure activity relationships. They are patented thereafter, usually worldwide. Those compounds selected for more comprehensive preclinical testing are evaluated via a battery of animal tests (pharmacological, toxicological, preclinical pharmacokinetic and initial metabolism studies) with a chemistry and formulation workup for its suitability for intravenous versus oral (or other) route of administration. These data are accrued in accordance with Good Laboratory Practice and Good Manufacturing Practice (GMP).[47,48]

Most drug development of a preclinical nature is performed by multinational companies and there is little or no input from the WHO concerning such work.

4.1.2 Clinical Development

Clinical development comprises phases I to III evaluating the pharmacokinetic, pharmacological (including drug interactions) and safety profile for appropriate dosing for clinical trials of (comparative) efficacy and safety. Clinical trials are performed in accordance with Good Clinical Practice, now encompassed in guidelines from the International Conference on Harmonisation (ICH) [see section 4.2.3]. The general intention of Good Clinical Practice[49] is to ensure that trial participants are protected from unnecessary risk via studies which are well thought out, that trial data collected are of good quality to fulfil the original purpose, that there is a means of auditing and that resources have been expended to best effect.

The WHO issued guidelines for the conduct of clinical trials in 1995;[50] these guidelines function as a good standard for reference by Member States. However, with growing interest in the ICH guidelines, the WHO guidelines could be viewed as being gradually superseded by the former, which are much more detailed.

4.1.3 Regulatory and Ethical Requirements

Drug development is highly monitored and regulated. The thalidomide tragedy in the early 1960s[51] was the springboard for stricter preclinical and clinical safety controls of medicines which are reviewed increasingly and more rigorously by regulating bodies. For the conduct of clinical trials, regulatory permission is sought. Review of the planned research is also required via local hospital or regional ethics committee and patients are required to provide written informed consent in accordance with the latest revision of the Declaration of Helsinki (most recently revised by the WMA in 2000; version 17.C/WW4/2000/C). The accrued clinical data are compiled into a (standardised) regulatory dossier for submission to regulatory agencies.

Drug development up to the end of phase III is conducted often after some degree of formal face-to-face consultation with regulatory bodies to satisfy ethical, scientific and medical questions. It can also provide some confidence for the pharmaceutical company that it has selected an appropriate development path for the NCE. There is no formal consultative process between the industry and WHO for drug development, although for tropical diseases there may be exceptions.

Drug development is time, money and labour intensive; development costs for an NCE are approximately $US800 million (2000 values).[52] A dossier may be rejected or require further, costly trials if new, external, scientific information affects how the drug is perceived or if there are debates over efficacy and safety.

4.2 Specific Areas of Intersecting Interest to the WHO and Pharma

The following topics are areas where there is a currently definable WHO or pharmaceutical industry policy. The areas where policies or position are established tend to be contentious (to a varying extent), in contrast to other areas which, currently, do not generate much public discussion. The order of presentation of these topics is intended to mirror

the timing of these considerations during drug development.

4.2.1 International Non-Proprietary Name

The WHO programme on the selection of International Non-Proprietary Names (INNs) for pharmaceutical products is coordinated by the WHO EDM (QSM team) cluster. The WHO collaborates with national nomenclature committees to select a single worldwide name for an active substance that is to be marketed as a pharmaceutical, via a specified set of procedures.[53] This function appears to be relatively non-controversial. Prior to INN, there was the opportunity for drug names to differ between countries; for example, for the same chemical entity, the name adrenaline was used in the UK but called epinephrine in the US. This very difference is a potential source of prescribing or administration error and the INN concept avoids this problem. The INN system also protects patent safety through the unique name being publicly recognisable and accessible. New INNs are published in the WHO Drug Information Journal.

4.2.2 Intellectual Property

Intellectual property is probably one of the most contentious areas between the WHO in its fight to improve public health in developing countries and the pharmaceutical industry since it embraces the factors of money, politics and medical need. Intellectual property rights (via patents, trademarks, copyright, and registered designs) are a valuable way of protecting the rights and profits of a company over an individual product.

To be patentable,[54] a product or process must:

- be new
- involve an inventive step
- be capable of industrial application
- not be otherwise excluded.

The timing of patent submission is important: too early a submission puts pressure on achieving product registration and risks losing time for recouping the investment.[55]

Once marketed, drugs may be prescribed via their trade names; this links the branded NCE with an individual company. A trademark allows identification of the origin of goods or services[54] and its registered status permits a statutory monopoly over its use in relation to the goods for which it is registered. For ethical and business reasons, it is inappropriate that other trademarks are similar or close enough to permit confusion in the course of their use.

Until the mid 1990s, the patent situation varied between countries; some countries granted patents for the pharmaceutical product and also process inventions whereas others granted patent protection only for process inventions. Furthermore, other countries granted no protection for inventions in the pharmaceutical sector (e.g. India) and the duration of the patent protection varied greatly between countries. The TRIPS Agreement[56] has established minimum common standards for protecting and enforcing all types of intellectual property rights for WTO members. This translates as a patent life for any invention of a pharmaceutical product or process that fulfils established criteria of novelty, inventiveness and usefulness of 20 years from date of patent filing. TRIPS allows some limited exceptions (e.g. exceptions which facilitate prompt marketing of generic drugs such as the 'Bolar'[2] provision) and compulsory licensing,[3] It does not prevent members from allowing generic labelling or substitution, nor does it prohibit parallel importation.[4] Both the industry and WHO emphasise different sections of TRIPS to defend their standpoints or propose actions in response to specific issues.

With a time to market, for example, of 12 years, only 8 years remain to recoup the company's investment before generic compounds can be manufactured by competitor companies with a conse-

2 The Bolar provision permits companies to perform early developmental work on their versions of branded pharmaceuticals before their patents expire.

3 Compulsory licensing enables a government to license the use of an invention to a third-party government agency without the consent of the patent holder subject to specified conditions.

4 Parallel trading within the European Union is movement of goods of 'essential similarity' from a low to a high priced country without the consent of the holder of the 'marketing authorisation'.

quent drop in product price, unless there is a new patent filed for a new application for the drug. Recognising this limitation, some authorities permit extension of these patents via a 'supplementary patent certificate' which takes effect at the end of the term of the basic patent for a period equal to the time it took to first register the drug from the date of lodging the patent application minus 5 years, with a maximum duration of this certificate of 5 years. Additionally, the holder of a marketing authorisation may be granted a period of marketing exclusivity (usually between 6 and 10 years) to protect its investment against generic competition. Clearly, maximising the life of the patent (by developing a drug in the shortest time possible or by patenting other formulations or a new indication) and/or taking advantage of the 'supplementary patent certificate' and market exclusivity paths, is in the interest of the company. In contrast, this additional patent protection although not welcomed by the WHO, is actively criticised by more vocal charitable or consumer groups.

Various items may be excluded from patentability e.g. diagnostic, therapeutic and surgical methods for human or animal treatment. Non-patenting of plants, herbal tinctures or extracts may affect large company interest in 'herbal' drug development since the lack of a guarantee of patent protection may limit the return on an investment for a new herbal medicine. However, since a high percentage (up to 80%) of the global population relies on traditional medicines for its primary healthcare needs, there is concern that the economic and trade value of traditional medicine is safeguarded and this issue appears to be under review.[57,58]

Transitional periods were permitted for national legislation in WTO member states to be enacted in line with the TRIPS provisions (1996 for developed countries, 2000 for developing countries, 2005 for developing countries who had not introduced patents before joining the WTO and 2006 for the least developed countries). Individual countries may be granted an extension to this period. The provisions apply only to new patent applications made after the entry into force of the WTO Agreement. Once in force, unauthorised copies of patented drugs are prohibited. Countries breaking this rule will incur trade sanctions if a dispute settlement process has run its course and the specific country has failed to comply with the decisions in the dispute process.

Patents provide industry with price protection in two ways: by there being no direct generic competition during a drug's patent life cycle and by permitting the manufacturer to set the price of the product. The research-based pharmaceutical industry is highly dependent on intellectual property and particularly patent protection since this period of market exclusivity allows companies to sustain vast R&D costs for new medicines and therapies, including those that never reach the market. TRIPS style protection is claimed to stimulate a globalisation of effort to find cures for disease via access to more modern technology. Also, this Agreement, by promoting quality of products being traded, may contribute to better efficacy and safety of medicines.[59]

Thus, IFPMA advocates maximal patent protection with the minimal application of compulsory licensing and parallel importation. Price reduction occurs during a drug's patent life, since a medicine faces competition from other products and treatment techniques and price is thus subject to market (and price) forces. Current R&D has been concentrated in industrialised countries with adequate patent protection. That the industry in countries such as India can see social, economic and political benefits in complying with TRIPS and that Canada has seen an increase in R&D since dropping compulsory licensing in 1992, supports this view. Furthermore, IFPMA has argued that increasing access to medicines is a far more complex process than simply decreasing medicines price. To improve access to medicines in developing countries, IFPMA outlined the following recommendations:[60]

- encouragement of more public-private partnerships for development and distribution of medicines and vaccines [e.g. Global Alliance for Vaccines and Immunisation (GAVI) and Medicines for Malaria (MMV)] fostering of local industry investment in R&D and transfer of

know-how through timely adoption of TRIPS standards
- encouragement of local innovation by avoiding price controls
- stimulation of affordable and high-quality generics by working to inculcate the importance of GMP among local producers
- governments can ensure supply of needed drugs by working to prevent parallel trade (the benefits of lower prices are not usually passed to the consumers and also, another party must pay more through this diversion)
- creation of publicly financed research centres in a geographic region to pool scientific expertise and foster medical research and to concentrate resources with an aim to develop effective treatments for various diseases of regional interest
- implementation of model anti-counterfeiting legislation via collaboration with judicial authorities, police and industry professionals in order to reduce organised crime in medicines distribution
- adoption of global review standards to speed new drug approval (c.f. ICH)
- empowerment of consumers to choose well and use medicines correctly via good information.

The WHO (via the Drug Action Programme) produced a summary of and its position on this Agreement from the perspective of its impact on drug accessibility,[61] and an update in March 2001.[62] The WHO promotes principles converse to the interests of the industry. The WHO priority of maximal drug accessibility to all humans is affected by drug price, which is protected by patents. The WHO also wants to see that patent protection will ensure investment in medicines needed for tropical diseases and the poor. Its suggested methods to optimise drug accessibility via TRIPS are summarised below:[62]

- health ministries should work closely with other ministries to ensure that legislation considers public health needs
- countries should establish their own criteria for the definition of 'new' and 'inventive' intellectual property so that standards are not so broad that they contribute to effectively extending a patent life to >20 years
- national legislation introducing TRIPS should be worded such that introduction of new generic drugs is not delayed (e.g. via compulsory licensing)
- national patent and related legislation should incorporate exceptions, trademark provisions, data exclusivity and other measures to support generic competition
- governments should consider carefully public health interests before supporting or instituting TRIPS-plus (e.g. limits on compulsory licensing not required by TRIPS) provisions
- countries which are not members of the WTO should evaluate TRIPS requirements and incorporate into national legislation the elements to benefit public health interests.

In accordance with the WHA Resolution 52.19, WHO will use four questions to evaluate the public health impact of TRIPS:

- Are newer essential drugs more expensive than they would have been if not under patent?
- Is the introduction of generic drugs being slowed?
- Are more new drugs for neglected diseases being developed?
- Are transfer to technology and direct foreign investment in developing countries increasing or decreasing?

Its findings may affect the legislation enacted by developing countries concerning intellectual property rights.

Furthermore, having observer status on an *ad hoc* basis on the WTO Council for TRIPS, the WHO should be able to monitor all relevant issues discussed that may have implications for the health sector.

