

World health dilemmas: Orphan and rare diseases, orphan drugs and orphan patients

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Abstract

According to global annual estimates hunger/malnutrition is the major cause of death (36 of 62 million). Cardiovascular diseases and cancer (5.44 of 13.43 million) are the major causes of death in developed countries, while lower respiratory tract infections, human immunodeficiency virus infection/acquired immunodeficiency syndrome, diarrhoeal disease, malaria and tuberculosis (10.88 of 27.12 million) are the major causes of death in developing countries with more than 70% of deaths occurring in children. The majority of approximately 800 million people with other rare diseases, including 100000 children born with thalassaemia annually receive no treatment. There are major ethical dilemmas in dealing with global health issues such as poverty and the treatment of orphan and rare diseases. Of approximately 50000 drugs about 10% are orphan drugs, with annual sales of the latter approaching 100 billion USD. In comparison, the annual revenue in 2009 from the top 12 pharmaceutical companies in Western countries

was 445 billion USD and the top drug, atorvastatin, reached 100 billion USD. In the same year, the total government expenditure for health in the developing countries was 410 billion USD with only 6%-7% having been received as aid from developed countries. Drugs cost the National Health Service in the United Kingdom more than 20 billion USD or 10% of the annual health budget. Uncontrollable drug prices and marketing policies affect global health budgets, clinical practice, patient safety and survival. Fines of 5.3 billion USD were imposed on two pharmaceutical companies in the United States, the regulatory authority in France was replaced and clinicians were charged with bribery in order to overcome recent illegal practises affecting patient care. High expenditure for drug development is mainly related to marketing costs. However, only 2 million USD was spent developing the drug deferiprone (L1) for thalassaemia up to the stage of multicentre clinical trials. The criteria for drug development, price levels and use needs to be readdressed to improve drug safety and minimise costs. New global health policies based on cheaper drugs can help the treatment of many categories of orphan and rare diseases and millions of orphan patients in developing and developed countries.

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Key words: World health issues; Global diseases; Orphan drugs; Orphan diseases; Rare diseases; Orphan patients; Thalassaemia; Deferiprone; Deferasirox; Deferoxamine; Iron overload

Core tip: The major world health problems are related to poverty and other monetary health issues, including the supply of orphan drugs for the treatment of rare and orphan diseases. Differences in disease profile, disease burden and monetary health policies influence the mortality and morbidity rates of patients in developed and developing countries. The inexpensive developmental procedure of the iron chelating drug, deferiprone, used in thalassaemia is proposed as a paradigm for orphan and rare drug development. Improve-

ments in worldwide health policies including procedures for inexpensive drug development and alleviation of poverty could reduce the mortality and morbidity rates of patients worldwide.

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INTRODUCTION

The efforts of international organisations such as the World Health Organisation (WHO) and The United Nations Children's Fund, as well as many other national government organisations and non governmental organizations are continuously improving health standards worldwide and global health care is becoming a reality^[1]. However, at the same time there are many challenges, ethical dilemmas and major issues related to health policies and strategies that still need to be addressed and resolved globally, including the treatment of patients in developing countries and patients worldwide with rare diseases. Major limiting factors for addressing such problems are the ability to provide successful treatments and the availability of financial resources^[2,3].

Despite continuous medical progress in the treatment of diseases in the last few decades, the level of poverty and malnutrition, as well as the lack of health facilities and medicinal products are still considered the major factors leading to the high mortality and morbidity rates observed globally and mostly in developing countries^[3]. In the developed countries, the disease profile classification affecting the mortality and morbidity rate is comparatively different with obesity, ageing and environmental pollution being considered as some of the major causes of many illnesses^[4].

Monetary issues are very important in relation to the provision of health care and unless patients are self-sufficient financially, relevant decisions and priorities for selecting which disease, which drug and which patient to be treated are not yet fully clarified in each country or even in each hospital. Such dilemmas are more prevalent in developing countries, where financial resources are very limited. For example malnutrition and diarrhoea in infants and treatment of diseases such as malaria and human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) are priorities for long-term health strategies in the developing countries, whereas cancer, cardiac and neurological diseases are treatment priorities for most developed countries^[1,2].

Among the major obstacles affecting the level of global health care is the availability and cost of medicinal drugs. There are many economic, ethical and other issues affecting the supply of drugs for different groups of patients in each country^[5-7]. Within this context, regulatory procedure differences, preventative and diagnostic pro-

cedures, marketing influences and monetary factors can variably affect the treatment of patients in each country^[8-10]. Many such treatments usually involve the use of vaccines, generic and sometimes new patented drugs.

In many cases, the progress of the disease and the outcome of the treatment may be affected because of wrong evaluations and choices regarding the available therapeutic options. Similarly, the risk/benefit assessment for the use of specific drugs is not in many cases clearly defined and in some cases is not necessary. For example, the widespread use of antibiotics for the treatment of the common flu is inappropriate because the common flu is caused by a viral infection. Other related issues are the toxicity of drugs, where the risks outweigh the benefits and can sometimes cause severe damage or can even be fatal.

Incentives for the development of new drugs, especially for diseases where effective treatments are not currently available, are considered a major challenge for academic and pharmaceutical industry researchers. In general, the development of new drugs is market driven and has little to do with rare diseases in the developed countries or serious tropical diseases in the developing countries. However, monetary incentives have been introduced in recent years in the United States, Japan and European Union (EU) countries, for the development of "orphan drugs" for "orphan diseases", where a small number of patients in these countries are affected by a rare condition in comparison to the general population. The motive in most cases for orphan drug development is the lucrative profit from monopolies of patented drugs and not humanitarian concerns for the well-being of the small group of patients with rare or orphan diseases in developed countries or the lack of treatment for patients in the developing countries (orphan patients)^[11].

The expansion of the pharmaceutical industry in the developing countries and the local production of generic drugs are major advances in the treatment of local patients and the overall health levels in these countries^[7]. However, despite the encouraging progress and the production of medicinal drugs in developing countries, many patients especially those with chronic conditions cannot afford the cost of even the locally developed generic drugs or newly available technologies^[12].

A major obstacle in the introduction of new drugs for the treatment of any diseases is the anticipated high cost of drug development^[13]. A further obstacle in the supply of new drugs in the developing countries is the high cost due to the drug monopolies implemented by world trade laws. It appears that such laws mostly benefit multinational pharmaceutical companies which are based in the developed countries^[14].

Despite the fact that in many cases there are substantial improvements in the treatment of diseases due to the introduction of new patented drugs, there are also many other cases where the opposite result is observed. The latter may be caused by many factors including wrong decision making by those responsible for the approval and supply of the drugs due to misinformation regard-

ing drug safety and efficacy. Within this context there are many grey areas in the development and use of such new drugs, which in the long-term may worsen the treatment of affected patients and ultimately decrease the progress in the treatment of related diseases.

The design of new patented drugs, which is a major research task for pharmaceutical companies and academic institutions, usually involves many stages including the synthesis of many analogues, *in vitro* and *in vivo* screening studies and clinical trials. For example, in the case of the iron chelating drug, deferiprone (L1), which was invented and developed in academic institutions, more than one hundred analogues and other similar compounds have been designed and tested for possible application in the treatment of iron overload in thalassaemia and other diseases^[15-18].

Despite the fact that thousands of new compounds are designed, tested and patented for possible application as new pharmaceuticals, only a very small number of these compounds reach the stage of investigational new drug (IND) or new medical entity and selected for further development.

Excessive costs for toxicological, carcinogenicity and other screening, clinical trials and post-marketing surveillance, as well as other costs such as patent fees make it impossible for individuals or academic institutions to proceed to the full development of a new drug. It is estimated that the cost for the introduction of a new drug from the stage of design to post-marketing monitoring is about 0.5 billion USD^[19]. However, most of this expenditure is not related to the scientific evaluation and development of the drug, but due to its marketing. This procedure adds substantially to the price of a drug and to the overall public health spending, while at the same time it reduces the prospect of drug availability in developing countries^[20]. In contrast, the development of academically based orphan drugs such as L1 can cost less than 5% of the above amount.

Present practices suggest that irrespective of how effective and safe new INDs might be, these are not likely to be developed, unless they are under patent monopoly and can potentially make huge profits following their registration and marketing. This issue is indicative of the current role of multinational pharmaceutical companies in societies, where profit is the major target for drug development and not the treatment of diseases. Pharmaceutical companies involved in the production of generic drugs are also trying to maximise profits. In the latter case, the profit levels are lower due to competition with other companies because of the absence of monopolies.

A paradigm which could affect future strategies in drug design, development and use are the iron chelating drugs. These drugs are primarily used for the iron removal treatment in thalassaemia and other transfusional iron loaded diseases such as myelodysplasia and sickle cell disease. In chemical terms, chelation can be considered a chemical reaction involving the formation of bonds between a metal ion and a chelator (Greek: $\chi\eta\lambda\eta$ -claw of a crab) resulting in a metal-chelator complex. A chelator

can be a natural or synthetic chemical compound, or in this case a drug molecule capable of forming a heterocyclic ring with a metal ion as the closing member *i.e.*, like a crab holding the metal ion in its claw. In transfusional iron loading conditions the aim of the administration of iron chelating drugs is the binding and removal of excess toxic iron from the body^[15-17].

HEALTH ISSUES AFFECTING GLOBAL MORBIDITY AND MORTALITY

Global health is related to a dynamic state of interactions, involving many factors and many players such as the WHO, local and governmental health authorities. Some of these factors include the availability of financial resources, the severity, transmission and extent of infectious, communicable and other diseases and the differences between ages and gender. In an ever expanding world population, major issues such as health provision and resource allocation have a major impact on human survival, morbidity, mortality and quality of life. Within this context, human activities such as monetary policies, wars, accidents and injuries, food production and distribution, health education, provision of medicines and health care as well as environmental pollution, infectious, chronic and genetic diseases, all interact and influence health outcomes in each country and worldwide^[21].

Health models and schemes have been designed where diseases and patients have been included in different categories. At the same time, different strategies have been developed for addressing local and international health problems with one of the major limiting factors being the availability of financial resources. In all cases, financial resources for health care are limited and many classifications have been designed for outlining the importance, impact, morbidity, and mortality of each disease on a national and international scale (Table 1)^[22-28].