A further complicating factor is the increasing input regarding patents and drug pricing of philanthropic associations. MsF was reported to have urged 15 francophone developing countries to not ratify a patent treaty intended to bring their intellectual property regimes into line with TRIPS,

since the treaty included rules on compulsory licensing and parallel importation that were more stringent than TRIPS.[63]

TRIPS has brought patent and pricing issues into prominence for public and governmental debate. Although its impact on drug accessibility and pricing is not predictable, a domino effect can be anticipated if a successful pricing containment strategy in one country is adopted by others. The WHO is in the delicate position of needing to promote generic use and low drug pricing in its strategy to assist developing countries to maximise drug accessibility. For the same reasons, it has advocated working in partnership with the industry and the expansion of drug development in tropical diseases. Some type of compromise or combination of the WHO and IFPMA approaches to address the drug access issues could be considered. Pricing cuts appear to offer some short-term help to developing countries, whereas the benefits suggested by IFPMA from stronger patent protection to stimulate business and mobilising communities to be self-reliant on a healthcare and research basis, would appear to be a helpful longer term strategy. Pilot schemes designed to address the suggestions of IFPMA with evaluation of their impact by WHO are a way in which the value of these schemes could be properly addressed.

An Example of the Conflict of Intellectual Property Rights and Drug Legislation

The TRIPS agreement and the freedom of countries to use their legal system to influence drug accessibility and price was challenged over drugs for HIV/AIDS treatment in the first and second quarter of 2001 in South Africa. The industry, represented by South Africa's Pharmaceutical Manufacturers' Association, argued against sections of South Africa's Medicines and Related Substances Control Amendment Act, which allows the health minister to override patent law and import generic drugs in cases of overwhelming public health concern. Kenya had stated that it would implement the same type of legislation as South Africa,[64] which may have been a contributing factor in the decision to take legal action. Obviously, other countries could have followed suit. The court case, dropped by the industry[65] was surrounded by company price discount offers from GlaxoSmithKline (GSK), Bristol-Myers Squibb (BMS), Abbott, and Merck & Co. Inc., and others after Cipla, a Bombay manufacturer of generic drugs, announced it would make cheap copies of HIV medicines available to the world's poor to MsF. Cuba also offered to export generic versions of patented HIV/AIDS drugs to South Africa and Brazil.[66]

However, even at discounted prices indicated above, HIV therapy is well out of the reach of many African patients. Thus, the court case was not solely about the patent law, HIV drug costs and drug supply in South Africa but also concerned drug price maintenance on a global basis. For industry, the potential passage of drugs to richer countries, a threat to price and profits, is a consequence with obvious problems. One criticism levied against the industry is the size of its profit margins of around 30% or more leaving it vulnerable to public attack.[6,34]

The court case bore the brunt of public disfavour. Demonstrations were held around the world. MsF set up a petition for the South African court case to be dropped. But other real obstacles to treatment in under-developed and developing countries, namely poverty, poor infrastructure and ineffectual or unstable governments are also responsible for inaccessible treatment. Interestingly, the issue of drug pricing is only set into this perspective by industry and not by charities. Subsequently, Senegal, Cameroon, Mali, Uganda, Rwanda and Cote d'Ivoire have accepted the price reductions offered for patients with HIV[67] and the real benefits to patients of these price cuts should be evaluated.

The Global AIDS and Health Fund, in the process of being established,[68] as one of its aims, plans to address drug supply problems in developing countries. Potentially, this fund ($US1 billion, 20 July 2001 costings) yields power, but its utility will be determined by the various questions covering drug, country and patient selection. Although much more funding is needed to benefit the massive numbers of patients with HIV/AIDS, manage-

ment of this fund and its priorities and areas of allocation will be a challenge for its governing body.

This example of drug accessibility and price is not limited to Africa. US consumers pay a higher price for drugs than their European or Canadian counterparts and yet these drug discount offers only concern developing countries; poorer patients in industrialised countries may also be deprived. Yet it is drug sales in the western world, as opposed to developing countries, on which the bulk of company revenues are based. It is unlikely that a policy to address all these issues and which limits a company to specific actions will be formulated in the near future. Much more likely is a step-by-step approach to handling the criticism and legal assaults on the patent rights of companies, which does not limit a company to specific actions globally and hence does not have such an impact on share price and profit.

Given the importance of TRIPS to the industry and consequently, general trade, there will be undoubtedly further disputes and negotiations between the interested parties for the foreseeable future. This court case focused on HIV/AIDS treatment only; extrapolating pricing and supply policy to all diseases in developing countries would be an extremely difficult task for the industry. But are price cuts the only solution?

4.2.3 The International Conference on Harmonisation

Following discussions between Europe, Japan and the US in the late 1980s and the WHO Conference of Drug Regulatory Authorities in 1989, the International Conference on Harmonisation[69] was established in April 1990. ICH is a joint initiative between regulators and industry from Western Europe, the US and Japan as equal partners in the scientific and technical discussions for the safety, quality and efficacy testing procedures for new medicinal products. Industry was seeking global markets but having to undergo national registration procedures with their different requirements to arrive at these markets. The need for regulations to be rationalised and harmonised, and duplication removed has been driven by rising health costs, increasing R&D costs and making new treatments available to an increasingly aware public with a minimum of delay. ICH guidelines, via an established process, are introduced to the relevant regulatory authority [the US Food and Drug Administration (FDA), the Japanese Ministry of Health & Welfare or the European Agency for the Evaluation of Medicinal Products] and are then implemented by that authority according to its own process. IFPMA provides the Secretariat of ICH and participates as a non-voting member of the Steering Committee.

Prior to ICH, differences in national guidelines left a company with a quandary for clinical development decision making. There was also no commonality of approach by the regulatory authorities, which further compounded a company's difficulties. Various expert working groups under ICH auspices have produced guidelines for the preclinical and clinical development of ethical drugs to achieve a registration dossier acceptable for drug registration in Europe, the US and Japan. Draft and finalised 'basic' guidelines for standardisation of chemical, formulation, animal and clinical testing and their reporting have been produced that will allow subscribing regulatory authorities to ICH [Japan, US, European Union (EU)] to receive and assess the same documents presented in the same standardised format in a common regulatory document package (the Common Technical Document; operative from 2003).

IFPMA has defended this enforceable legislation for a 'level playing field' for the quality, safety and efficacy of all products as just. Clear guidelines for technical requirements for product registration are desirable provided there is sufficient flexibility for alternate approaches when scientifically justified. Industry directly benefits by:[70]

- reduced development times and resources, including an end to duplicate clinical trials due to ethnicity differences
- easier simultaneous launch of a new drug in many countries (including across three ICH regions)

- facilitation of intra-company globalisation via ICH guidelines being a recognised standard.

There are additional benefits:

- ICH allows regulators a better understanding of how studies were performed in foreign countries and may ensure more confidence in the data collection methods
- for industry there will be a more efficient use of human, animal and material resources
- patients may benefit because of the swifter market availability of new medicines.

New guidelines are under development and updates will be applied to existing guidelines. Another topic for future consideration is the Harmonisation of Regulatory Review Procedures, it being beneficial to have common standards for review and not just drug development. Greater interaction between the relevant authorities and more transparency in the review process are preferable and achieving a common standard for review benefits all involved. Work on harmonisation in gene therapy approaches is ongoing.[71]

Despite being a 'live' process which adapts to changing medical needs and practices, ICH gives priority to issues affecting westernised (and not developing) countries. The role of the recently established Global Cooperation Group is to make available and act as a resource for information on the ICH process and guidelines to non-ICH regions. WHO has been formally approached to join this group.

There are possible benefits for non-ICH (including developing) countries who adopt these standards:

- regulatory agencies, especially those with limited resources, may benefit from the evaluations done by experienced and well-established agencies
- ideally, adoption of ICH guidelines by developing countries will allow, ultimately, products developed to gain access to prescribing markets faster
- duplication of checks already performed by regulators in other nations could be avoided.

One issue, not mentioned to date in the scientific or ICH press, is that by performing studies to ICH standards, investigational sites in poorer countries, which do not routinely participate in clinical trials, could be included in sites for clinical development. The consequent benefits are the opportunity for local medics to learn about a new medication and clinical trial conduct, as well as the interaction with medics from other countries and a potential exchange of ideas. The benefit to the industry is the same as in countries where there is considerable drug development. To consolidate this suggestion, however, the ethics and logistics of running clinical research in a specific country or region would need to be examined since these considerations are not necessarily the same in developing versus industrialised countries.

ICH was not originally intended to be a benchmark for global standards. However, the large amount of work and consultation involved internationally in the production of the guidelines and the emphasis on their high quality does not justify 'de novo' creation of guidelines for the same topics. Within the ICH process there is the opportunity for public comment on the draft versions of guidelines. There is strong logic for updating or adapting these guidelines to local needs as required. Duplication of this work by any party cannot seem to be a good use of resource.

A WHO commissioned report raised the following concerns recently about the ICH process.[72]

- ICH represents 17 countries (15% of the global population) which accounts for 90% of the $US200 billion annual sales made by multinational research-based pharmaceutical companies. Therefore, around 85% of the world's population is not represented within the ICH process.
- Criticism has been voiced over the composition of groups creating guidelines (e.g. concerning ethics committees and informed consent) since there has been little consultation with patient or consumer groups or key officials in non-ICH countries for the relevant guideline development.
- The appropriateness of IFPMA to provide the secretariat has been questioned because of possible industry-led bias to the agendas.

- The benefits from the stringent guidelines for impurities in new drug substances have not been demonstrated, but the costs of such standards may exclude smaller or generic companies (either locally or outside the ICH countries) from drug manufacturing. A possible consequence is negative impact on the availability of essential drugs in developing countries.

The continuation of WHO as an ICH observer in a more actively involved capacity was recommended to ensure that public health issues are considered sufficiently when guidelines are developed. The following questions can be debated about ICH:[72]

- Does the process function optimally or could it achieve its aims faster?
- Do the guidelines cover all the areas of drug development requiring attention?
- Could and will the structure of ICH be changed to allow a more active role of the WHO?
- Are modified guidelines of use to the developing world?

If ICH is able to achieve faster drug development times, then there is compelling logic for developing countries, where possible, to adopt or adapt the guidelines to assist the development of the compounds needed to treat local or regional (tropical) diseases.

4.2.4 Drug Safety

Both during the clinical development and the post-marketing period for an NCE or drug combination, all adverse events reported during trials are assessed. A drug dossier contains safety information from all doses tested of an NCE, although these data have been accrued from a relatively limited number of patients versus the numbers to which it will be prescribed once registered. In the post-marketing period, companies are required to assess the safety of the NCE (for which there are several methods employed)[73] in higher patient numbers exposed to the drug and to provide feedback in the appropriate format[74] to the regulatory authorities, who may have differing requirements. Clearly, there is no interest for either a company or a regulatory agency to register a 'toxic' or unsafe drug.

Following the thalidomide tragedy in 1962,[51] the WHO established the Programme for International Drug Monitoring for assessing adverse reactions to drugs. To do so, a continually updated Drug Dictionary was established, and the WHO adverse reaction terminology (ART) was developed to aid this monitoring. Common reporting forms, approach to data entry, terminology and classification and also compatible systems for transmission, storage, retrieval and dissemination of data were agreed. The WHO Collaborative Centre for International Drug Monitoring at Uppsala, Sweden is operationally responsible for the programme (shared in part with the QSM team of the EDM) and the massive database to which now more than 50 countries contribute data.[75]

Because of ICH, companies now apply the Medical Dictionary for Regulatory Activities (MedDRA) terminology for coding adverse events reported from clinical trials. Enquiry to the Uppsala Monitoring Centre in 2000 (Olsson S., personal communication)[76] indicated that MedDRA was used in the US and that cost issues slowed its implementation in Europe. Subsequent enquiry in 2001 indicated that despite EU conversion to MedDRA in the coming years as the centralised EU pharmacovigilance data base becomes operational, the WHO will not adopt the MedDRA dictionary for the WHO programme but instead integrate WHO-ART and ICD, using MedDRA (operated by private enterprise) in parallel (Olsson S., personal communication).

Drug safety information is exchanged between WHO and Member States at a regulatory level via a network of designated national information officers. Notification of drugs withdrawn from the market for safety reasons is published in the 'WHO Pharmaceuticals Newsletter' and the WHO one page 'Alerts'. Relevant regulatory decisions are compiled in the 'UN Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or not Approved by Governments'. Consequently, companies must review drug safety (and efficacy) issues on a global rather than national scale. Although, a company would

normally do this, the presence of the WHO acts as an independent safeguard. Thus, for a specific (local) safety issue, the future of a compound staying on the market or having a change, usually a restrictive one, to its prescribing instructions has the potential of international ramifications. In such instances, the consequences are usually a decrease in revenue to the company because of these additional imposed limits. Apart from the ethical concerns of patient exposure to drug-related safety hazards, this issue becomes even more of a problem when legal liability issues surface and the company is obliged to pay compensation for drug-related injury.

4.2.5 Anatomical Therapeutic Chemical/Defined Daily Dose Classification

In 1981, the WHO Regional Office for Europe recommended that the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification be used for drug utilisation studies. Data collection and classification is performed at the WHO Collaborative Centre in Norway. An ATC classification is created for a drug once a marketing authorisation has been submitted in at least one country. The classification may affect the marketing strategy (e.g. market segmentation) for a compound and also its price (e.g. in France, the second drug in a class is automatically subject to a 20% price reduction on the price of the first arrival in the class). The ATC/DDD classification itself does not attract much public debate whereas pricing and marketing issues to which it contributes indirectly are more controversial.

4.2.6 Marketing of Drugs

Drugs launched for prescribing (and eventually self-medication), receive marketing support to boost drug sales. To recoup the substantial development costs, large budgets are expended on drug promotion via detailing by representatives to health professionals; advertisements in medical and non-medical journals and sponsorship of meetings etc. using promotional methods described elsewhere.[77]

Where possible, new formulations and/or new indications for the NCE are developed to extend the product's life cycle (so called life cycle management). In the modern industry structure, this work is managed by product life cycle teams, whose role often commences from initial development of an NCE. There is currently no restriction on registration of a compound which arrives later in its therapeutic class but evidently, later arrivals in a drug class will need strong marketing support to obtain a reasonable percentage of the market.

Promotion of medicines is regulated by national industry organisation directives; information presented for marketing purposes must comply with the registered indication. Companies are encouraged to have their own standard operating procedure for the review of these materials to ensure that the promotional materials comply with both company policy and national and international Codes for marketing.

The WHO position on drug promotion was consolidated in 1988;[78] its aim being to 'support and encourage the improvement of healthcare through the rational use of medicinal drugs'. The WHO document covers: advertising to healthcare professionals and the general public; the conduct, training and remuneration of medical representatives; free samples; meetings; post-marketing studies and surveillance; packaging and labelling; and the promotion of exported drugs and information (destined for doctors and patients).

IFPMA is a proponent of self-regulation of marketing practices,[79] considering it to be both an efficient and cost-effective mechanism for imposing standards for advertising and promotional practices, but still working in tandem with appropriate and enforceable national legislation. The IFPMA's own Code recognises the value of the WHO guideline;[80] it is binding on all its members and 'intended to define universally applicable baseline standards of marketing practices'. First approved in 1981 by member associations, the latest revision of the Code was in January 2000 to take into account the use of the Internet. A complaints procedure exists for breaches of the Code. All complaints are referred to the company and not dealt with directly by IFPMA. The 'offending' company has either to jus-

tify its promotion or acknowledge fault. Regardless of the outcome, the IFPMA Code is always secondary to local (national) laws and regulations.

Generally, companies maintain a zealous watch over the advertising and marketing activities of their competitors and institute a complaint if these standards are breached. Medical practitioners in the western world also are reported to complain against inappropriate marketing activities. These breaches are reported in the pharmaceutical press. The benefit of the WHO Code is in its independence as an advisory document and role to which any body may refer. Developing countries are likely to derive greatest benefit from the WHO Code, provided there is the infrastructure in place to complain about marketing practices that are not Code-compliant. The real problem for the WHO with marketed medicines in developing countries probably lies, not only with the assurance that marketing codes are followed by a company, but in the promotion of branded products versus generics. This produces greater prescribing of more costly, branded products by the doctor and a higher cost to the patient.[7]

4.2.7 Drug Pricing

After regulatory approval, pricing is negotiated. Price is affected by its (non)inclusion in a national (subsidised) drug formulary, or in local formularies or those formularies held by health insurance organisations. A good return on investment is anticipated via a higher prescription rate of a formulary product instead of a possibly small(er) turnover at a higher, non-subsidised price. Negotiations for formulary listing are pressured and even more so with increasing requirement for justification of drug price via cost effectiveness studies.

Drugs which are too expensive or not subsidised for formulary use, either may not be available at a specific clinic or hospital or may not be considered by the prescribing clinician because of cost, leading to potential therapeutic detriment of the patient. In developing countries where usually no national subsidy exists, drugs are paid for directly by the patient and drug cost probably has relatively greater importance for more individuals than for those in developed countries. Drug price has the potential to adversely affect patients in all societies.

Predictably, the WHO champions the lowest possible drug price to maximise accessibility, promoting the concept of differential pricing whereby poorer countries would pay less than high-income countries for essential drugs. In collaboration with other groups such as MsF, the WHO recently published price information on drugs to treat patients with HIV/AIDS.[39]

Via the patent protection claimed to underpin the finances of the R&D pharmaceutical industry, the IFPMA promotes some form of drug price maintenance. The IFPMA logic, supported by its defensive arguments, is clear; insufficient profit from low prices equates to reduced research and development. Moreover, the pattern of market advantage has changed for drugs in the last 20 years and direct drug competitors, which are likely to have a direct effect on sales and price, arrive on the market more swiftly than before. Inderal®, introduced in 1968 had no brand/NCE competitor for 10 years whereas in the late 1990s, Norvir® (1996) followed Invirase® onto the market within 1 year. IFPMA has made a case against uniform drug pricing, citing other factors as to why prices differ among markets: market structures, income levels, exchange rate fluctuations, taxes, distribution costs and margins, and generic presence[81] to show that there is no single equation for market price calculation. That said, a floor price must be calculated so a company can anticipate its pay-back for drug investment and thence, profits.

The issue of HIV drug pricing in South Africa reinforces the potential problems of discounting price in one area of the world and its impact on price elsewhere (see section 4.2.2) to which the industry is forced to react. Not only might pharmaceutical profits suffer but the calculation of anticipated revenue with its consequences on future planning for company resources and drug development could be greatly affected. Whilst price cuts would benefit patients in the short term, the potential impact of profit restriction on the structure of

pharmaceutical companies and consequently, R&D could be enormous. A major concern is how less R&D funding would affect innovation. Another unstated possibility is whether price cuts will allow maintenance of the same levels of industry-sponsored support to developing countries.

There is no guarantee that innovation will ensue from a longer patent life of medicines but without sufficient funding for R&D, logic dictates that innovation must suffer. Because price is one of the factors that affects patient access to drugs, then this area will continue to be debated by the industry, the WHO, relevant consumer groups and charitable organisations such as Oxfam and MsF. Despite advocating the level of drug prices sufficient to ensure continued R&D, IFPMA has been considering the concept of a two-tier essential drugs list,[82] which indicates a willingness to consider the problems of the developing world.

4.2.8 Quality Assurance

The manufacture of medicinal products for marketing must be performed in accordance with GMP using the processes described in the approved regulatory dossier/product licence.[54] This practice ensures that there is a traceable level of quality in the processes of drug production consistent with local standards. Regulatory agencies may choose to inspect production sites; this can affect the timing of dossier approval or interrupt production once a product is marketed.[54,83] Clearly, developed countries with empowered, responsible regulatory agencies will be less affected by poor quality of marketed drugs manufactured locally than in countries without the same degree of regulatory control. However, when drugs are imported, there is no control over quality of manufacturing and traceability becomes crucial. Although, apparently less of a problem in the EU, particularly for drugs recently approved under the centralised or mutual recognition procedure where the manufacturing processes can be identified, conceptually the problem still exists for drugs arriving from outside the EU. The same problems apply to developing countries. The WHO Certification Scheme for transport of medicines[84] assists verification of quality of imported product since the product source or origin can be identified.

The WHO is active in the sphere of quality assurance (QA). The EDM QA programme is responsible for setting standards, developing guidelines and advising Member States on pharmaceutical issues (including the starting materials for medicines production), and with a specific emphasis on generics. Developing countries with smaller, probably under-funded regulatory agencies and inexperienced staff most benefit from the WHO work. The WHO guidelines for QA,[85] prepared after extensive consultation with other external experts (including industry, national institutions and NGOs) also exist for:

- national drug regulation
- product assessment and registration
- drug distribution
- basic tests and laboratory services.

Thus, in functioning as a policy-maker for QA, the WHO also has an educational role via its QA training workshops, as it does for other drug-related issues.

There is no disagreement between IFPMA and the WHO on the need for medicinal products of good quality or to have quality assurance processes in place. IFPMA has stated that all elements of the manufacturing, research and development process are equally critical to the whole and that quality costs money.[86] Without quality assurance there are risks to patient safety, potentially prolonged disease recovery times, public health consequences and wastage of spoiled drug batches. Despite the spirit of agreement between the two bodies, quality in developing countries still poses problems, particularly with generic products where lower price may mean poorer quality ingredients and lower quality assurance standards.

4.2.9 Counterfeiting

Trade in counterfeit drugs is big business. 750 cases of counterfeit drugs were reported from 28 countries in the period 1982 to 1997, 25% emanating from industrialised countries and 65% from developing countries (10% unspecified).[87] The medical consequences of counterfeiting are cruel.

A recent report of an HIV-positive patient, who self-medicated with zidovudine for herpes zoster bought in Zimbabwe, is a good example of the risks. The tablets were found to contain no active ingredient. Despite the treatment being ineffective, there was also relief that the tablets contained no harmful ingredients.[88]

Detection and deterrence of the manufacture and distribution of counterfeit drugs is another WHO priority. Guidelines for regulatory authorities on developing measures to combat counterfeiting have been established.[89] A database for drug counterfeit reports now exists.[90] Coupled with the WHO work in the QA area (see section 4.2.8), the assault on counterfeit drugs is gathering momentum. Clearly, the WHO Certification Scheme for transport of medicines[84] will help counteract trafficking in these goods but cannot completely solve the problem.

Counterfeiting does not serve industry interests. Apart from loss of revenue, IFPMA cites the lack of quality assurance and regulatory control, risk to people's health, and also the harm to a company's reputation as reasons for counterfeiting of medicinal products to be indefensible. Implementation of the TRIPS agreement (Article 61) permits penalties to be applied to WTO members in cases of counterfeiting or copyright piracy. IFPMA advocates a discrete exchange of information between companies and government agencies so that confidence in legitimate products is not eroded and a company's reputation not damaged by 'irresponsible' disclosures. To minimise or avoid the risk of counterfeiting, no more than 3 stages in the chain are recommended: from licensed manufacturer to reputable wholesaler and thence to a supervised dispensary or retail outlet.[91]

The Pharmaceutical Security Institute was founded by IFPMA in 1997, and by July 31, 2001, comprised 15 member companies. The main focus of the Pharmaceutical Security Institute is on the collection, collation and dissemination of information to the member companies, bearing on illegal acts of counterfeiting. Details of counterfeit cases have been recorded since 1998.[35]

The goals of reducing counterfeit trafficking and ensuring production of good quality medicines, which are intertwined, are common to both the WHO and the industry. However, the means proposed to achieve these goals may be different. An aggressive strategy, which is swiftly implemented and includes exchange of information between appropriate parties, is needed to reduce the number counterfeit cases. The impact of this strategy should be evaluated and further modifications implemented if needed.