In an attempt to prioritise the impact and severity of different diseases, including effects on the survival rate and quality of life of patients, several parameters have been introduced such as quality-adjusted life years (QALY), disability-adjusted life year (DALY) and years lived with disability (YLDs) which are mostly used in the developed countries for comparison among diseases and individual patient cases. QALY is a term referring to a calculated score for the comparison of different health-care interventions which takes into account an average life expectancy and the quality of life or both. For example one year of perfect health is equal to 1 QALY, death is 0 QALY and a year of less than perfect health is scored between 0 and 1. A parameter related to health resource allocation is the cost/QALY, which is different for each intervention.

A DALY is another term used for measuring the amount of health lost due to a disease or injury. It is calculated as the present value of the future years of disability-free life that are lost as a result of premature death or disability occurring in a particular year. YLDs is another

Table 1 Main causes of death in developed and developing countries excluding malnutrition

People in developed countries (2002)	Millions	People in Developing countries (2002)	Millions	Globally (2011)	Millions
Heart attack	3.08	LRTI	2.81	Heart attack	7.00
Stroke	1.78	HIV/AIDS	2.55	Stroke	6.20
LTB cancer	0.61	Heart attacks	2.53	LRTI	3.20
LRTI	0.45	Infections at birth	1.78	COPD	3.00
COPD	0.42	Diarrhoeal disease	1.53	Diarrhoeal disease	1.90
Colon, rectal cancer	0.35	Stroke	1.45	HIV/AIDS	1.60
Diabetes	0.24	Malaria	1.25	Diabetes	1.50
Self inflicted injuries	0.23	Tuberculosis	0.96	LTB	1.40
Hypertensive heart disease	0.23	COPD	0.76	Cancer	1.30
All causes	13.43	All causes	27.12	Road injuries	1.30
Estimates 2006 ¹		Malnutrition	36.00	All causes	62.00

¹The total number of deaths globally in 2006 was estimated to be about 62 million, of which 32 million were related to hunger and malnutrition. COPD: Chronic obstructive pulmonary disease; LRTI: Lower respiratory tract infections; LTB cancer: Lung, tracheal and bronchial cancer. Adapted from ref^[22-28].

term also used for health resource allocation of different interventions.

The main cause for the highest rate of mortality globally is hunger and malnutrition, which is found almost exclusively in the developing countries. It is estimated that one in twelve people worldwide is malnourished and that 58% of the total number of deaths is related to hunger or diseases due to deficiencies in micronutrients (Table 1). Despite the fact that world food production is adequate for feeding the entire human population, several causes such as insufficient food production, supply and distribution in the developing countries, as well as excess food use and waste in developed countries are the main reasons for the observed rate of malnutrition and human mortality today. In contrast, the high incidence of obesity, physical inactivity and smoking are some of the main causes for the high mortality and morbidity rates observed in relation to the most common diseases in the developed countries such as cardiovascular diseases, cancer and diabetes (Table 1)^[22-28].

The cost/QALY for feeding the malnourished population in the developing countries is considered the lowest cost intervention globally. However, the adopted global food and health policies for solving this problem are insufficient and controversial. Similar controversial and ethical issues apply in the spectrum of diseases as well as related strategic policies aimed at increasing the survival and quality of life of people in developed and developing countries.

In relation to morbidity, the global outlook of diseases has general characteristics and individual variations between developed and developing countries. It is esti-

mated that 13% of the global burden of disease is related to global mental health, surpassing both cardiovascular disease and cancer^[29]. Depression, Alzheimer's disease and other dementias, epilepsy, schizophrenia, migraine, insomnia, multiple sclerosis, Parkinson's disease, alcohol dependence and other mental, neurological and substance-abuse disorders are included in this category of diseases^[29]. Examples of the impact of diseases related to mental health is the annual rate of mortality from suicide which is estimated as 900000 people worldwide (200000 in China, 170000 in India, 140000 in high income countries) and the cost of dementia treatment, which for the United States alone has been estimated at 609 billion USD in 2009^[29-31].

With the improvement of health practices and treatments there has been an overall increase in life span worldwide and a related increase in prognosis. Corresponding increases in expenditure have also been observed for many diseases in the developed countries, especially chronic diseases such as cardiovascular and neurological diseases, diabetes and cancer. The global burden of cancer for example, in 2002 was estimated at 10.9 million new cases, with 24.6 million persons alive with cancer (within 5 years of diagnosis) and 6.7 million deaths (61% in developing and 39% in developed countries). The incidence of cancer in men is as follows: lung followed by prostate, stomach, colorectal and liver cancer, and in women is breast followed by cervix uteri, colorectal, lung and stomach cancer. It has been suggested that the major causes of cancer in the United States are smoking (29%-31%), diet (20%-50%), infection (10%-20%), reproductive hormones (10%-20%), alcohol (4%-6%) and occupation (2%-4%)^[32]. Cardiovascular disease was estimated to cause more than 17 million deaths worldwide in 2007 and this is projected to increase to 26 million in 2020, with 19 million in the developing and 7 million in the developed countries^[25,26]. The major causes of cardiovascular disease are related to physical inactivity, tobacco use, high blood pressure, obesity, unhealthy diet, diabetes mellitus and alcohol use^[33].

The estimated global burden of diabetes mellitus was 366 million people in 2012 with a projected increase to 552 million in 2030. Patients with prediabetes are estimated to reach 470 million by 2030 with a parallel increase in associated complications such as nephropathy, neuropathies and vascular complications^[34].

In relation to transmitted diseases, a prominent position globally is HIV/AIDS with an estimated prevalence in 2007 of 33.2 million people living with HIV, including about 5% of adults in sub-Saharan Africa and with an annual incidence of 2.5 million new cases and mortality of 2.1 million. Mortality due to HIV/AIDS has been reported to have decreased in 2011 due to prophylactic measures and new, more effective treatments (Table 1)^[35,36].

Infectious diseases are one of the top groups of diseases with the highest morbidity and mortality rate affecting mainly patients in developing countries (Table 1). Neonatal and infant children are more susceptible to

Table 2 The largest health care companies in the world based on annual revenues

Rank	Company	Country	Total annual revenue (USD billions)
1	Johnson and Johnson	United States	61.90
2	Pfizer	United States	50.01
3	Roche	Switzerland	47.35
4	GlaxoSmithKline	United Kingdom	45.83
5	Novartis	Switzerland	44.27
6	Sanofi	France	41.99
7	Astra Zeneca	United Kingdom/Sweden	32.81
8	Abbott Laboratories	United States	30.76
9	Merck and Co.	United States	27.43
10	Bayer HealthCare	Germany	22.30
11	Eli Lilly	United States	21.84
12	Bristol-Myers Squibb	United States	18.81

The companies were ranked by revenue as of March 2010 according to their released 2009 annual reports.

such diseases, especially in poor areas with poor sanitary conditions and lack of clean water. More than 70% of deaths in this category are related to neonatal causes, pneumonia, diarrhea and malaria^[28].

Many factors influence the morbidity and mortality rate for each disease with variations in different areas of the world. The major risk factors include malnutrition, sanitation, unsafe sex, tobacco, alcohol and illicit drugs, physical inactivity, obesity, hypertension and environmental pollution^[37-39]. The global burden of diseases is in a dynamic state of continuous change, which can be monitored and hopefully will allow predictions and future strategies to be developed including the introduction of preventative measures and prognosis^[22-39]. Such strategies can only be implemented if the necessary financial resources become available. Public spending on health, including the cost of drugs and services is under continuous evaluation and any adjustments may help to decrease current morbidity and mortality rates in many countries and also globally.

THE CONCEPTS OF ORPHAN DRUGS AND ORPHAN DISEASES

The attempts for global health coverage continue progressively and new national and international strategies for achieving this goal are steadily increasing with major successes^[1-3,40,41]. The development of new drugs is part of this strategy and involves pharmaceutical companies mainly in Western countries where investment is available and revenues from sales could be colossal (Table 2).

A major challenge for global health coverage is also the development of treatment strategies for orphan and rare diseases and the development of orphan drugs. The term “orphan drugs” was introduced by governments of developed countries to help in the production and marketing of medicinal drugs by the pharmaceutical industry for patients suffering from rare conditions living in their own countries. This concept was based on monetary

incentives and regulatory relaxations for attracting pharmaceutical companies to orphan drug production since it was assumed that the cost of developing and bringing to the market such a medicinal product cannot be recovered by the expected sales. On ethical grounds this concept is intended to help patients suffering from rare conditions to be entitled to the same quality of treatment as other patients with diseases affecting large numbers of the population.

Orphan drug legislation varies among the developed countries and was introduced at different times, first in the United States in 1983, Singapore in 1991, Japan in 1993, Australia in 1997 and in the EU in 2000. In the EU, an orphan medicinal product is intended for the diagnosis, prevention and treatment of an orphan disease with a prevalence of less than 5 affected per 10000 persons. The term orphan drug can also apply to a seriously debilitating condition even if its prevalence is more than 5 per 10000 persons. In the United States an orphan drug is intended for any rare disease with an incidence of less than 200000 persons. It is estimated that there are about 7000 orphan diseases ranging from genetic diseases such as thalassaemia to rare infections in the West such as malaria, tuberculosis and blinding trachoma. In addition, subsets of commoner diseases such as Crohn's disease of the oesophagus are also classified as orphan.

It is estimated that about 350 orphan drugs for 200 orphan diseases have been developed since 1983. Before the United States act of 1983 fewer than 40 products were developed, whereas between 1983 and 2009, the food and drug administration (FDA) approved 275 orphan drugs for 337 orphan indications and during the 2000s it was estimated that orphan products comprised 22% of all new molecular pharmaceutical entities^[42]. Among the incentives for pharmaceutical companies in the United States, are market exclusivity for 7 years, grants of up to 30 million USD per annum, waiving of user fees (approximately 1.2 million USD for every application) paid to the FDA for review of the sponsor's application, tax incentives and easier to gain marketing approval. Similar conditions and relaxations are included in the EU legislation, but market exclusivity is for 10 years. It is estimated that global orphan drug sales have increased about 10% per year between 2005 and 2011, and are now approaching 100 billion USD annually^[13].