4.2.10 Generics

Since cost issues preclude the widespread use in underdeveloped countries of many medicines available in westernised economies, the WHO promotes the use of generic drugs. The latest WHO Essential Drugs[5] List (11th version) contains an estimated 90% of drugs likely to be off-patent. However, there is a risk of quality and hence patient health being compromised for lower priced drugs.[92] Where newer (still in patent) compounds are listed (e.g. lipid-lowering agents) the WHO recommends drug selection in accordance with the national drug policy if there is no clear evidence of therapeutic differences between the compounds.

IFPMA distinguishes the need for a minimum list of essential drugs (mostly generics) from restrictive formularies, which it does not favour, the latter imposing a maximum number of medicines leading to limitation of prescribing freedom.[93] It concedes the market validity of generic medicines once an adequate period of market exclusivity i.e. financial return, for the original manufacturer has passed, provided that the principles of free and fair competition are respected. The IFPMA stance on generics is represented by the following:[94]

- that there should be patent protection such that a potential copyist cannot develop and launch a competitive product immediately upon patent expiry (i.e. an 'anti Bolar' approach)
- that the generic product is truly bioequivalent, producing the same therapeutic effect

5 Essential drugs are those that meet the health needs of the majority of the population.

- that the prescriber can choose to indicate drug choice by brand or generic version and that the patient receives the prescriber's choice (i.e. no generic substitution)
- that the system allows ready identification of the product supplier.

With the majority of essential drugs being generic products, the WHO aims to ensure that newer, innovative generics are not delayed from coming to the markets of developing countries. Patent extensions are possible causes of such delays. It is not clear whether, particularly in developing countries, better quality generics need raise generic price and whether prescribing would shift back towards the original branded product. It is interesting to speculate what would happen if generics were banned and the branded products, once off patent, had an obligatory price reduction; this would still return the revenue to the innovative company whilst maintaining quality. In any case, better quality generics and better policing of same would start to address the problems of counterfeiting and its negative consequences for patients.

4.2.11 Drug Donations

Developed in response to problems created by the donation of drugs to emergency-hit countries, updated guidelines for drug donations[95] were released by the WHO in 1999. The drug donation should:

- be based on an expressed need and be relevant to the disease pattern in the recipient country
- not be sent without prior consent by the recipient
- be on the national or WHO list of essential drugs, and where possible be in strength and formulation similar to those used in the recipient country
- be obtained from a reliable source and comply with quality standards in both donor and recipient country
- not include returned drugs or drug samples
- have a shelf-life of at least 1 year after arrival (exceptions are permitted if the recipient is aware in advance of delivery and if drug administration can occur before expiry of the drug shelf-life)
- be labelled in an understandable language including INN or generic name, batch number, dosage form, strength, name of manufacturer, quantity in the container, storage conditions and expiry date
- be presented in larger quantity units and hospital packs
- be packed in accordance with international shipping regulations, and be accompanied by a detailed packing list which specifies the contents of each numbered carton by INN, dosage form, quantity, batch number, expiry date, volume, weight, and any special storage conditions
- not be mixed with other supplies in the same carton, with weight per carton not exceeding 50kg
- have a declared value based on the wholesale price of its generic equivalent in the recipient country, or, if such information is not available, on the wholesale world-market price for its generic equivalent.

Additionally, drug donors should inform recipients of proposed donations and pay costs, unless specifically agreed otherwise with the recipient in advance.

IFPMA endorsed the initial (1996) WHO drug donation guidelines[96] but expressed concern that donations were limited to those on the WHO or the relevant national essential drugs list and that the minimum required 12-month shelf-life would lead to fewer donations. One recent study claimed that the majority of US drug donations were relevant to recipient country needs although there was still a substantial proportion which were not. However, insufficient shelf-life (<1 year) in 30% of cases and disposal of unwanted drugs because of need for an high-temperature incinerator were two of the issues that posed problems.[97] The study suggested better matching of drug to need would be helpful and underlined that drug donation by industry should not be discouraged because of bad press by industry critics. The updated (1999) WHO guidelines take into account the need for better matching of drug to request. They have been endorsed by the IFPMA and other bodies e.g. The Partnership for

Quality Medical Donations in the US[98] and Transfers d'urgence de l'industrie pharmaceutique in France,[99] several of which are supported by industry, established to address the issue of donations of medical supplies.

4.2.12 Self-Medication and Herbal Medicines

Although the focus of this article is on ethical (prescribable) medicines, pharmacologically active compounds in the self-care sector[6] should be mentioned. Generally, orthodox or western medicine has been slow to recognise a formal place for herbal treatments although western interest in alternative treatments[7] is growing, both from the consumer and regulatory perspective.[100] In the US and Europe, regulations for herbal medicines are less stringent than those for ethical medicines; the majority are frequently covered by dietary supplement regulations on both continents. The clear exception in the EU is Germany where almost all herbals are medicines.[101] Herbs and their preparations are used frequently in developing countries.

Herbal medicines are difficult to control from a quality perspective. Despite suggestions that herbal development be formalised via randomised, controlled clinical trials,[102] even with appropriate medical and regulatory control, herbal preparations are potentially dangerous (e.g. *Aristolochia fangchi*, which has been associated with cancer).[103] Ethical OTC medicines have already undergone safety (toxicology) evaluation, while herbal preparations have neither modern preclinical or clinical assessment. OTC medicines have been evaluated as prescription medicines before the switch to self-medication, although this does not guarantee that all adverse effects have been recognised (e.g. the cardiac effects associated with certain H_1-receptor antagonists and their subsequent market withdrawal). The consequent lack of western knowledge contributes to suspicion about this form of therapy.

The WHO supports Member States to formalise the knowledge and produce policies concerning local herbal (traditional) medicine. The WHO has formulated its own policies for self medication[104,105] and has produced a regulatory review of worldwide herbal medicine status.[106] However, this field of activity appears secondary to its work with ethical medicines.

Industry, represented by the WSMI, has supported education projects for pharmacists on self-medication products and the production of expert monographs on medicinal plants. The WSMI has also reviewed with WHO their regulatory guidelines on self-medication products.[107]

With increased focus on self-medication and herbal products, continued surveillance of self-medication and traditional medicines usage is needed. OTC purchases are (usually but not always) selected by patients who pay for the medication (with no burden to a national purse). This process diminishes, if not removes, the monetary factor driving controversy in healthcare approaches between the WHO and industry. Not only is continued interaction between industry and the WHO desirable in this field but in removing the factor of money driving this controversy, there is a great opportunity for collaborative work between the WHO and the industry.

5. Challenges and Opportunities for the Pharmaceutical Industry and the WHO

The basic problems associated with poverty in developing countries are not about to disappear, but may be overshadowed by the consequences of climate change. Global warming, via its geographic effects, is expected to inflict changes in disease epidemiology on the world's population with consequences for future medical needs. If global warming is a reality, it can be anticipated that in underdeveloped countries the disease burden will not even out but will worsen. Moreover, a shift in the geographic occurrence of tropical or other diseases could be anticipated which would suggest a larger potential population could be affected by transmissible disease.

6 Self-medication for the purposes of this article comprises OTC 'ethical' pharmaceuticals and also herbal remedies.

7 Alternative therapies include but are not limited to herbal medicines, homeopathy and acupuncture.

5.1 The Implications of Climate Change

A February 2001 report by the UN's Intergovernmental Panel on Climate Change (from the work of 700 international scientists who have been studying the global warming since 1990), predicted changes before the end of the century which include:

- melting polar icecaps and glaciers
- the disappearance of countless species of animals, birds and plant life
- farmland turning to desert
- coral reefs and Caribbean and Pacific islands shrinking.

The consequences to human life were predicted to be droughts, famine and floods on an unimaginable scale.

Regional predictions were made which, in disease and illness terms encompassed a rise in deaths from heat stroke in cities, the arrival of diseases such as malaria and the West Nile virus in Europe, the further spread of infectious diseases in Africa, and a spread of diseases in Australia currently restricted to some areas of the continent. The physical effects predicted were global warming of between 1.4 to 5.8°C and sea level rises of between 0.09 to 0.88 metres over the next century.[108] Efforts of the 1997 Kyoto Protocol, particularly without the US buy-in, are unlikely to be sufficient to slow the increase in global regional temperature, let alone maintain the climate as we know it today.

By the time the main reasons for climate change have been deduced,[109] it is possible that changes in disease epidemiology will already have occurred. With global temperature change, management of current disease problems may become more difficult, even without the threat of disease spread to westernised countries.

This could be a motivating factor or an opportunity for the industry if regions with lucrative drug markets (e.g. the EU) require drugs locally for what are presently tropical diseases normally confined to the African, South American and Asian subcontinents. Strategic planning for medicines development, may need to give a higher priority to R&D of treatments for malaria and other tropical diseases, not only for altruistic reasons, but also for health and commercial reasons. Addressing these issues now leaves time to develop new medicines and to establish an armamentarium of drugs to combat these diseases with others in reserve when, inevitably, drug resistance occurs. Furthermore industry, presently under increasing public pressure and criticism from charitable and consumer organisations, would groom its public image and optimise business opportunities derived from larger markets. The gain to patients everywhere would be better servicing of drug needs. Focus of this section is on African sub-continent although these future health problems must affect, similarly, Asia and South America.

5.1.1 Diseases

Various transmissible diseases affect millions of people in the African sub-continent; these include malaria, trypanosomiasis (sleeping sickness) and the viral haemorrhagic fevers. The management of these conditions is handicapped by inadequate or no therapy, drug resistance problems or lack of medicines due to their high cost or to distribution problems. The problems associated with their management provide a flavour of the obstacles faced for the future.

Trypanosomiasis

Trypanosomiasis, having virtually been eliminated by the 1960s, has returned. It is invariably fatal if not treated; infection by one subspecies (*Trypanosoma bruceii gambiensii*) produces a chronic condition and the other (*T. bruceii rhodiensii*), an acute illness which causes death within a few weeks. Draconian measures have been employed in the past to limit the spread of the causal agent and its vector. Yet the disease has returned due to wars in the region, which have obliterated national healthcare programmes and displaced infected individuals who migrate with their parasites. Barrett[110] estimated that 60 million of 400 million people in the 36 sub-Saharan countries are at risk.

Previous treatments including the organic arsenical, melarsoprol, are estimated to have cured about 90% of patients without serious complications; however, a certain proportion of patients die

from a reactive encephalopathy whilst receiving treatment or within 2 years.[111,112] The increasing failure rate of treatment where no second line drug has been available with a concurrent increase in the incidence of the disease leads to understandable concern. Since this disease has CNS effects, compounds with trypanocidal activity need to be able to cross the blood brain barrier. Some investigational agents are Ames-test positive and hence have been considered inappropriate for clinical trials. Whether or not this limitation on drug development is (in)appropriate for the African setting needs to be considered for what could be viewed as a different risk-benefit ratio in drug treatment.[113,114]

Eflornithine, approved by the FDA as an orphan drug in 1990, was produced by Hoechst Marion Roussel in two batches and the patent given to the WHO.[115] Despite collaborative efforts, no manufacturer for the intravenous formulation was found.[116] Two other cheaper alternatives, suramin, whose availability is under question,[117] and pentamidine[115] are licensed for treatment.