Research in orphan diseases was until recently carried out mainly by academic institutions, biotech companies and smaller, specialty drug companies. Large pharmaceutical corporations have also lately taken interest, mainly for exploiting the orphan drug legislations by targeting sub-groups of common diseases^[42].

Examples of a list of orphan-designated drug products with at least one marketing approval in the United States for a rare disease indication are shown in Table 3^[43-45]. The drugs approved are mostly related to various cancers and other conditions with low prevalence in the developed countries. Marketing approval in the United States was also provided for orphan-designated drug products for both common and rare disease indications

Table 3 Examples of orphan-designated drug products with at least one marketing approval in the United States for a rare disease indication

Drug product name	Orphan indications
Alglucerase injection	Replacement therapy in Gaucher's disease
Alitretinoin	Acute promyelocytic leukemia
Alpha1-Proteinase Inhibitor	Cystic fibrosis
Ambrisentan	Idiopathic pulmonary fibrosis
4-Aminosalicylic acid	Crohn's disease
Amifostine	Chemoprotective agent in cancer
Anagrelide	Polycythemia vera
Anti-tac (human)	Prevention of acute graft- <i>vs</i> -host disease
Arsenic trioxide	Multiple myeloma, MDS, CML, CLL
Atovaquone	<i>Toxoplasma gondii</i> encephalitis
Azacitidine	Acute myeloid leukemia
Beractant	Newborn infants with pneumonia
Bosentan	Idiopathic pulmonary fibrosis
Busulfan	Primary brain malignancies
Calfactant	Acute respiratory distress syndrome
Canakinumab	Juvenile idiopathic arthritis
Capsaicin	Erythromelalgia
Cladribine	Non-Hodgkin's lymphoma, CLL, AML
Clofarabine	Acute myelogenous leukemia
Coagulation factor VIIa	Bleeding in Glanzmann thrombasthenia
Cysteamine hydrochloride	Huntington's disease
Cytarabine	Gliomas
Daunorubicin liposomal	Acute myeloid leukemia
Decitabine	Sickle cell anemia, CML, AML
Eculizumab	Dermatomyositis
Epoprostenol	Replacement of heparin in hemodialysis patients
Filgrastim	Myelodysplastic syndrome and AIDS
Fludarabine phosphate	Non-Hodgkins lymphoma
Heme arginate	Myelodysplastic syndromes
Idarubicin	AML in pediatrics, MDS and CML
Ifosfamide	Bone and soft tissue sarcomas
Iloprost solution for infusion	Heparin-associated thrombocytopenia
Indium ¹¹¹ pentetreotide	Neuroendocrine tumors
Interferon gamma-1b	Idiopathic pulmonary fibrosis
Lenalidomide	Mantle cell lymphoma and CLL
Levocarnitine	Pediatric cardiomyopathy
Mecasermin	Amyotrophic lateral sclerosis
Mecasermin rinfabate	Burns that require hospitalization
Melphalan	Cutaneous melanoma
Mesna	Inhibition of the urotoxic effects
Miglustat	Neurological manifestations
Mitomycin-C	Refractory glaucoma
Mycophenolate mofetil	Pemphigus vulgaris
Nilotinib	Gastrointestinal stromal tumors
Nitazoxanide	Intestinal amebiasis
Nitisinone	Alkaptonuria
Nitric oxide	Acute respiratory distress syndrome
Pentostatin	Cutaneous T-cell lymphoma and CLL
Porfimer sodium	Cholangiocarcinoma
Pralatrexate	Diffuse large B-cell lymphoma
Primaquine phosphate	<i>Pneumocystis carinii</i> pneumonia
Protein C concentrate	Replacement therapy in protein C deficiency
Procarbazine hydrochloride	Malignant glioma
Quinine sulfate	Non <i>Plasmodium falciparum</i> malaria
Rapamycin (mTOR) inhibitor	Tuberous sclerosis complex
Rifabutin	<i>Mycobacterium avium</i> disease
Riluzole	Huntington's disease
Sermorelin acetate	Induction of ovulation in women
Sodium phenylbutyrate	Sickling disorders
Sodium thiosulfate	Platinum-induced ototoxicity
Somatropin	Induction of ovulation in women with infertility
Succimer	Mercury toxicity and kidney stones

Synthetic human secretin	Diagnostic procedures in pancreatic carcinoma
Synthetic porcine secretin	Diagnostic procedures in pancreatic carcinoma
Temozolomide	Advanced metastatic melanoma.
Tetrabenazine	Moderate/severe tardive dyskinesia
Thalidomide	Graft <i>vs</i> host disease in BMT
Topotecan HCl liposomal	Gliomas
Tretinoin	Acute and chronic leukemia
Trimetrexate	Metastatic carcinomas
Vorinostat	Multiple myeloma and mesothelioma

ALL: Acute lymphoblastic leukaemia; AML: Acute myeloid leukaemia; CML: Chronic myeloid leukemia; CLL: Chronic lymphocytic leukaemia; MDS: Myelodysplastic syndrome; BMT: Bone marrow transplantation. Adapted from references^[43-45].

as shown in the examples in Table 4^[43-45]. In this group of orphan-designated drug products, new formulations and new indications of commonly used drugs (*e.g.*, doxorubicin, bleomycin and cyclosporine) have been included (Table 4)^[43-45]. A list of drugs approved for rare diseases in the EU is also shown in Table 5^[46]. The list includes many drugs intended in most cases for the treatment of various cancers, infectious diseases and other conditions with low prevalence in the EU (Table 5)^[46]. It is estimated that there are about 2000 orphan diseases in the EU and 6500 in the United States^[46,47].

The orphan diseases with the highest number of drug designations and most orphan drug approvals are shown in Table 6^[48,49]. With the exception of malaria, which is a very rare condition in developed countries, but a major problem in developing countries, all other 13 diseases are rare diseases found in developed countries (Table 6)^[48,49]. It is estimated that 11 tropical diseases related to helminth, protozoan and bacterial infections affect about 800 million people in developing countries, excluding malaria, communicable, environmental and genetic diseases (Table 7). Overall, the neglected tropical and other diseases found almost exclusively in developing countries are extremely rare in developed countries and are not a priority for orphan drug development in developed countries (Table 7). It is evident that the orphan drug and orphan disease concepts are mostly based on monetary considerations and not an effort for the treatment or elimination of rare and neglected diseases with high incidence in the developing countries. Patients suffering with neglected tropical and other rare diseases in developing countries can be considered as orphan patients. Similarly, as budgetary limitations on health are expanding in the developed countries the concept of orphan patients is also adopted for patients with rare and other diseases in the developed countries.

DILEMMAS IN MEDICAL ETHICS AND ORPHAN PATIENTS

Present Western philosophies and medical ethics are based upon monetary concerns, which affect local and global health levels. For example, enough food is pro-

Table 4 Examples of orphan-designated drug products with marketing approvals in the United States for both common and rare disease indication

Drug product name	Orphan indications
Adalimumab	Paediatric Crohn's disease
Aldesleukin	Primary immunodeficiency disease
Allopurinol	<i>Ex vivo</i> preservation of kidneys for transplants
Aminosidine	Tuberculosis and <i>Mycobacterium avium</i>
Azathioprine	Graft- <i>vs</i> -host disease
Aztreonam	Improvement of symptoms in bronchiectasis
Bevacizumab	Ovarian, stomach and pancreatic cancer
Bleomycin sulphate	Pancreatic cancer
Cetuximab	Pancreatic cancer
Cisplatin liposomal	Osteogenic sarcoma metastatic to the lung
Colchicine	Behcet's Syndrome
L-Cycloserine	Gaucher's disease
Cyclosporine	Prophylaxis and treatment of GVH disease
Cyclosporine A implant	Prevention of rejection in cornea transplant
Cyclosporine liposomal	Bronchiolitis obliterans
Doxorubicin	Hepatocellular carcinoma
Doxorubicin HCl liposomal	Soft tissue sarcomas
Doxorubicin nanoparticles	Hepatocellular carcinoma
Eflornithine HCl	<i>Pneumocystis carinii</i> pneumonia in AIDS
Epoetin alpha	Myelodysplastic syndrome
Erlotinib HCl	Malignant gliomas
Etidronate disodium	Degenerative metabolic bone disease
Everolimus	Gastroenteropancreatic tumors
Histrelin	Acute intermittent and other porphyrias
Immunoglobulin	Juvenile rheumatoid arthritis
Infliximab	Chronic sarcoidosis
Interferon alfa-2a	Esophageal carcinoma
Peginterferon alfa-2a	Chronic myelogenous leukemia
Interferon alfa-2b	Ovarian carcinoma, brain tumors
Peginterferon alfa-2b	Chronic delta hepatitis
Metronidazole (topical)	Perioral dermatitis
Metronidazole	Pouchitis
N-acetylcysteine	Acute liver failure
Paclitaxel	Pancreatic cancer
Paclitaxel aqueous gel	Esophageal and brain cancer
Paclitaxel micellar	Ovarian cancer
Paclitaxel protein-bound	Stage II B to IV melanoma
Sorafenib	Stage II B through stage IV melanoma
Ribavirin	Haemorrhagic fever with renal syndrome
Rituximab	Immune thrombocytopenic purpura
Thiotepa	Haematopoietic stem cell transplantation
Tranexamic acid	Hereditary angioneurotic edema
Urofollitropin	Initiation and re-initiation of spermatogenesis
Ursodiol	Cystic fibrosis liver disease

GVH: Graft versus host. Adapted from ref^[43-45].

duced to feed the whole world population, but large quantities are wasted or destroyed based on existing market policies. This allows millions of people to die from hunger and malnutrition. Similarly, market policies are also partly responsible for the limited success in the effort to prevent or eliminate many diseases and for the lack of basic medicines in developing countries. In general, access to drugs and treatments and health levels for each individual and each country depends on their ability to pay. This happens even in developed countries for example in deciding by clinical boards who can receive a kidney, heart, liver and other transplants or hip replacement or cardiac surgery. Similar dilemmas exist in deciding who can be treated with haemodialysis machines or by new, but very

expensive drugs for the treatment of cancer and other serious conditions. Within this context the vast majority of orphan patients are in the developing countries, but there are also many orphan patients in developed countries, where treatments may be available, but patients have no access to them due to limited availability and health resources^[22-27].