After various discussions and negotiations, Aventis will manufacture and supply as much as is needed of eflornithine, pentamidine and melarsoprol subject to a 6-monthly review by the WHO of these drug needs (see section 6.2).[118] The Aventis initiative is meritable. However, to ensure that trypanosomiasis is once again controlled and does not resurge, drug efficacy and development of drug resistance should be monitored. The need for other, back-up compounds should not be forgotten due to the time to market lag in new drug availability.

Malaria

The problems with trypanosomiasis, although considerable, pale in comparison with the global preoccupation with HIV/AIDS. However, also of considerable concern is the prospect of untreatable malaria as medicines which are affordable lose their effectiveness; this ongoing problem will probably be exacerbated with climate change with consequent spread of malaria further north in the Northern Hemisphere. Until recently, uncomplicated acute malaria could be effectively treated for little more than $US1 in children who received prompt attention (in contrast, the high costs of ARVs is marked). However, with the occurrence of resistance to chloroquine, which is becoming widespread in Africa and also resistance to the combination sulfadoxine/pyrimethamine (S/P), aside from amodiaquine there are no cost-effective antimalarials in reserve.[119,120] Both amodiaquine and S/P have disadvantages.

Amodiaquine in the early 1990s was disfavoured due to concern over its toxicity linked with long-term prophylactic use. A high level of resistance has developed to the S/P combination in *Plasmodium falciparum* following its introduction into South East Asia and South America. With the continued use of chloroquine and the failure to formalise drug policies against malaria throughout sub-Saharan Africa, more than 1 million children die annually because of *P. falciparum* infection.[119,120] The resistance of *P. falciparum* to the S/P combination has been correlated *in vitro* with mutations in the parasites' dihydrofolate reductase and dihydropteroate synthase genes. However, the same mechanism of resistance has also been demonstrated between this combination and the combination of trimethoprim-sulfamethoxazole in *Streptococcus pneumoniae*.[121,122] Thus, there is a risk that expanding the use of S/P combination might lead to a compromise in treatment of pneumonia in countries where the S/P combination is used.

It has been suggested that combination therapy be given using drugs with different mechanisms of action. Experience gained in South East Asia over the past decade has shown that generalised use of combination therapy between mefloquine and the artemisinin derives has not created a problem with development of resistance. The concept of combination therapy would preserve the value of the long established antimalarials, at least until new and effective drugs become available.[119,120]

Ultimately, although this may be an initial solution to the resistance problems, drug treatment in developing countries must be cheap. Drugs such as Malarone® with a market price of circa $US40 (1999 values) for an adult course of treatment will not permit long-term treatment in developing

countries. Donations of drugs, although useful and well meaning, will only be of benefit to limited patient numbers in the short term, even if donated supplies are retained for their intended use and do not leak into the private sector. That such donations divert attention from the need to develop viable policies for the management of malaria has been recognised[123] for the Malarone® project. The lessons learnt could be extrapolated usefully to other projects.

Limited experience has been gained in chloroquine resistant malaria using chlorpheniramine, an histamine H_1 receptor antagonist (used for chloroquine-induced pruritus) in combination with chloroquine, with the suggestion that the antihistamine facilitates uptake and concentration of chloroquine in the organism.[124,125] The clinical evidence suggests an acceptable cure rate (around 80%) with comparable efficacy to the S/P combination but not necessarily superior to the newer antimalarials.[124] A slight clinical advantage of using chlorpheniramine with the S/P combination has also been reported.[126]

Alternative antimalarials such as mefloquine, halofantrine and artesunate derivatives are all more costly than the first line options. However, Novartis has recently agreed to supply its new antimalarial Riamet® (artemether and lumefantrine; also known as Co-Artem®) at cost for use in Africa,[127] and if sufficiently cheap, should have a major impact on the recommendations in national policies for malaria treatment. The choice of combining first line treatments or adding chlorpheniramine is still more costly than the first line medicines alone; even a difference in price of a few cents is important in the African setting. These options, although useful, cannot be assumed to be permanent solutions to the resistance problems.

Continued vigilance on both treatment choice and development of new antimalarials is necessary. MMV, a public-private partnership, working under WHO's Roll Back Malaria Campaign, claims capability of managing both drug discovery and development.[128] Development of new treatments for use in Africa demands evaluation *in situ*; conceivably a full clinical development programme should be cheaper to conduct in Africa than in industrialised countries.[129]

Furthermore, involvement of local scientists, medics and paramedics in a dedicated African drug development scheme would double as an excellent training opportunity, with experienced coordination and advice from western (public and private sector) groups. The pharma industry being expert in drug development could provide both the drug molecules and the necessary development advice. The ideal, of course, is that an effective antimalarial vaccine (work is ongoing, for example, at GSK)[119,130] can be developed before the presently available first-line drugs are discarded as obsolete.

Viral Haemorrhagic Fevers

Compared with other diseases such as HIV/AIDS, tuberculosis (TB) and malaria, there is less media coverage given to the viral haemorrhagic fevers such as dengue and yellow fever. Dengue viral infections (transmitted by mosquitoes) are reported to affect up to 100 million persons per year with a mortality of 25 000 cases annually.[131] Infection with the dengue arboviruses produces a spectrum of clinical illness and infection with the haemorrhagic form is reported to have increased.[132]

Dengue fever is prevalent in tropical and subtropical Asia, America and Africa. Preventive measures rely on vector control and personal protection. Four different but distinct dengue viruses have been identified, with types 2 and 3 being relatively more pathogenic; all four serotypes can cause severe illness or fatality. Infection with one of the four virus serotypes does not offer cross-protection for the others and may increase the risk of more serious disease in the case of sequential infection. To date, treatment is supportive, mainly via rehydration fluids. There is no anti-dengue drug treatment although a tetravalent vaccine is being tested in clinical phase I/II trials (phase II in Australia) by Aventis, in collaboration with Mahidol University, Thailand.[133] Response to the different serotypes may complicate decisions on the efficacy or utility of the tetravalent vaccine. Registration and

marketing of this vaccine, if effective, cannot be anticipated for at least another 4 to 5 years.

Yellow fever has re-emerged across Africa and South America. Between 1987 and 1991 18 735 cases were reported and 4522 deaths. These figures represent the greatest number of cases for any 5-year period since 1948. The mosquitoes responsible for its transmission are present in urban sectors of the Americas including southern parts of the US.[134] As with dengue fever, yellow fever produces a wide range of signs and symptoms of varying severity; the fatality rate of severe yellow fever is of the order of 50% or more. Yellow fever is estimated to affect up to a quarter of a million people in Africa and South America, causing an estimated 30 000 deaths annually. The predominant group affected in African epidemics since the 1980s is children.[135] An effective vaccine for yellow fever exists, but insufficient finance and lack of priority hampers use of the vaccines.[136]

The problems for the dengue fever and yellow fever vaccines are presently at the different ends of the drug development spectrum. If the dengue fever vaccine is successfully developed and does become available for prescription, the funding for its use in developing countries will probably pose problems and certainly debate. The situation with the yellow fever vaccine shows where future problems with the use of the dengue vaccine may lie; an effective yellow fever vaccine exists but its use is not given sufficient priority or funding. This has resulted in sub-optimal vaccination and consequent resurgence of the disease.

The ongoing research in this area to develop appropriate vaccines needs continued support from companies and governmental agencies; work is still required on other diseases such as the hantavirus, the arenavirus (Lassa fever) and the filovirus (Ebola). However, regional (sub-continental) policies could be formulated, instituted and their importance re-emphasised to ensure that the initial efforts are not wasted. The fact that immunisation days have been negotiated for polio vaccination could be extended to other diseases where needed. Companies, in collaboration with universities or research bodies, can address the issues of vaccine development and subsequent manufacture. Vaccine supply and pricing mandates discussion between companies and health and governmental agencies. However, the responsibility for policy making for national immunisation and immunisation days in war-torn African areas rests fairly and squarely on the WHO and the relevant Member States.

5.1.2 Drug (Antibiotic) Resistance

The suffering and destructive consequences due to infection from bacteria and viruses is well recognised historically. Through the centuries there have been stories of outbreaks of smallpox, typhus, plague, cholera, influenza and genitourinary diseases in various regions of the globe. In the twentieth century, TB, genital herpes and HIV have afflicted millions in both the western and developing world. Malaria continues to pose a problem, mainly in tropical countries. There is no reason to expect epidemics or at least outbreaks of such infections to cease, unless the repositories of the infecting agents can be effectively treated or effective vaccines or curative treatments developed. Smallpox is an example of a successful management intervention and the recent proactive campaign against polio is systematically reducing annually the number of cases reported for this disease.[137]

Effective treatments have been developed during the 1900s and particularly in the last half of the century, for microbial and fungal infections and some viruses. These organisms can mutate relatively quickly via natural (and unstoppable) selection. Resistance, which can exist for a single or combination of drugs, has been recorded in varying but increasing percentages in bacterial, plasmodial and viral isolates from biological samples taken from patients suffering from many infective conditions. Antibiotic resistance does not respect national boundaries. For example, multi–drug-resistant TB continues to be a serious problem, particularly in some of the eastern European countries, and also in China, Iran and Denmark, although some countries seem to have contained the prevalence of resistance through TB-control programmes.[138]

Combined therapy to treat resistant infections (e.g. TB, HIV and malaria) appears to have success. However, complacency in using multi-drug treatment for resistant infections without back-up options is dangerous, particularly given the 8 to 12 years it takes to develop NCEs as stated earlier.

From a healthcare perspective this is worrying since currently used drugs either have or are in the process of becoming obsolete for (some of) the infections they are used to treat. WHO has warned of the rising level of resistance of infectious organisms to drugs.[139] Since the 1960s there have been no new classes of antibacterials developed.[140] WHO claims that only a small percentage of global health R&D funding is presently devoted to infectious conditions [acute respiratory infections, diarrhoeal diseases, malaria, TB and AIDS]. The relative paucity of available backup anti-infective compounds for use in infections where causative agent resistance has been identified compounds these concerns.

Development of resistance is blamed on inappropriate antibiotic treatment and also lack of any new antibiotic alternatives.[139,140] Situations which lead to the development of resistance include:

- lack of appropriate diagnostic facilities leading to misdiagnosis of a condition or the wrong antibiotic was selected
- defensive prescribing due to patient pressure to receive antibiotics (individual drugs may have been specified)
- in developing countries insufficient drug doses are prescribed or purchased or a drug course is stopped once the patient feels improved
- counterfeit drugs either contain no or the wrong (toxic or not) active ingredient or insufficient doses of the active principle
- use of broad spectrum where narrow spectrum drugs will suffice
- inadequate basic hygiene
- use of antimicrobials in animals as growth promoters
- international travel and trade.

The WHO Strategy to address resistance problems includes:[139]

- adoption of WHO endorsed policies e.g. Directly Observed Treatment Short Course (DOTS) for TB, collection of antimicrobial resistance surveillance data and distribution of results and corresponding updating of disease specific-guidelines and national drugs policies and lists
- education of health workers and the general public on appropriate drug use
- hospitals to be encouraged to develop local treatment guidelines and infection-control measures and to monitor drug use
- reduction of antimicrobial use in livestock and also other, non-medical uses of these same compounds
- increase research for new drugs and vaccines via several programmes (GAVI, MMV) and encourage the pharmaceutical industry to develop new treatments
- building alliances and partnerships between governments, international organisations and NGOs to improve and increase access to antimicrobials and the most cost-effective regimens
- increase availability of the essential drugs (c.f. the WHO Model List of Essential Drugs) since rational use of such drugs discourages unnecessary dispensing of non-essential drugs
- make effective products (e.g. mosquito nets, condoms, rehydration therapy and medicines) available to poor people.