There are many conflicting interests, ethical and other issues affecting the healthcare of each individual at local and global levels. Healthcare strategies and policies are developed based upon different approaches, influences and philosophies. The ultimate decisions affecting healthcare resource allocation rely on government policies and legislations, which are influenced by political groups, commercial interests, patient groups, and other society groups in general^[2].

Government policy in most countries relies on political dogmas between the capitalist approach suggesting that healthcare is another way of spending money and if people cannot afford it that is their bad luck, whereas in the socialist approach it is suggested that the distribution of healthcare is a matter of social justice and all individuals should be treated as equals. Many developed countries are using the utilitarian approach on healthcare resource allocation, which is for the greatest good for the greatest number of people and is measured by QALY. However, there are many dilemmas in resource allocation on healthcare related to QALY measurements, where terms such as good and quality of life have not been fully defined. For example there are age related issues, where treating younger patients will save more years of life, or social worth issues where contribution to the society may be considered as a morally relevant factor, or personal responsibility where individuals such as smokers and obese people are personally responsible for their ill health.

Health economics are increasingly becoming a major part of healthcare and medical education with a major emphasis on better allocation of resources by minimising costs and maximising healthcare output in the primary state control and run sector. This sector is the main healthcare provider in most countries and allocates the funds from taxes. Cost benefit, effectiveness and utility analysis are a major part of healthcare strategies since it is becoming increasingly clear that there are not enough professionals and not enough money to provide a comprehensive state controlled healthcare service in many countries. For example it was estimated in 2010 that medicines alone cost the National Health Service in the United Kingdom more than £13 billion per annum, which accounts for around 10% of the overall health budget^[50].

In many developed countries expert independent committees have been instituted to tackle healthcare problems and design healthcare strategies. An example is the United Kingdom national institute for health and clinical excellence (NICE), which uses QALYs to determine which treatments are most suitable for each disease. Accordingly, clinicians use the advice of NICE to decide which treatments to prescribe their patients^[50,51]. However, despite the fact that such efforts are necessary the

Table 5 List of drugs approved for rare diseases in Europe

Rare disease category	Drug product name (Indication)
Leukaemias, lymphomas and related diseases	Histamine dihydrochloride and Decitabine (AML)
	Ofatumumab (CLL)
	Nilotinib (CML)
	Mercaptopurine and Clofarabine (ALL)
	Cladribine (Hairy cell leukaemia)
	Ponatinib (Philadelphia chromosome positive ALL and CML)
	Dasatinib (CML and AML)
	Azacitidine (Myelodysplastic syndromes, CML, AML)
	Bosutinib (Philadelphia chromosome positive CML)
	Nelarabine (T-cell ALL and lymphoma)
Carcinomas and related diseases	Brentuximab vedotin (Hodgkin lymphoma and anaplastic large cell lymphoma)
	Ruxolitinib (Primary and other myelofibrosis cases)
	Plerixafor (Lymphoma and multiple myeloma)
	Sorafenib tosylate (Hepatocellular carcinoma, renal cell carcinoma)
	Mitotane (Adrenal cortical carcinoma)
	Mifamurtide (Osteosarcoma)
	Temsirolimus (Renal cell carcinoma and mantle cell lymphoma)
	Trabectedin (Soft tissue sarcoma, liposarcoma, ovarian cancer)
	5-Aminolevulinic acid hydrochloride (Malignant glioma)
	Thalidomide and Lenalidomide (Multiple myeloma)
Chelating drugs and haemoglobinopathy related diseases	Deferoxamine, Deferiprone and Deferasirox (Iron overload in beta thalassaemia)
	Dexrazoxane (Anthracycline extravasation)
	Hydroxycarbamide (Sickle Cell Syndrome)
	Zinc acetate dehydrate (Wilson's disease)
Pulmonary hypertension	Eculizumab (Proxymal nocturnal haemoglobinuria and haemolytic uraemia)
	Bosentan monohydrate (Pulmonary arterial and systemic sclerosis)
	Iloprost (Primary pulmonary hypertension)
	Ambrisentan and Sildenafil citrate (Pulmonary arterial hypertension)
Cystic fibrosis	Mannitol, Aztreonam and Ivacaftor (Cystic fibrosis)
	Tobramycin (<i>Pseudomonas aeruginosa</i> in Cystic Fibrosis)
Enzymes used as drugs	Velaglucerase alpha (Type 1 Gaucher disease)
	Alpha-glucosidase (Pompe disease)
	Galsulfase (Mucopolysaccharidosis VI)
	Idursulfase (Hunter syndrome)
Drugs used in other rare conditions	Proteolytic enzymes enriched in bromelain (Burns)
	Carglumic acid (Hyperammonaemia due to n-acetylglutamate synthase deficiency)
	Betaine anhydrous (Homocystinuria)
	Stiripentol (Severe myoclonic epilepsy in infancy)
	Pirfenidone (Idiopathic Pulmonary Fibrosis)
	Icatibant acetate (Hereditary angioedema)
	Amifampridine (Lambert-Eaton myasthenic syndrome)
	Alipogene tiparvovec (Familial lipoprotein lipase deficiency)
	Mecasermin (Growth failure in primary insulin-like growth factor 1 deficiency)
	Rufinamide (Lennox Gastaut syndrome)
	Sapropterin dihydrochloride (Phenylketonuria and tetrahydropterin deficiency)
	Romiplostim (Immune thrombocytopenic purpura)
	Nitisinone (Hereditary tyrosinemia type 1)
	Ibuprofen (Patent ductus arteriosus)
	Caffeine citrate (Primary apnea)
	Hydrocortisone (Adrenal insufficiency)
	Zicotide (Chronic pain)
	Teduglutide (Short Bowel Syndrome)
	Pasireotide (Cushing's disease)

Thiotepa (Haematopoietic progenitor cell transplantation)
Everolimus (Tuberous sclerosis complex)
Tafamidis (Transthyretin amyloidosis)
Anargelide hydrochloride (Essential thrombocythaemia)
Miglustat (Type 1 Gaucher disease and Niemann-Pick type C disease)

ALL: Acute lymphoblastic leukaemia; AML: Acute myeloid leukaemia; CML: Chronic myeloid leukemia; CLL: Chronic lymphocytic leukaemia. Adapted from ref^[46].

task is colossal considering that there are so many medicinal products available including 50000 drugs. These efforts are also limited by many conflicting interests such as conflicting literature, rivalry between pharmaceutical companies, rivalry between academics, differences between regulatory authorities, different priorities by health authorities, different patient group interests and society concerns^[5,7,9,52]. The decisions by NICE are based on several factors including the guidance from ministers on the resources available, the clinical needs of patients in relation to other available technologies, the National Health System's priorities, the broad balance between benefits and costs and the potential impact on other National Health System's resources.

The ultimate decision to choose which treatments can be prescribed for the patients is made by the clinician or group of clinicians in charge. Despite the fact that treatment decisions by clinicians are expected to be guided by the Hippocratic oath, which broadly suggests that the treatment regimen to be followed should be according to the doctor's ability and judgment for the benefit of patients, many other factors and influences are involved. For example, the United Kingdom General Medical Council states that doctors should provide effective treatments based on the best available evidence, but also making efficient use of the resources available. On the other hand, thousands of pharmaceutical company representatives are continuously lobbying clinicians and other related groups to influence their decision in choosing appropriate treatments in favour of their products (Figure 1)^[5,20].

One of the most important factors influencing healthcare economics and resource allocation is the cost of drugs. Patient requirements for drugs, the role and effects of pharmaceutical companies on drug pricing, efficacy and safety are in most cases being evaluated by expert committees. Within this context, pharmacoeconomics is a new expanding scientific area, influencing decision making of major healthcare resource allocation organisations such as NICE, the National Institute for Health in the United States and similar national organisations in many other countries worldwide.

DRUG DEVELOPMENT AND LARGE PHARMACEUTICAL COMPANIES

The lucrative market of pharmaceuticals and the patent monopolies of new drugs is a major contributory factor

Table 6 Orphan diseases with the most orphan drug approvals

Disease	Drug designation	Drugs approved
AIDS	57	8
Acute myeloid leukaemia	34	5
Ovarian cancer	34	4
Multiple myeloma	32	6
Glioma	29	4
Chronic myelogenous leukaemia	19	4
Acute lymphoblastic leukaemia	17	6
<i>Pneumocystis carinii</i> pneumonia	15	5
Respiratory distress syndrome, infant	14	6
Multiple sclerosis	14	5
Growth hormone deficiency	13	9
Idiopathic pulmonary hypertension	12	4
Kaposi's sarcoma	11	5
Malaria	11	4

Adapted from ref^[48,49]. AIDS: Acquired immunodeficiency syndrome.

to the national economy and income of the most affluent developed countries. The revenue of the twelve top multinational pharmaceutical companies exceeded 445 billion USD in 2009 (Table 2). It should be noted that in the same year the total government expenditure for health in the developing countries was 410 billion USD^[2]. Only, 6-7% of this expenditure was received as foreign aid from developed countries. For example, the global health fund of the United States over 6 years (2009-2014) was 63 billion USD^[21]. The biggest selling drug of all time is the statin, Lipitor (atorvastatin), from the United States pharmaceutical company Pfizer with lifetime sales of 100 billion USD, until patent expiration in 2011^[53].

Six of the twelve top pharmaceutical companies including the top two are based in the United States, two in Switzerland, two in the United Kingdom (one jointly with Sweden) and one each in France and Germany (Table 2). Rarely such companies are involved in the development of orphan drugs, unless they are familiar with the market potential and the income is similar to the non-orphan drugs. An example of an orphan drug is deferasirox (DFRA), which is marketed by one of the top twelve companies (Novartis) and used in the treatment of iron overload in thalassaemia and intended for many other iron loaded conditions^[54].

Despite the fact that the standard regulatory authority procedures and laboratory tests needed for drug approval may differ slightly between organisations such as the United States FDA and EU European medicines agency (EMA), the major aspects of screening are based on similar preclinical and clinical testing. In general these procedures involve preclinical testing and usually four distinct clinical phases carried out over many years.

Drug design and development is usually undertaken by pharmaceutical companies in developed countries, due to suspected high expenditure requirements. The drug discovery period can take on average about 10 years and in general involves the design and screening of a large number of known chemical compounds of different classes from chemical libraries. Computer aided technol-

Table 7 Examples of neglected tropical and other diseases in developing countries

Disease categories	Diseases
Genetic diseases	Thalassaemias, sickle cell disease
Helminth infections	Ascariasis, hookworm, trichuriasis, schistosomiasis, lymphatic, filariasis, onchocerciasis, dracunculiasis
Protozoan infections	Human african trypanosomiasis chagas disease, leishmaniasis
Bacterial infections	Buruli ulcer, leprosy, trachoma
Environmental poisoning	Arsenate toxicity, bantou siderosis, mining industry, nuclear industry
Communicable and other diseases	HIV/AIDS, tuberculosis, malaria

HIV/AIDS: Human immunodeficiency virus infection/acquired immunodeficiency syndrome.

ogy is a new method of drug design and development. Such methods involve, among others, the mimicking of existing drugs and introduction of structural modifications which may lead to higher efficacy and lower toxicity. However, such approaches are limited due to the complexity of the biological and physiological systems, which cannot be theoretically fully evaluated. Following the identification of leading groups of compounds, new chemical compounds are synthesised and screened to select the most promising ones for further evaluation and development. The screening process for the identification of a new product is tedious and success is limited. For example in the pharmaceutical company Hoechst during the period between 1972 to 1985, out of the 120000 new compounds synthesised and tested, it has been possible to launch only 15 new products.

Structure/activity correlation and preclinical safety testing can take 2-6 years and clinical safety and efficacy studies can take 6-10 years. In the case of orphan drugs, the preclinical and clinical testing period is shorter and involves fewer procedures. The testing requirements and regulatory approval for orphan drugs appear to be different between the United States, EU and other countries. For example, the iron chelating drug L1 was first approved in India in 1994, in the EU and other countries in 1999 and the United States in 2011^[55].

The preclinical testing of new drugs involves *in vitro* and *in vivo* experiments. Chemical, biochemical and cell studies, including mutagenicity studies, are carried out during the *in vitro* testing. In the *in vivo* testing, animal studies in at least three different mammalian species using different doses are assessed to evaluate preliminary information on efficacy, absorption, distribution, metabolism and excretion (ADME), pharmacokinetics and toxicity. Following this initial screening procedure the drug could be selected for further evaluation as an investigational new drug (IND).

The clinical testing can be initiated, provided the preclinical testing is satisfactory. In the clinical testing, the initial studies (Phase I) involve in general the administration of low sub-therapeutic doses of the IND to a small number of (*e.g.*, 10-15) normal volunteers to establish whether the drug is tolerated and to derive

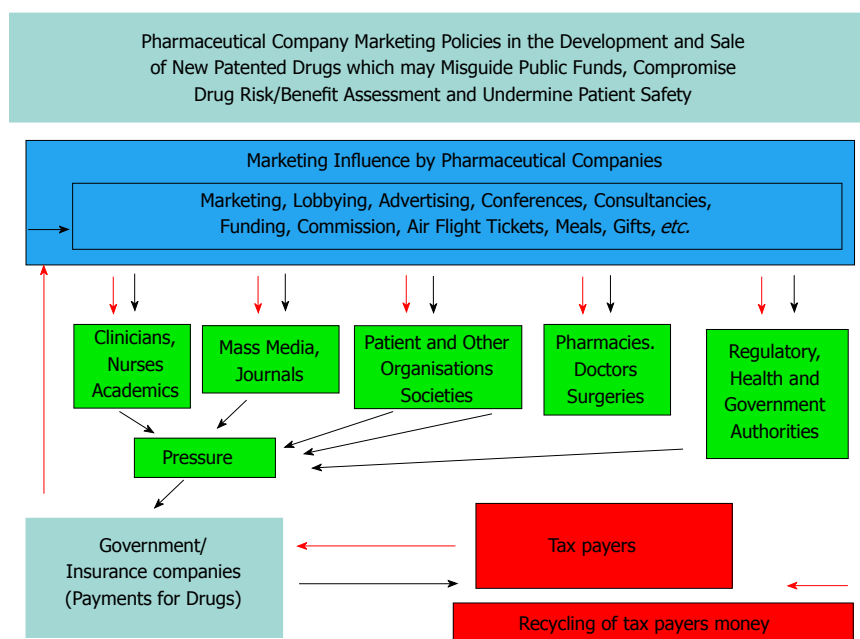


Figure 1 Ethical issues arising from the influence of pharmaceutical companies. A diagram of a theoretical model describing the marketing influence of pharmaceutical companies on various sectors and organisations in relation to new patented drugs and its effect on public spending.

pharmacokinetic, pharmacodynamic and metabolic data. Provided that the preliminary data are satisfactory, further clinical studies involving a larger number of normal volunteers (*e.g.*, 20-100) or sometimes patients are carried out using escalating doses in order to establish a therapeutic dose range, and to assess safety and tolerability. More information on pharmacokinetic and pharmacodynamic data are gathered at the higher dose levels and other parameters are investigated such as the effect of food on drug absorption if the drug is planned to be administered orally.

Phase II clinical trials involve a larger number (*e.g.*, 300) of normal volunteers and patients, with the major aim of establishing safety and efficacy ranges. The identification of a therapeutic dose range and further pharmacokinetic studies are also carried out at this phase.

Phase III studies involve many more patients (*e.g.*, 1000) over longer periods, usually in randomised controlled multicentre clinical trials, with the main aim of comparing the new drug to the current gold standard drug. The duration of the studies depends on the medical condition and is much longer for chronic conditions. In addition to long-term toxicity monitoring in this phase, other toxicity parameters such as carcinogenicity and drug interaction studies are also carried out. Provided the phase III trials are successful and the safety and efficacy results are satisfactory then all the data from chemistry to human studies are submitted and the drug could be registered and approved by the regulatory authorities for marketing. Specific recommendations on the labeling for directions of use and list of adverse effects are included in the marketed product. Following approval by the regulatory authorities, the assessment of the drug may be extended to different patient subgroups and diseases.

Post-marketing surveillance, which is also known as phase IV trials or pharmacovigilance, can be introduced to detect any rare or long-term adverse effects in a much

larger patient population, which was not available during the previous clinical trial phases. Many drugs have been withdrawn or their use restricted due to toxicity at this stage, *e.g.*, rofecoxib^[56]. In many cases phase V, which is also sometimes referred to as translational research, is now being used to compare the overall effect of the new treatment with other treatments and its impact on public health and the general patient population^[20].

It should be noted that there are many variations in the clinical testing procedures and phases for each drug that can affect the length of studies. These include for example the seriousness of a condition, the categories of patients that can be treated, the concomitant use of other drugs and new requirements on safety and efficacy that may be requested by the regulatory authorities. Similarly, other parameters that can also contribute to the length of development and marketing of a drug are whether the drug is needed for urgent treatments or untreated conditions or orphan diseases. In all cases of the introduction of a new drug, a risk/benefit assessment and comparison with the standard treatment should prevail. However, in most cases the major factor for the development and sale of a new drug is financial gain through patent monopoly and intensive marketing.

A major issue in drug development and subsequent use is the level of toxicity. Despite the fact that all drugs have toxic side effects and each individual's susceptibility to toxic side effects is different, no major effort or procedures have been instituted in the drug development or subsequent post-marketing period for studying and reducing or reversing the cause of drug toxicities. The same lack of interest also applies to the design of diagnostic and prophylactic procedures for reducing the incidence of drug toxicities for generic drugs.

Emphasis in both the case of new and generic drugs involve marketing methods for increasing sales, but not improvements for patient safety such as protocols for

minimizing or preventing the toxic side effects or the production of drug antidotes. Within this context, the introduction of patents of new drug formulations, which in most cases have similar efficacy and toxicity to the old formulations, is another area exploited by multinational pharmaceutical companies for making additional huge profits due to the patent monopoly restrictions.

It is estimated that there are about 50000 different drugs available globally, which cause about 8000 different toxic side effects most of which affect patients to a different degree. It is also estimated that approximately 5% of the patients in hospitals are receiving treatments related to the toxic side effects of drugs. There are also many patients affected by toxicity due to impure drugs, idiosyncratic reactions, drug interactions and organ function complications.

The investigation of individual variations in drug response such as pharmacogenomics and metabolomics, as well as the introduction of drug combinations are fast expanding areas in drug development and for the application of personalised medicine.

THALASSAEMIA AND ORPHAN IRON CHELATING DRUGS

Thalassaemia and sickle cell disease are some of over 200 inherited haemoglobinopathies which are included in the category of orphan diseases. Similar to other orphan diseases there is a need for the development of orphan drugs for their treatment. Within this context, iron chelating drugs which are essential for the treatment and long-term survival of thalassaemia patients are classified as orphan drugs. The development of iron chelating drugs requires a basic understanding of iron metabolic processes and methods targeting the effective elimination of iron^[17].

Iron is an essential element required by many biological processes and for normal physiological function. There are many iron metabolic disorders affecting millions of people. Iron deficiency is thought to affect a quarter of the world's population, but is not considered to be a severe condition and can in most cases be treated with iron supplements. In contrast, iron overload is considered to be the most common metal toxicity condition worldwide, with severe implications in morbidity and mortality^[57]. The most common conditions of iron overload are caused by increased gastrointestinal iron absorption (primary haemochromatosis) or multiple red blood cell transfusions (secondary haemochromatosis) or a combination of these two processes. While in normal individuals there is a balance of iron intake and iron loss, in iron overloaded patients there is a net intake of iron. The rate of net iron intake in patients with primary haemochromatosis is slower (about 2-6 mg/d) than that of transfused patients with secondary haemochromatosis (about 15-30 mg/d)^[57].

It is estimated that in general patients with refractory anaemias such as β -thalassaemia are regularly transfused

with 1-3 units (1 unit = 200 mg of iron) of red blood cells every 1-4 wk. An excess of 100-125 g of iron, which is equivalent to about 500 units of red blood cells can be stored in the body of β -thalassaemia patients by the time they reach adulthood. Most of the iron accumulated from transfusions and increased iron absorption is not excreted, but is stored as excess, mostly intracellularly in the form of the iron storage proteins ferritin and especially haemosiderin. The organs mostly affected are the liver, heart, spleen and endocrine system. The damage to these and other organs due to iron overload toxicity is detectable when about 50-100 units of red blood cells have been transfused and is so extensive that in many cases it can become irreversible and fatal, unless iron chelation therapy is commenced^[58].