An even better understanding of how drug resistance occurs across the different types of anti-infective products is needed. Since multi-drug treatment appears to either slow development of drug resistance in bacterial (e.g. TB), viral (e.g. HIV/AIDS) and plasmodial (e.g. malaria) infections, the lessons learnt may usefully be evaluated and applied to other resistant organisms and infections. Elucidation of the mechanisms of chlorpheniramine to augment or maintain the antimalarial efficacy of chloroquine may also be extrapolated to permit its combination use with other antimalarial treatments or in the selection of some other agent to achieve the same effect.

Development of new antimicrobial, antifungal and possibly non-HIV antiviral agents is needed.

Microbial drug resistance continues to present therapeutic dilemmas in the western world, particularly for hospital-acquired infections. Without new antibacterials or other approaches, drug resistance problems and their subsequent untreatable infections will increase in number. New drug candidates for treating TB and also *Helicobacter pylori*, methicillin-resistant *Staphylococcus aureous* and vancomycin-resistant enterococcus have been discovered and now need the financial sponsorship to continue evaluation.[141,142] Direct positive feedback and early requests to encourage the industry to give a priority for work in these areas should not be overlooked.

5.1.3 Plants and Herbs as a Source for Future Therapies

With contemporary increasing interest in the effect of plant medicines in the western world there are corresponding business opportunities for their formal development. Already, the identification and development of herbal or plant medicines is being pursued actively by some companies in Mexico and India with also their current local applications being studied.[143,144] One German company has already created a natural product library that can be scanned to discover new therapeutic products.[145] Other companies have business interests in the identification and isolation of molecules from natural sources for use in modern medicines (e.g. Calyx, Phytera, Phytopharm, Shaman, Molecular Nature Ltd etc.), with the aim of developing these types of treatments.[146,147] Companies pursuing knowledge about plants may also return something to the local community, either financially[144,148] or in terms of training.[143] Whether the return to the local population is sufficient cannot be judged presently, but should be reviewed once the efficacy of these medicinal plants has been evaluated to ensure that the compensation is of an appropriate and 'ethical' amount.

The effect of global warming on plant life, particularly those plants used in herbal treatments, has not gained media attention. If, as predicted, there is widespread drought and loss of arable land during this century, thousands of plant species will be lost. To set this statement into context, it is inconceivable that all potential antiretroviral recipients in South Africa (where around 80% of the world's HIV-infected population reside) will receive effective therapy in the immediate future, despite drug price reductions. What is striking is that 80% of this HIV affected population has access to a poorly regulated, unsubsidised but culturally appropriate 'alternative' system where patients apparently benefit from scientifically researched plant remedies and supplements supplied by an ethnobotanist, including unwele (*Sutherlandia fructans*) an herbal immunomodulator with proven anticachexia and anti-HIV actions.[149] Further clinical evaluation of these data is needed which may ultimately benefit other developing and westernised nations alike. Loss of plant remedies through climate change may deprive (developing) countries of identified cheap plant therapies.

Even without the decision to evaluate all herbal medicines used currently on the African sub-continent, there is a compelling logic for documenting all herbal medicine preparations, use and, if possible, therapeutic effects and adverse profiles. An archive of these plants in designated botanical gardens would allow time for reflection on how these medicines could be developed.

The patent situation regarding plants is unclear and needs to be revisited. Protection of traditional knowledge was on the agenda of the inaugural WIPO meeting in Switzerland April 30 to May 3, 2001.[58] Patentability of plant substances being possible would add in a business incentive to the decision to examine phytotherapies with an ensuing stronger push to examine the use of herbal medicines. To have lost plants and the opportunity to understand their benefits through not having conserved the plant species is an avoidable tragedy.

6. Current Philanthropic Projects Sponsored by the Pharmaceutical Industry

Various philanthropic programmes are sponsored by the industry. For the purposes of this article, only the programmes applied in underdevel-

oped and developing countries based on the IFPMA and corresponding company websites (up to July 15, 2001) are described (although some companies sponsor charitable projects in industrialised countries e.g. Pfizer, which subsidises or provides drugs for non-insured US patients). The focus of these programmes is on improving drug access for specific diseases by donation or price reduction of marketed drugs.

6.1 Examples of Industry Philanthropic Programmes to Aid Developing Countries

The Pfizer Annual Report, 2000, claimed that since 1996, research-based pharmaceutical companies have committed more than $US1.2 billion to long-term programs to fight diseases in sub-Saharan Africa and in other lesser developed areas. Despite this large amount, the sum is insufficient to address all the urgent health issues.

The following examples of industry philanthropy apply to a limited number of diseases. With the exception of the vitamin A projects all relate to transmissible/communicable diseases. HIV/AIDS programmes appear to have received the largest amount of financial support.

Lymphatic filariasis (LF), affects 120 million persons in more than 80 countries with an estimated one billion at risk of the disease. The GSK programme (estimated value $US1 billion i.e. $US50 million per annum) incorporates a donation of albendazole (circa 4 to 5 billion tablets over 20 years) for the time it takes to eliminate the disease plus grants to the LF centre at the UK Liverpool School of Medicine. Merck & Co. Inc. have donated ivermectin to all who need it for as long as needed in 32 of 35 countries in Africa, Latin America and Yemen. Merck also helps in harmonising the registration procedures for ivermectin where onchocerciasis or loiasis and LF are endemic in Africa. AMRAD ICT has a resource commitment to train staff in endemic countries to use their ICT card diagnostic test.

At the end of 1999, 30 countries were still reporting polio outbreaks. Aventis, a participant in GAVI, whose goal is eradication of polio by 2005, donated 40 million doses of oral polio vaccine for use in Africa between 1997 and 1999. An additional 50 million doses between 2000 and 2002 (at a cost of $US5 million) was estimated to produce savings of more than $US1.5 billion per annum from polio eradication.

The main eight countries affected by leprosy are Angola, Brazil, Guinea, India, Madagascar, Mozambique, Myanmar and Nepal. The global prevalence rate at the end of 1999 was 1.25 cases per 10 000 population, which if reduced to <1 case per 10 000 should permit elimination of the disease by 2005. Novartis has supported the Global Alliance for Leprosy Elimination, an initiative set up by the WHO in November 1999 by providing free multi-drug therapy (dapsone, rifampicin and clofazimine with $US30 million value) plus country level support for an estimated target population of between 2.5 and 2.8 million from 2000 to 2005. Ten million blister packs were shipped to approximately 80 countries in 2000.

An estimated 6 million people are blind from trachoma and 540 million at risk of visual impairment. Pfizer, supporting the International Trachoma Initiative, donated free Zithromax® (single annual dose) from 1998 to 2000 ($US66 million) and provided grants and technical assistance to confront this disease.

Around 200 to 300 million children aged <5 years are at risk of vitamin A deficiency. Each year 500 000 children go blind, many of whom die subsequently from infection. F. Hoffmann-La Roche Ltd via the Task Force SIGHT and LIFE programme since 1986 has given support of different types to Africa, the Americas and Asia. The funding between 1986 and 2000 was circa $US24.5 million. Since 1986, more than 38 million vitamin A capsules for children aged 1 month to 5 years and other support for more than 1500 projects (e.g. education materials, newsletters, support of other organisations) in at least 80 countries has been provided. In 2000, the company was involved in related projects requiring technical assistance (number of projects = 4), scientific research (10) education and training grants (52) and donations (189).

An estimated 300 million cases per year in sub-Saharan Africa, South East Asia and South America develop malaria. The GSK Malarone® (atovaquone + proguanil) Donation Programme comprises a controlled donation of 1 million patient treatment courses per year within the context of coordinated malaria control campaigns and supplied within the terms of regulatory approvals pertaining to the countries concerned.

TB affects about one-third of the global population with mortality ranging between 2 and 3 million cases per year. Through the Action TB programme, GSK supports an open research collaboration encouraging discussion between research groups (specifically the pathogenesis of *Mycobacterium tuberculosis* and identification of new drug targets and surrogate markers for drug-response) with rapid publication of findings aimed to develop new drugs and vaccines to overcome TB. More than 20 coordinated academic preclinical research groups in the UK, US, South Africa and Canada benefit from this funding of 10 million pounds sterling over 5 years from 1993 and again in 1998 (the total sum estimated for the purpose of this article to be equivalent to $US30 million).

Approximately half a million people are affected in sub-Saharan Africa and an estimated 60 million are at risk in 36 countries from African trypanosomiasis. Aventis will produce as much pentamidine, melarsoprol and eflornithine as needed to treat the disease in line with a six monthly WHO review of country requirements. MsF will coordinate the distribution of the drugs. Aventis will also provide financial support (circa $US25 million) for training, re-equipping centres, disease and drug resistance surveillance and research. BMS will fund supply of bulk material for production of 60 000 vials of eflornithine (an approximate 1-year supply).

Approximately 34 million people live with HIV or AIDS. Most of the affected persons are in the developing world (70% of whom are in sub-Saharan Africa). Several companies participate in or manage their own programmes.

GSK participates via several programmes. For the UNICEF prevention of mother to child transmission (MTCT) project GSK initially gave a free start-up supply of 10 000 treatments of Retrovir® in 11 countries; this is now extended to 30 000 treatments (2.5 million tablets) in 25 countries. Two clinical trials have been supported in settings where breast-feeding is difficult to replace with formula feed and aid has been given to countries to implement MTCT programmes (based on preferentially priced Retrovir®). Via the Positive Action programme (funding of circa $US50 million) GSK supports those living with HIV/AIDS in developing countries. There are various projects which include community-based AIDS prevention and care in Africa; production of a positive women's survival kit; strategic development of African networks of people living with HIV/AIDS (organisational management, fundraising, lobbying and negotiating skills) and support of regional conferences.

The GSK Global Business Council (established by Glaxo Wellcome, UNAIDS and the UK National Aids Trust) has a membership of 15 companies. It advocates increased involvement and participation of businesses in the management of the personnel with the disease. Its policies encompass equitable employment and workplace education programmes, philanthropic support, and commercial initiatives (e.g. cause related-marketing).

BMS is involved with the Secure the Future™ Programme which provides help for women and children with HIV/AIDS in South Africa, Senegal, Cote d'Ivoire, Mali, Burkina Faso, Botswana, Namibia, Lesotho and Swaziland. Grants have been made to facilitate medical research in women and children in 9 countries (via the BMS HIV Research Institute). The BMS Foundation Community Outreach & Education Fund aids NGOs and community based organisations to meet demands for services, including orphan and home-based care. There are also grants to expand capacity-building education initiatives (e.g. a 1-year university programme at the Medical University of South Africa) and support for development of an HIV nursing curriculum for Africa. This funding is approximately $US115 million over 5 years. Along

with other companies, BMS funds the ACCESS Initiative and has a commitment to expand access to its ARVs didanosine (Videx®), stavudine (Zerit®), and also megestrol (Megace®) and oral Fungizone®.

Boehringer Ingelheim (BI) has donated Viramune® in accordance with WHO guidelines for a 5-year period (from mid 2000) for the prevention of MTCT of HIV-1 in developing economies with an expressed need. Via the IAS-SHARE Treating Programme for Physicians, BI also supports training initiatives for the developing world.

Pfizer created the Diflucan Partnership which gives free diflucan for opportunistic infections in HIV/AIDS patients for as long as needed in more than 50 least-developed countries identified by the UN as where HIV/AIDS is most prevalent. Through the Pfizer Foundation and with the Academic Alliance for AIDS Care and Prevention in Africa, the construction of a clinic (with both diagnostic and treatment facilities) in Kampala, Uganda to open late 2001/early 2002 is being funded. Given that there are an estimated 820 000 persons in Uganda with HIV/AIDS, the objectives are to increase the patient number treated and to determine which ARVs are appropriate for Africa. This project will also strengthen medical infrastructure in Uganda through training. Ultimately, replication of the same set-up across Africa with use of the latest medicines may be possible.