Transfusional iron overload in refractory anaemias has the highest mortality and morbidity rate worldwide by comparison to any other form of metal overloading condition. The most seriously affected group of transfused patients are those with β -thalassaemia, but there are also increasing numbers in other transfused categories of patients affected such as sickle cell anaemia and myelodysplasia. In the latter two conditions, iron chelation therapy may not be critical since the overall iron accumulation in most cases is less and accordingly the rate of mortality caused by iron overload toxicity is lower in comparison to β -thalassaemia.

The epidemiological data of regularly transfused patients with different conditions has not yet been fully evaluated. It is estimated, for example, that 100000 children are born with β -thalassaemia and about the same number with sickle cell disease each year^[59]. The latter is prominent in the black populations in African countries and their descendants in other continents, especially North America. A smaller number of patients with sickle cell disease can also be found in other countries such as those of the Middle East. β -thalassaemia is found mainly in countries in the Mediterranean area, Middle East and South East Asia. More than 80% of β -thalassaemia patients live in South East Asia and the Middle East and less than 10% worldwide receive adequate transfusions and iron chelation therapy mainly due to the unaffordable cost of treatment. The vast majority of β -thalassaemia patients in developing countries are left to die untreated.

In countries like Cyprus, β -thalassaemia heterozygotes are estimated to be 16% of the population, whereas in India it is 1%-10% of the population depending on the area. The incidence of thalassaemia in Western Europe and North American countries is very low and is related to the flow of immigrants from endemic areas. In Western Europe and North America, β -thalassaemia is considered an "orphan disease" because of the small number of patients in comparison to the rest of the population, who are not carriers of the β -thalassaemia gene^[59]. There is a 25% chance that a couple who are heterozygotes, carriers of the β -thalassaemia gene, can give birth to a β -thalassaemia major child. β -Thalassaemia major patients can only survive if they receive regular red blood cell transfusions from normal haemoglobin blood

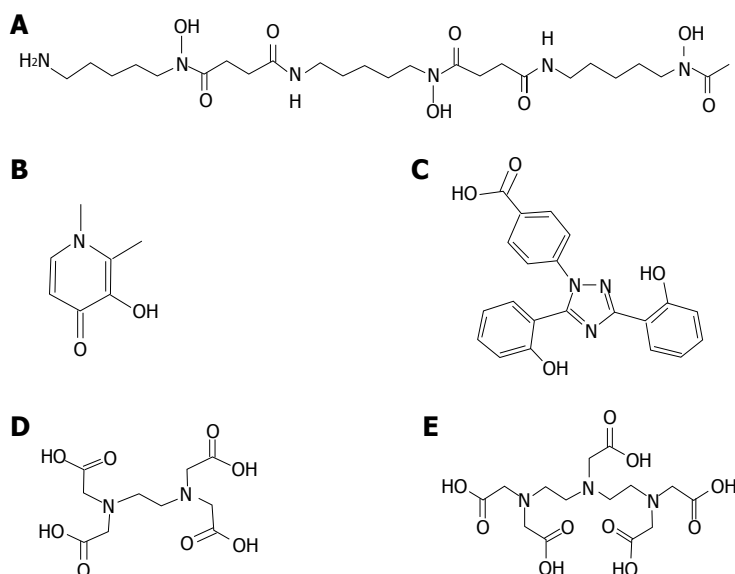


Figure 2 The chemical structure of chelators in clinical use. The chemical structures of the three orphan iron chelating drugs (A-C) which are used for the treatment of iron overload in thalassaemia and two other chelators used in other conditions (D and E): (A) deferoxamine (DF); (B) deferiprone (L1), (C) deferasirox (DFRA), (D) ethylenediaminetetraacetic acid (EDTA) and (E) diethylenetriaminepentaacetic acid (DTPA).

donors in order to replace their ineffective erythrocytes, which contain an abnormal non-functional haemoglobin, unable to transport oxygen to the tissues.

Heart failure as a result of iron overload toxicity from repeated red blood cell transfusions has been until recently the major cause of death in β -thalassaemia patients, which usually occurs before the age of twenty years^[58]. This can be minimised or prevented with iron chelation therapy, especially since L1 was introduced^[60]. In many developed countries, bone marrow transplantation is used instead of transfusions and iron chelation therapy. This method of treatment is usually applied to a small percentage of mostly very young β -thalassaemia patients and incurs a mortality rate of about 5%-9%^[61]. Most global efforts are focused on the prevention of births of β -thalassaemia children using prenatal diagnosis and antenatal procedures^[59].

Iron chelating drugs are primarily used for the treatment of iron overload in thalassaemia, which is considered an “orphan disease” in the EU, United States and many other developed and developing countries. The general objective for the design and development of iron chelating drugs for the worldwide treatment of iron overload in thalassaemia and other diseases is that they should be inexpensive, orally effective and non-toxic. However, in addition to thalassaemia and other diseases of transfusional iron overload there has recently been an increased interest in the use of chelating drugs as the main, alternative or adjuvant therapy in many non-iron loaded diseases. The design of iron chelating drugs for clinical applications other than the treatment of iron overload requires different selection criteria and developmental procedures^[62].

There are three main iron chelating drugs in clinical use at present, which are used for the treatment of transfusional iron overload, namely deferoxamine (DF), L1 and DFRA (Figure 2). The chelating drugs ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA) have been previously used

in transfusional iron overload, but were not selective for iron and are currently used for the detoxification of other toxic metals^[63]. In particular, EDTA is used in millions of patients in alternative medicine worldwide and DTPA in the detoxification of plutonium and other radionuclides in the nuclear industry^[55,64,65].

There are many controversial, ethical and other issues surrounding the design strategies that led to the discovery and development of the oral chelating drugs L1 and DFRA, their comparison to the injectable drug DF and their current therapeutic use in developed and developing countries.

CONTROVERSIES IN THE USE OF IRON CHELATING DRUGS

The historic development of the iron chelating drugs including efficacy, toxicity, cost and ethical aspects as well as other issues can be followed chronologically through the published medical literature. Within this context, there have been many exchanges questioning the role of pharmaceutical companies and academia in the development of iron chelation therapy.

Both DF and L1 are generic drugs, whereas DFRA is a relatively new patented drug and all three are marketed in many countries worldwide. Deferoxamine has been the mainstay of iron chelation therapy since the 1960's and was marketed by Ciba Geigy (now Novartis). Both DF and L1 are currently marketed by several companies worldwide. In contrast, DFRA is marketed by Novartis worldwide except India, where a local company (Cipla) has registered DFRA based on a local court ruling and is sold in India at a price 60-times cheaper than in the EU and United States (Scrip 2008: S00990226)^[66,67].

Deferiprone was invented in 1981 in the United Kingdom and selected as a leading chelating compound out of about 150 related analogues and other compounds^[15-18]. It was developed as an academic initiative, which at the first stages was mostly financed by the thalassaemia patient's

organisation in the United Kingdom. Following many pre-clinical studies, L1 received approval for clinical trials from the local hospital ethical committee and the Department of Health of the United Kingdom in 1986^[68,69]. The encouraging clinical trial results in the United Kingdom prompted the expansion of the clinical trials in many European countries, in Canada and in India^[70-74]. The multicenter clinical trials were part of an academic initiative involving mainly thalassaemia patients who were unable to receive DF due to toxicity, low compliance or both. Deferiprone was first registered in India in 1994 and then in the EU, Asia and other countries in 1999 and the United States in 2011^[55]. The cost of development of L1 in the United Kingdom up to the stage of multicentre clinical trials was less than 2 million USD.

There were many controversies and exchanges regarding L1, amongst academics and between academics and pharmaceutical companies, with one case reaching the mass media involving a Canadian pharmaceutical company (Apotex) and an academic clinician claiming liver toxicity during clinical trials^[75-77]. Similarly, embryogenic and other toxicity caused by L1 in non-iron loaded animals was claimed by the company Ciba Geigy (now Novartis), which was then manufacturing DF^[78]. In both cases the toxicity was not confirmed by other groups studying L1 in clinical trials with thalassaemia patients and in iron loaded animals^[79-81]. These controversies and exchanges highlight the marketing tactics of competing pharmaceutical companies on drugs, which in this case may appear to have been planned to delay the use of L1 until a new owned drug, in this case DFRA was introduced. Similar exchanges were published regarding the possible use of L1 in thalassaemia patients in developing countries, since the high price of DF was prohibitive for the vast majority of patients, who could not afford chelation therapy^[81,82].

Deferasirox is a known compound developed by Novartis, which was selected out of a library of more than 1000 compounds and was provisionally approved for clinical use in 2005. The preclinical studies with DFRA were limited and did not address many of the *in vitro* and *in vivo* efficacy and toxicity studies, which were carried out and published during the preclinical development of L1. Initial clinical trials with DFRA in 2003 showed that negative iron balance was not achieved at the then maximum dose of 30 mg/kg per day^[83]. Higher doses were not then recommended because of the prospect of renal damage^[83]. The maximum dose has now been increased to 40 mg/kg per day for better efficacy, but with increasing prospects of toxicity^[84]. Regarding the cost of chelating drugs, it is estimated that in the EU and other developed countries the approximate yearly cost of effective dose protocols for a 50 kg man at 45 mg/kg, 5 d per week on DF is about 5000 euros (excluding needles and pumps, *etc.*) and for L1 at 80 mg/kg per day, 8000 euros. For DFRA at 30 mg/kg per day the cost is about 33000 euros and at 40 mg/kg per day about 60000 euros. The cost of the L1/DFO combination, *e.g.*, the ICOC L1/DFO combination protocol of using L1 during the day (80-100 mg/kg per day) and of subcutaneous DF (40-50 mg/kg

at least 3-4 d/wk) is 11000-14000 euros. Deferiprone is sold in India at a price around 4 times cheaper than comparison in Europe and is even sold at a much cheaper price by a local company in Thailand. The same applies for DFRA, where the sale price in India is more than 60 times lower than in Europe and the United States (Scrip 2008: S00990226).

It is estimated that DFRA is costing about 150 euros per patient per year to manufacture and is sold at 60000 euros, with most of the cost claimed as marketing expenses^[20]. Both L1 and DFRA can be sold at a price more than 100 times cheaper by non-profit organizations in developing countries, but such initiatives are still lacking, despite the fact that 80% of the thalassaemia patients die untreated in these countries.

Regarding the treatment aspects of transfusional iron overload in thalassaemia, DF is considered to be effective when administered subcutaneously or intravenously at 40-60 mg/kg per day and for oral L1 at 75-100 mg/kg per day, whereas the efficacy of oral DFRA at 20-40 mg/kg per day is still questionable and under investigation^[83,85-89]. Iron removal from the heart, which is the main cause of mortality in iron loaded thalassaemia patients, is achieved mainly by L1 and to a lesser extent by DF and DFRA. The latter two chelators appear to be more effective in iron removal from the liver.

In terms of efficacy, the International Committee on Chelation (ICOC) L1/ DF combination protocol is considered to be the most effective because it reduces iron load to normal range body iron store levels^[90-93]. The introduction of the ICOC L1/DF combination was an academic initiative based on a model for improving efficacy and reducing toxicity. Many drug combinations are widely used for other diseases in clinical practice without the need for regulatory approval. In contrast, almost all pharmaceutical companies disapprove of such synergistic combinations unless the drugs prescribed are both owned by the same company. Monotherapy with DF, L1 or DFRA are generally less effective than the ICOC L1/DF combination protocol and only L1 has been shown to reduce and maintain thalassaemia patients' body iron store levels to normal physiological ranges^[92,94].

Another major issue in relation to the efficacy of chelation therapy is compliance, which is reduced in patients receiving DF due to the long term 8-24 h daily injections, whereas it is much higher in patients receiving the oral chelators L1 and especially DFRA. In addition to efficacy and compliance, the toxicity properties of the chelating drugs are also a major factor in the overall risk/benefit assessment. Optimal chelation therapy is based on the selection of the appropriate chelating drug(s) and chelation protocol in each condition and for each patient. As shown in many other conditions, each patient appears to have an individual ADME, sensitivity, toxicity and efficacy profile for each chelating drug. Such individual response profiles are currently investigated within the framework of different parameters such as pharmacogenomics, metabolomics and proteomics, which are essential requirements for designing personalised medicine

protocols^[85,95].

Different toxic side effects have been reported during the 50 year long-term use of DF and 27 years for L1 in different cohorts of patients. However, in contrast to the other two chelators and despite the fact that toxicity in the medical literature is rarely reported, it is evident from post-marketing reports that DFRA has one of the highest rates of fatal toxicity among new patented drugs, which is associated with renal, hepatic, gastrointestinal and bone marrow failure^[96-102]. In FDA and user community toxicity monitoring, 4113 fatalities in patients using DFRA were reported in 2012. Previous FDA individual case based reports of 2474 deaths, suggest that there has been uncontrollable and indiscriminate use of DFRA in many categories of iron loaded and non-iron loaded patients, as well as a lack of toxicity monitoring and absence of prophylactic measures^[100]. In a post-marketing report in 2009, DFRA was listed as the second most frequent suspect drug in reported patient deaths following rosiglitazone, with 1320 and 1354 fatalities, respectively^[98]. In an EMA meeting the same year, an 11.7% mortality rate (1935 cases out of 16514 patients) was reported and a warning was issued that DFRA's toxicity is likely to increase when the maximum recommended dose increases from 30 to 40 mg/kg per day^[99].

A few fatalities have also been reported in the case of DF mainly in relation to mucormycosis, yersiniosis and bone marrow aplasia^[103-105]. Similarly, a few cases of fatal agranulocytosis have also been reported with L1, especially in patients who did not adhere to mandatory weekly or fortnightly blood counts, which are used as prophylaxis^[106-108].

In addition to these fatal cases, there were many other non-fatal, but serious toxic side effects reported for DFRA which were mainly associated with damage to kidneys, liver, bone marrow and gastrointestinal tract, as well as several other organs such as ocular and auditory abnormalities and skin rashes^[109-113].

The toxic side effects in the case of DF were ocular and auditory abnormalities, administration site (injection) related complications of mainly topical or sometimes systemic toxicity and yersiniosis^[17]. The toxic side effects of L1 included in addition to agranulocytosis, cases of neutropenia, joint and musculoskeletal pain, gastric intolerance and zinc deficiency, all of which may affect about 5%-10% of patients^[17].

The selection of optimal iron chelation therapy protocols in thalassaemia mainly includes the use of DF and L1. The overall risk/benefit assessment suggests that for the vast majority of patients the combination of L1 with DF is the most effective, least toxic protocol and where it is appropriately used it has resulted in a substantial decrease in morbidity and mortality in different thalassaemia patient cohorts^[114-116]. This therapeutic approach has changed thalassaemia from a fatal to a chronic disease^[116]. Similarly, the ICOC L1/DF combination protocol has resulted in normalisation of the iron stores in thalassaemia patients, which can in most cases be maintained by low doses of L1 monotherapy^[90-95]. Despite these encourag-

ing findings, many patients are still treated with DFRA monotherapy which has a better compliance but lower efficacy and a much higher risk/benefit ratio in comparison to DF, L1 and their combination. Only a small proportion of patients can benefit from the use of DFRA, especially those having toxicity complications with DF and L1^[85,89-95]. Many patients are also using DF and L1 monotherapy, where iron overload is stabilised, but not eliminated to the extent of achieving normal range body iron store levels.

The variation in iron chelation treatments in different hospitals, countries and overall worldwide, reflects the influence of doctors on drug selection, patient safety and treatment outcome. This variation also reflects the marketing influence of pharmaceutical companies on doctors, health authorities and governments, and highlights the factors influencing the ability of doctors and health authorities to identify and select appropriate therapy protocols for patients^[20].

Further developments in the area of iron chelation therapy are the ongoing clinical trials and uncontrolled clinical use of DFRA in other categories of transfused iron loaded patients such as myelodysplasia and sickle cell disease, and in non-transfused iron loaded patients such as hereditary haemochromatosis, thalassaemia intermedia, and post-transplanted thalassaemia patients. This wider use approach and development undermines patient safety and increases the risk/benefit ratio since any long or short-term benefits on morbidity and mortality from the use of DFRA in other categories of patients and especially in myelodysplasia and sickle cell disease patients are questionable and not yet confirmed^[117,118]. Similarly, venesection in hereditary haemochromatosis and post-transplanted thalassaemia patients is a much safer and inexpensive procedure in comparison to DFRA treatment. The same applies to many non-transfused thalassaemia intermedia patients, where chelation therapy with L1 and DF is also safer than DFRA^[119]. The wider use of DFRA in the above conditions indicates the pharmaceutical company's marketing potential and the influence it exerts on the risk/benefit assessment of chelation therapy by individual clinicians.

The use of iron chelating drugs in patients with non-iron loaded diseases is another expanding area attracting a lot of interest among clinical investigators and pharmaceutical companies. Similarly, the application of iron chelating drugs could include rare and tropical diseases where no effective treatment is currently available^[120-126]. The safety of L1 in non-iron loaded patient categories seems to be higher in comparison to DF and DFRA, as shown from many short and long-term clinical trials in neurodegenerative, renal, infectious and other diseases^[62,127]. In contrast, fatal and other serious toxic side effects have been observed in clinical trials using DF, in non-iron loaded patients such as in mucormycosis and rheumatoid arthritis patients^[104]. Similarly, in one of the FDA related reports it was estimated that of the 2474 individual fatal cases reported for DFRA at least 500 were not related to transfusional iron overload, but included

cancer, cardiovascular, neurological and other patients with normal iron store levels^[100]. Within this context, L1 appears from the various clinical trials with non-iron loaded patients to be relatively safe and promising for wider clinical use as a main, alternative or adjuvant therapy in many diseases, and as a pharmaceutical antioxidant^[62,128,129].

The evaluation methods and the controversies which were identified in relation to the development and use of chelating drugs may help in the introduction of new approaches and strategies for the design, development and use of orphan and other drugs. Such academic approaches may benefit the treatment of millions of patients with many other conditions worldwide. Within this context, the paradigm of the design and development of chelating drugs, and especially L1, which was based on academic initiatives, may help to illustrate the need for new strategies in drug development. The use of this approach can increase the accessibility to new drugs due to low drug prices and decrease the morbidity and mortality observed in many diseases in both developed and developing countries.

Drug development based on academic initiatives can minimise costs and increase the prospects of the introduction of new drugs, which can be applied in the treatment of many diseases in both the developing and developed countries. At present the high prices of new patented drugs which are the result of high costs in drug development are not affordable for the vast majority of patients.

In addition to new strategies for the reduction of costs in the production of orphan and other drugs, several other initiatives can be taken to improve patient treatments worldwide. These include further research challenges involving better understanding of the heterogeneity in the underlying mechanisms of disease processes, inter-patient variability in drug responses and better risk/benefit assessment procedures.

CONTROVERSIES IN DRUG DEVELOPMENT AND PATIENT SAFETY

In almost all cases of the development and marketing of new patented drugs, which are mostly undertaken by private multinational pharmaceutical companies, a number of marketing strategies are developed for maximising sales and profit for their product such as advertisements, publications, lobbying and conferences (Figure 1). Within this context, a large marketing plan is constructed involving among others the recruitment of consultants who are usually internationally known influential academics in clinical departments of public hospitals mainly in Western Europe and the United States. These consultants are usually involved in seeding clinical trials and the promotion of their new drug product in publications, conferences, patient organisations and regulatory authorities^[20,130].

The market plan also involves arrangements where

company representatives personally visit all clinicians who have jurisdiction over potential patient/customers, with the prospect of advertising and promoting their drug to be used by their patients and in most cases offering in exchange different forms of support or gifts ranging from a meal, to the covering of expenses for their participation in conferences where the drug is promoted, consultancies, grants and other benefits (Figure 1).