The Hoffmann-La Roche BlueSky Initiative supports the SHARE courses on prevention and management of HIV infection; gives assistance to local projects; supports the HIV-NAT collaboration among clinical researchers in Thailand, Australia and The Netherlands; supports studies in Africa and also UN operations. The company products and diagnostic services are being used in two UNAIDS pilot studies.

Merck & Co. Inc., via Merck Company Foundation, has established its Enhancing Care Initiative. Nine areas have been developed by the its Enhancing Care Initiative as a framework for broadly evaluating HIV/AIDS care in Thailand, Senegal, Brazil and KwaZulu-Natal (in South Africa). The projects address voluntary HIV testing/counselling; basic medical care services; laboratory and diagnostic services; HIV/AIDS clinical management; new therapies; community based care; social services; care education and information dissemination and supportive care including care of the dying. The company developed and manages the Botswana Comprehensive HIV/AIDS Partnership which aims to improve care of HIV patients, reduce HIV spread; and to increase awareness, prevention, diagnosis and treatment of HIV/AIDS in Botswana. Merck also contributes ARVs to the programme. Its contribution is valued at $US50 million over the ensuing 5 years from its announcement in mid 2000 (to match funding from the Gates Foundation).

Unilever Public Limited Company also supports the Botswana Comprehensive HIV/AIDS Partnership providing expertise in setting up the distribution systems, and the public communications and awareness programme.

Four research-based companies, namely, BI, BMS, GSK and Merck Sharp & Dohme manage the Accelerating Access to HIV/AIDS Care and Treatment Initiative, whose emphasis is on drug donation and price reduction. This move also involves the active leadership of the relevant governments and UN support to address healthcare infrastructure and drug distribution aspects in more than 25 countries. There is price reduction of ARVs by up to 75% by GSK; free drug from BI for MTCT and subsidy of virological services and tests.

Via GAVI, American Home Products (Wyeth Lederle Vaccines Unit) has provided vaccines (10 million doses) for about 3.3 million children against *Haemophilus influenzae* type B over a 3 year period from 2000, with a project value of $US40 million.

Also via GAVI, Merck & Co. has donated 5 million doses over a 5-year period of Recombivax HB® ($US100 million) for vaccination against hepatitis B. 350 million people are believed to be affected worldwide with 1 million deaths annually. Merck & Co. Inc. have given also a second donation of the measles, mumps and rubella combination vaccine of approximately 650 000 doses to Honduras over a 2-year period from 2000 (300 000 doses were donated in 1999).

As previously stated, drug quality and counterfeiting poses problems for patients, practitioners and companies alike. The German Pharma Health Fund (GPHF) established by a research-based pharmaceutical industry in Germany has created the 'GPHF-Minilab', a simple drug quality control kit for 19 drugs (and 1 drug combination) with user manuals in English (the production of French and Spanish manuals is ongoing). Over 30 GPHF-Minilabs have been integrated into health projects in 14 countries in Africa, South America and Asia.

Drug donations for emergency situations (e.g. war/natural disasters) require appropriate selection and management. Various organisations handle drug donations, one industry-led example being Transfers d'urgence de l'industrie pharmaceutique established by Syndicat National de l'Industrie Pharmaceutique, France. These donations in emergency situations are handled in accordance with WHO recommendations and comprise tin trunks containing 50kg of essential medications (the donated range of products is updated by the WHO and field medical teams) and minor medical and surgical equipment. In 1999, 817 tin trunks and 174 tons of medicines on pallets were donated.

6.2 Review of These Charitable Projects

The information above is based on communications from the IFPMA and related company websites. Initiatives from only 11 companies, and not all industry-sponsored philanthropic efforts, are reported. Except for AMRAD, these are all major pharmaceutical companies. However, this is a small number of donor companies with respect to the total number of R&D companies. One explanation may be that only the large pharmaceutical companies have sufficient resources to address drug development in malaria, HIV/AIDS, polio, LF, trypanosomiasis and hepatitis B, these diseases being endemic mainly in poorer countries (with the obvious exceptions of HIV/AIDS and to some degree, hepatitis B). These areas are complicated in terms of the science of the disease, their management and the needs for a drug development programme. Because of their experience in these disease areas, logic dictates that it is on these companies that pressure would be exerted to initiate charitable projects.

Other pharmaceutical companies will have donated drugs to countries in emergency situations (due to war or natural disaster) and may have charitable policies not described above. Even so, the value of funding presented in the previous text, show that the ten large companies have provided support of circa $US786 million. This is an underestimate since not all activities (e.g. some drug donations, nor various education or health programmes nor the construction of the clinic in Uganda) had budgets indicated. Ongoing drug development programmes are excluded from this figure. Thus, the industry-sponsored philanthropic efforts easily amount to over $US1000 million in donation value, funded mainly in the period 1996 to 2005.

Overall, the industry support takes the form of drug donation or price reduction; financial support for diagnostic or laboratory testing; and research and education grants. These are the philanthropic activities in which a company would be expected to engage since they are directly drug-related.

Evidently, to implement and to achieve success of these initiatives, collaboration with governments and other organisations is necessary. Drug donation or price reduction in isolation, although helpful, cannot be expected to resolve or even to have the maximum impact on the drug supply/accessibility problems and health issues confronting the deprived peoples in these countries, when there are other health management factors which, too, are inadequate. Given the great number of patients in inaccessible regions requiring chronic and/or intermittent drug treatment, it is simplistic to expect this. Moreover, the financial sponsorship by some companies in other projects (e.g. effective drug distribution systems and education) could be of long-term benefit. The experience of the Malarone® Donation Programme confirms this. The pilot phase of this programme reported that the seven pilot sites in Kenya and Uganda benefited from improved malaria diagnosis and treatment as well as a better understanding of malaria control, but that it was

not an efficient and effective use of resource to reduce patient suffering and death. Consequently, the programme ceased upon completion of the pilot phase.[150]

By analogy, the Malarone® experience leads to questioning the value and benefits of other drug donation programmes conducted in isolation. To predict success of a programme, various factors would need to be considered; the size of the affected population must be a determinant of programme manageability and therefore, success. Programmes for diseases where only intermittent (e.g. annual) drug dosing is required are easier to administer and more likely to have a clear benefit than where daily drug intervention is needed. It is easy to see why vaccines for malaria and other transmissible diseases are needed.

But has the pharmaceutical industry contribution or role been optimised in terms of the type of projects sponsored or supported?

It is noteworthy that there is reference to construction of one clinic (for HIV/AIDS in Uganda) being supported by industry (Pfizer). Although not specifically the concern of industry, diverting some industry charitable funds to clinic construction instead of price cuts for new drugs, may for a particular time period, be an optimal or better use of such funds, particularly if cheap drugs for management of a specific disease are already available. Hospitals or clinics could be constructed such that the building(s) could also be multi-use for drug quality assurance evaluation, laboratory testing, drug storage etc. This would also allow schemes to address the issues of drug availability, supply and distribution, and medical and patient education to be tested. A series of primary care, computer supported and linked clinics within a target country or set of countries may be of greater long-term benefit to local communities than costly drug donations, which treat one disease only. It would be useful to establish the need, on a geographic basis, for construction of such new clinics. Is the WHO or some other body already doing this?

The existence of a coordinating body for all these industry-sponsored programmes needs to be established. Duplication in these projects is not desirable given the large number of health issues requiring funding. It is reasonable to, via the WHO and IFPMA, follow up on all industry projects to ensure avoidance of duplication and also permit linking of relevant projects (e.g. assessment of drug distribution channels plus donations of drugs). Even without a change in the nature of these philanthropic projects (i.e. maintaining drug donation as the prime type of project) some form of central coordination, if not already established, should optimise their benefits.

7. Discussion and Conclusions

7.1 Discussion

Pharmaceutical companies are in business to stay in business. Industry takes risks not only in the area of drug discovery, research and development but also has liability for unforeseeable health consequences from the drugs it develops, requiring financial reserves to cover such contingencies. The concerns with rhabdomyolysis from lipid lowering agents (e.g. Baycol®) exemplify this. Companies develop the best of the products in their pipeline; it is not in their interest to do otherwise. If resources are inadequate to develop a particular NCE, then it is good business sense to outlicense the compound. Conversely, if the pipelines are inadequate for business return or to satisfy an unmet medical need, then companies need to look elsewhere to find NCEs for development; they also will develop product extensions to support the current brand and to continue doing business.

Where there are insufficient molecules identified for development, companies need to look elsewhere for new sources of therapeutic inspiration (e.g. herbal medicines, genomics or proteomics) as well as continuing with established methods. New therapeutic approaches are potentially good business. However, delays in drug development are not automatically controllable, nor are the benefits of genomics and proteomics just around the corner. Time is needed until the first effects of such technology will be felt in the western world and it is

difficult to predict how developing countries could even start to address the utility of such approaches.

Inspiration for drug development comes from product or medical need. There are still unmet medical needs to treat (tropical) diseases such as malaria, trypanosomiasis and the viral haemorrhagic fevers. With impending climate change and its consequences, some of these diseases presently confined to the African sub-continent and parts of Asia and South America, could affect westernised countries in Europe and the USA. WHO already has a formidable set of health related problems to tackle which are both environment and drug related. Confronting the current health problems in developing countries could prevent or at least minimise worse situations to come.

7.1.1 Optimising Industry Aid to Developing Countries

There is no one dynamic in operation (e.g. drug cost) whose removal or minimisation will resolve all the healthcare problems in developing countries. Although cheap drugs are needed, the infrastructure for their effective storage and distribution is needed, as well as education to ensure their correct administration. Thus, a multi-factorial approach is required. Various charitable, collaborative programmes sponsored by industry are attempting to address the problems of malaria, polio, etc. Industry efforts have considerably aided the assault on onchocerciasis and the eradication of polio is within sight. Funding of clinic construction and related services may be another way in which industry can help WHO to aid developing countries. Follow-up of the Pfizer project in Uganda should yield solid information on this type of aid. Furthermore, the lessons from the Malarone® Donation programme should be shared to improve the benefits of other philanthropic projects. Industry-sponsored programmes should be effective in helping patients without duplicating effort or resource. Effective coordination by the IFPMA or the WHO which could optimise use of charitable funds may avoid this problem.

7.1.2 Opportunities for Industry

Drug resistance in bacteria, viruses and plasmodia, provides an ongoing need for continued discovery of new entities to defeat transmissible diseases. Apart from drug management policies at national and local level, the need for development of NCEs or vaccines to prevent or treat future infections in response to drug-resistance patterns has been signalled. Such R&D activity by pharmaceutical companies should be focussed on and of benefit to both westernised or the poorer countries.

Traditional, alternative or complementary medicine is, from a western world perspective, becoming a more popular form of treatment to explore as a primary step in healthcare. This interest is translating into a burgeoning market in industrialised countries. Simultaneously, herbal medicines are under regulatory scrutiny for their safety and working parties in regulatory bodies continue to review approaches to the development and registration of these preparations. Moreover, there is current discussion and evaluation of the possibility of patent protection for plants and their preparations. Well-developed and regulated herbal medicines or derivatives are an area for evaluation by large pharmaceutical companies. OTC (including herbal) preparations, are paid for by the consumer and are not government subsidised. Development of the OTC sphere for responsible and informed self-medication is a business opportunity for industry and reduces the political debate over treatment cost.

In Africa, some native African HIV/AIDS communities are being treated with herbal or botanic medicines with apparent success. These treatments require further evaluation. It is assumed that these plant medicines are affordable for the local communities. They may offer an alternative for wider use in sub-Saharan Africa, other developing regions and industrialised countries. Global warming is anticipated to decimate the landscape via droughts and floods leading to loss of arable land and plant species. Africa has been predicted to be at particular risk. These considerations together point to the common sense of archiving and inves-

tigating plants as medicinal products and provides another role for industry and the WHO.

7.1.3 Lessons from the WHO-Industry Intersecting Areas

Can the WHO-industry interface be synergistic or antagonistic? Of the three baseline factors of money, medical need and politics, the current and most controversial differences between goals of the WHO and of industry are based on the realities of inequality and poverty. With the best will in the world, the research-based pharmaceutical industry cannot redress this fundamental socio-political issue. However, it has shown repeatedly in recent years that it recognises the problem and that it is prepared to collaborate when the political climate is favourable in initiatives to provide products for communities in need.

There are medical needs still to be satisfied. If finances were not limited, there would be reduced need for political intervention to decrease drug price via compulsory licensing; similarly, companies would have reduced budgetary concerns for drug development. Areas of greatest contention are those where the consequences of a higher drug price limits accessibility of patients to effective (and safe) drug treatment, although there are other factors apart from drug price which affect drug accessibility. Nevertheless, drug pricing is an area which can be targeted and possibly contained by health authorities and prescribers.

Examination of the areas where the WHO and industry interests or activities coincide not only supports the statement that the problem is lack of money but may provide further insight as to how the gap between the WHO and industry goals could be bridged. Real problem areas are those that engender public debate. Topics, which involve industry dispute alone without clear public health consequences, do not receive wide public media attention.

The topics, which are not greatly contentious, are limited in number (INN generic names, but not trademarks, and arguably, ATC) and their subject matter merits little comment. These areas may be disputed by companies, but not to the same degree as other areas; probably due to there being either only a weak relationship in the case of INN or a more subtle relationship for ATC classification with drug pricing or accessibility.

Issues requiring active WHO-industry interaction and which demand position statements (e.g. patents/TRIPS, marketing codes, generics, drug donations) are clearly political, usually with economic implications. But even these areas vary in their degree of contention. There is general agreement between WHO and the industry that counterfeiting is wrong and that poor quality medicines are to be avoided. Original branded products tend to be of good quality, provided they are not counterfeits. Poor quality becomes more of an issue when generics with inferior starting materials or inadequate quality checks to maintain cheaper prices are used. The difference lies between how the WHO and the industry would address the issues. A combination of the suggested approaches by each body may allow some forward steps towards attacking these problems.

The concept of drug safety is relative; there is no argument that the industry must develop well-tolerated medicines. WHO functions as an independent, global safety monitor of drugs and their corresponding therapeutic classes. From the public perspective this is a safeguard; from the industry standpoint there is a monitor whose negative appraisal and dissemination of information may affect drug marketability. Public and financial interests are most pronounced when drugs are withdrawn from markets due to safety reasons. With regards to the marketing of medicines, there is agreement that codes of conduct should be followed. A concern of WHO is the promotion of branded compounds in developing countries whose sales may impinge on the affordability of other drugs or even on other aspects of a patient's life. Again, the central problem is monetary.

The implementation of ICH has aided standardisation for drug development for the US, Europe and Japan (which affects only 15% of the global population and yet provides 90% of the multinational pharmaceutical company sales). The benefits of ICH to its member states are clear, with the possibility of speeding up approval of NCEs in

these regions. How ICH applies to non-ICH states has yet to be determined. Given the encroaching problems of tropical diseases and drug resistance, priority needs to be placed on resolving the impact of ICH on the preclinical and clinical development drug needs and their consequences between industrialised and developing countries.

Intellectual property, drug pricing and generics are all current focuses of debate. The discussions and policies of WHO and industry for these three topics all arise from (differing) financial considerations. Patents protect the invention and hence, the investment by and financial return to the company for a product. Patents also affect drug price since the company does not have to address the effects of generic competition until after the patent has exhausted its term, although there are other determinants of drug price during the patent term. As mentioned previously, drug pricing affects patient accessibility to drugs. The WHO's aim to maximise the number of patients having access to effective medicines via cheaper branded drugs or generics is contrary to the needs of industry which requires a return on investment by maximising branded drug patent life. Having acted as the innovator by ploughing large amounts of money into NCE development, however, industry does concede the place of generics once a sufficient period of market exclusivity occurred. As a result of TRIPS, countries may invoke their rights of compulsory licensing or parallel importation. This can be expected to affect the shape and size of drug markets and revenue.

When sufficient funds are lacking to pay for drugs, politics (via government or a charitable association) intrude to push down drug price with the intention of increasing accessibility of patients to marketed medicines. Without this intervention, drug supply to the needy withers. This ignores the philanthropic efforts made by companies. It is also counterbalanced by the fact that companies must provide payouts to share-holders; without adequate dividends, shares will be sold with a consequential decrease in share-price and possible knock-on effects on company size. Furthermore, insufficient funding handicaps the breadth or depth of the search for, and development of, NCEs leading to reduced ability to satisfy medical need.

7.1.4 Future Possibilities

Although it is beyond the scope of this article to suggest what degree of financial return a company should receive from product sales, dwelling on the areas of antagonism and current problems is fruitless. An alternative is to consider how to synergise the work of the industry with that of the WHO to attain some of its objectives. Rather than rationalise the costs of the traditional drug development route in westernised countries, followed by registration and sale in developing countries, a development for tropical diseases could be instituted firstly in developing countries followed by marketing in the industrialised world.

The first step in this process is the recognition of two socio-political factors operating in the drug development environment. The pandemic of HIV/AIDS, although a global problem, is now foremost a problem of the developing world. The recent South African court case has portrayed the industry in an unfavourable light, regardless of the rights of industry or government to defend their respective positions. The Global Fund just established to address the management of HIV/AIDS, although well-intentioned, can only scratch the surface of the all the issues requiring work in the many countries affected. Secondly, there is disillusionment with the concept of pharmaceutical company globalisation and the considerable power yielded by the pharmaceutical industry. This is demonstrated by the amount of criticism of the industry displayed by e-mail discussion groups and the medical and lay press. Interestingly, the lack of obvious philanthropic gestures from generic drug companies, which are still in business to make profit, does not receive press.

Certainly, for future drug development and marketing, industry will be obliged to address the underlying socio-political hostility which has been created in part because of the plight of developing countries. At the same time, climatic change is becoming a potent factor in creating a demand for

novel anti-infective agents, which will be needed by developed and developing countries alike.

With each new drug discovery, particularly of a new drug class, there is a risk that industry may relive the experience with the antiretroviral and anti-AIDS drugs. Industry has a choice of opting out of drug development in the field of antimicrobials, despite the great medical need. It also has a choice of reorienting its marketing strategies, as it has done with vaccines, in a way to retain both business and general respect.

A major obstacle to be overcome is the cost of drug development for diseases which are unlikely to provide a good financial revenue for the company. Most ethical pharmaceuticals have been developed in westernised countries and then adapted for local use via changes in patient leaflets etc. The calculation of costs of these ethical medicines is based on development in industrialised countries, which is probably more expensive than in developing countries. Twenty years ago, Buckles[151] proposed that developing ethical pharmaceuticals for specific 'Third World' use would be important, particularly if the adaptation of existing products was not feasible, if alteration of the local environment was uncertain and if there were no markets in the developed world for products required in the local region. Buckles also indicated that lack of experienced product development personnel, lack of service organisations and lack of experienced regulatory personnel in reviewing NDAs affected these possibilities.

A third option merits formal industry evaluation, namely, inclusion of drug development sites in drug development programmes. Whilst theoretically feasible, the ethics of conducting clinical trials as part of a global drug development programme in developing countries may be different from those in industrialised nations. The real question is whether independent regional programmes can be established. Given the WHO support in developing countries and the existence of ICH, it is time to table again these issues and assess if products to treat local or regional diseases could be in part or specifically developed in developing countries; these projects could be sponsored by the multi-national or local industry.

For local development, it is likely that preclinical research for NCEs would still be needed in industrialised countries; some form of public-private collaboration could be established to ensure exchange of necessary information. Clinical research comprises a significant part of the costs of drug development. Clinical trials conducted in developing countries for diseases or conditions of local significance may be a cost-effective way to encourage drug development. The ethics of conducting clinical trials in developing countries are not necessarily the same as those for trials in industrialised countries. However, apart from adequate funding and training, there is no reason that R&D programmes dedicated to developing country needs could not be initiated with the appropriate standards in selected medical centres. With a small number of well-chosen centres, the development of an NCE could be manageable in terms of training of site staff and funding. Funding may also be needed to consolidate related support (e.g. laboratory services). Regulatory mutual recognition or acceptance of acquired data between different African states would also help minimise regulatory costs. Such an approach may allow the initial drug price on first entry to market to be lower than if the development had been conducted in industrialised countries. Subsequent clinical evaluation may be needed for use of the NCE by Caucasian populations but this development route may, in part, aid in the problems of drug price restricting drug access to developing countries, since the costs of drug development should have been minimised. It will also bring new drugs faster to the regions where they are needed.

To maintain the fastest possible development time and to try to avoid a two-tier level of quality of drugs or drug development, the applicability of the ICH guidelines for use in the developing world should be evaluated. The ICH guidelines are available for consultation by any country. A specific working group to address adaptation of the guidelines for use outside the industrialised nations is another

area where industry could assist developing countries to optimise the drug development path. What must be borne in mind is that duplication in documents or guidelines should not be permitted to continue (e.g. WHO versus ICH guidelines for clinical trials) if costs and resources are to be optimised. Such repetition is, arguably, an unethical duplication of resource. Taking the adaptation of ICH a step further, with the current interest and ongoing evaluation of herbal medicines, there also may be an opportunity for an equivalent set of guidelines to be produced for herbal preparations.

Although, traditionally the domain of the industry, there may be benefits of getting charitable and consumer groups involved early in this decision-making process. Charitable groups have local experience of healthcare and conditions in developing countries. Their inclusion in the consultative process may aid in shortening drug development times and also placate some of their criticism. To succeed, local drug development would entail the need for solid public-private partnership and WHO could be forced again into taking a political role in coordinating the input and decision-making from government, NGOs including industry, and charitable and consumer groups. However, the potential benefits could justify this approach. A formal working party could be established to examine the feasibility, time-scale, costs and benefits of this suggestion.

7.2 Conclusions

The WHO-pharmaceutical industry interface is hampered by the opposing interests of each, and particularly the issue of money. With sufficient money for the industry and WHO to pursue their own projects, politics would intrude less on their activities. External criticism of WHO and the industry by consumer groups affects their image adversely, placing WHO in a more political role than originally intended. Industry, established for business and not charitable reasons, nevertheless does commit considerable resources for aid programmes. Coordination of these industry-sponsored programmes is desirable to minimise duplication.

Since drug price is continually debated as a factor limiting drug accessibility for patients in developing countries, there are choices; a suggestion would be to find locally applicable solutions for local diseases. Local or regional development of ethical medicines for local or regional diseases, would possibly be cheaper than in industrialised countries. A different approach would be to evaluate formally and upgrade the prominence of local plant medicines in the treatment of these diseases, which may even be useful for application worldwide.

However, one approach which is more in keeping with the current R&D industry status is for multinational companies, which have the scientific expertise and budgets, in collaboration with public or governmental organisations, to sponsor local or regional drug development in developing countries. Such a suggestion requires formal financial evaluation and not a scaled down estimate of drug development costs in industrialised countries.

Whatever path were to be taken, considerable training and advice from experts is needed. Public-private partnerships could ease the path of drug development in terms of information and cost sharing. The adaptation of the ICH guidelines could be a basis for education, as well as streamlining medicines development. Antagonism cannot be avoided when the issue of patents and drug price are tabled using the traditional route of drug development in industrialised countries. However, this may diminish if local drug development for local diseases provides drugs at a lower price. Rather than being held captive by current practices, a new approach to drug development in developing countries may herald some opportunities for synergy between WHO and the industry and bring mutual and global benefit.

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