In many countries with no legal restrictions, pharmaceutical company representatives often offer a percentage of the sale of the drug they promote to clinicians and to other influential persons in health or regulatory authorities. A different marketing strategy is to offer a clinician a “compensation” for “enrolling” patients in clinical trials, with the prospect of the patients involved to remain on the treatment and the government health authorities to pay huge sums of money for the continuation of the expensive new treatments (Figure 1). For example, 5000 euros is paid to the clinicians in charge of the enrolment of each patient for post-marketing monitoring of one of the new patented drugs in Greece.

A number of cases involving bribery of clinicians by pharmaceutical companies have reached the courts, but corruption is so extensive and out of control that in one court case in Germany a limit of 10000 euros was allowed as a donation for such activities for private clinicians, most of whom are working for the National Health System^[131-135]. It should be noted that all the benefits paid to the clinicians for drug promotion are included in the cost of drugs as marketing expenses and are paid by the tax payers through the government health authorities (Figure 1). In developed or other countries with legal restrictions on the influence of private organisations, financial support by pharmaceutical companies is provided indirectly through donations to academic, patient, charity and other organisations associated with the supporters or promoters of their drug (Figure 1).

Within the framework of new drug development and marketing, multinational pharmaceutical companies can provide clinicians with financial support for different events and in some cases for research projects and clinical trials involving their drug, under a secrecy agreement^[136-139]. Usually, only positive results are allowed to be published by the investigators financed by the pharmaceutical company, which are under the scrutiny of their marketing, legal and medical writer's department^[137-140]. Similarly, reports of toxic side effects and studies of low or no efficacy are rarely published. Within this context, pharmaceutical companies influence academic research and academic affairs, including the impact factor of journals, the citations of articles and the citations for authors. Academic consultants of pharmaceutical companies can also influence publications of competing new or generic drugs, by serving in editorial boards or as referees. The unbiased role of journals is also questioned, since almost all journals are businesses and dependent on income from the pharmaceutical industry including advertisements, reprints and conferences^[140,141].

Similar influences can also be exerted in other aca-

ademic platforms and in medical conferences, especially when the pharmaceutical company is a sponsor. The number of conferences organised and sponsored by a single pharmaceutical company for the promotion of their drug is continuously increasing and support for independent conferences where competing drugs are presented is continuously decreasing.

In addition to targeting clinicians, a similar marketing strategy by pharmaceutical company representatives is also directed to other individuals or organisations, which may influence the sale of their drugs such as patient organisations, academic societies, regulatory authorities and other governmental bodies (Figure 1). For example, most of the conferences related to medicine including the expenses for participation by clinicians, nurses and patients are supported by multinational pharmaceutical companies introducing new drugs. Similarly, pharmaceutical companies are the major sponsors for medical societies, patients' organisations and selected medical departments in academic institutions (Figure 1).

Despite the fact that in some developed countries a number of restrictions have been introduced to reduce the influence of pharmaceutical companies in academic and public institutions, the influence is still evident. Such influences may not appear to be on a direct personal level, but are exerted indirectly, for example by donations or grants to academic institutions and societies^[137-141].

In general, the marketing approach is different for each pharmaceutical company, for each country and each "customer" and depends mainly on the local conditions and the potential market scale. This can be illustrated by the variability on the sale figures and the use of the three iron chelating drugs in different countries, hospitals and individual doctors.

The marketing influence of multinational pharmaceutical companies for safeguarding the sale of their new drugs and for generating new income worldwide is evident from many recent events such as the health scare in relation to the spread of A H1N1 influenza and other similar viruses, where vaccines worth billions of dollars were sold worldwide^[142]. It should be noted that national governments and the WHO endorsed and advertised the campaign for the pharmaceutical companies to sell and distribute these vaccines worldwide, even when these were not licensed^[66,142]. Following the scare warnings some of the national and international advisors in the decision making panels for the approval and supply of the vaccines were later identified also to be consultants for the pharmaceutical companies selling the vaccines^[66,142]. This and similar examples illustrate the need for the creation of independent public expert committees, *e.g.*, like NICE in the United Kingdom for safeguarding the rights of patients and for protecting and distributing national health resources according to the health needs of patients and not according to the influences of pharmaceutical companies^[143].

There are many other grey areas in the development and sale of pharmaceuticals involving marketing tactics and strategies which are jointly developed between phar-

maceutical companies such as price fixing, market sharing, market exclusivity and other arrangements between the companies selling the generic drugs and the new drug or competing drugs. In all of these cases public funds and spending on drugs is misappropriated and pharmaceutical companies make huge profits, which reduce health resources and in many cases may also affect patient safety^[20].

The protection and domination plan of the patent monopoly for a new drug product in specific diseases is another major part of the marketing strategy of the patent holder pharmaceutical companies. This may involve the discrediting of competing drugs for example through publication of possible adverse effects by academics supporting their drug or through legal conflicts in relation to exclusivity, or on therapeutic claims made by similar drugs. Other methods used include the acquirement of new patents and delaying tactics in the development of an investigational new drug that may influence the sale of their drug. These marketing and other tactics are pursued not only during the lifetime of a patent, which is usually 25 years, but also when the patent life of a drug is expired. As a result, the price of a drug when it becomes generic (*i.e.*, when there is no patent protection) remains about the same as when it was first introduced.

New patents are usually filed by the proprietor company on the same drug before the initial patent expires. The new patents may involve different drug formulations or related uses or different claims for the same or other diseases. This effort is usually undertaken by the initial patent holder company in order to safeguard the exclusivity of the monopoly, the high sale price and the level of the profits that can be made from the sale of their drug.

The sale price of a drug is another grey area affecting public health funding and drug availability in developed and developing countries. One of the contributory factors for the high price of new drugs is usually the inclusion of the marketing budget in the overall cost for drug development (Figure 1). For example, the costs for the organisation of conferences and the support for physicians to attend such conferences are included in the marketing budget and for fixing the price for the drug. Considering for example that the actual cost of producing and developing a new drug may be negligible, *e.g.*, less than 1 USD/g, the actual retail sale price may be in comparison greater than 1000 USD/g when the drug is under patent protection and produced by a multinational pharmaceutical company in a developed country. Similarly, if the same drug is not protected by a patent then the price could be less than 20 USD/g, if produced by a pharmaceutical company in a developing country. The same also applies when the patent expires and the drug becomes generic.

In general, the high price of drugs is a considerable obstacle in the provision of a better health care system in each country and diminishes the possibilities of supplying new improved drugs for the treatment of patients in developing countries and in some cases in the developed countries.

Many other controversial issues surrounding the development and use of new drugs include toxicity monitoring and differences between regulatory authority procedures among countries. Similar controversies involve the lack of transparency in the reporting of results of clinical trials, ineffective reporting of the adverse effects to the clinicians using the new drug by the pharmaceutical companies and the regulatory authorities, as well as misinformation on the risk/benefit assessment and criteria for the use of the new drug by comparison to generic drugs.

Although many pharmaceutical companies may be aware of the high toxicity of their newly introduced drug, they will continue selling it to acquire as much profit as possible. The new drug will not usually be withdrawn unless the company's profit margins are threatened or may be eliminated due to compensation claims or requests made by the affected patients and their legal representatives^[20,100].

The drive for profit by multinational pharmaceutical companies and the lack of strict regulatory procedures or ethical codes endanger the safety of patients and the prospect of introducing optimum treatments. Furthermore, the present system adversely affects the economy of developing countries and health care resources of most developed countries. Within this context, it is highly unlikely that a pharmaceutical company would support any academic research for identifying and decreasing the toxic side effects of their drugs, following regulatory authority approval for clinical use and marketing. The same approach applies to research with generic drugs despite the fact that the manufacturing company involved may still have a sale monopoly or the drug may be tested for a different formulation or patent application.

Drug research, development and availability are relying at present almost exclusively on market forces and pharmaceutical companies' initiatives, marketing policies and decisions. This approach is not in many cases ethical and may not lead to optimal treatments and best patient care solutions. Similarly, the lack of health strategies and policies on drug design, development and use can overall influence patient treatment and safety^[144].

There are no transparent procedures or specific ethical rules at present that will safeguard the rights of patients for the safest and most effective treatment for their disease or condition. The awareness and ethical approach for the treatment of each patient is the responsibility of the clinician in charge, who among others should provide the best care and prescribe the safest and most effective treatment and drugs. This responsibility is crucial for life threatening conditions, where the wrong risk/benefit assessment may result in ineffective treatments or serious toxicities and an overall increase in the morbidity and mortality rates. While organisations such as NICE in the United Kingdom may improve patient treatments and decrease costs, new organisations are needed to curb excess profits made by multinational pharmaceutical companies on new patented drugs. Such initiatives can decrease the cost of health care in developed countries and increase

accessibility to drugs by patients in developing countries.

Improved measures on transparency regarding the reporting of clinical effectiveness and toxicity may help in the selection of the most appropriate and safe treatments for general, but also for individual patient use. Cost/effectiveness assessment issues are also important and may help orphan patients in developed as well developing countries^[143].

Overall, it seems possible that with the appropriate health care policies, patient access to cheaper drugs can increase and waste on resources and health spending decrease. Such policies can benefit millions of orphan and other patients and may help in the treatment and elimination of many orphan diseases.

NEW OUTLOOK IN WORLD HEALTH ISSUES

Hunger, malnutrition, poor sanitation, impure water and lack of medicinal drugs appear to be the main causes of mortality and morbidity worldwide, affecting mostly children and infants in developing countries^[28]. These problems can be overcome by increasing the production and supply of food, vaccines and medicinal drugs, as well as by improving water and sanitation technologies^[1,2]. Within this context, a substantial reduction in the global mortality and morbidity levels can be achieved provided the appropriate health policies and strategies are implemented for each disease^[25-27]. Such strategies should include further research on the mechanisms, drug treatment and prevention of diseases, population control through family planning, reduction of food waste in developed countries and reduction in environmental pollution.

Health resource allocation is a worldwide problem affecting all countries, health services and institutions and most categories of patients. Among these categories are orphan patients with rare, tropical and orphan diseases found both in developed and developing countries, who usually have limited access to treatments and also increased requirements for basic medications. The development of orphan drugs for such diseases can help many millions of patients worldwide. However, present conditions and policies are insufficient for overcoming these problems because of many limitations such as loopholes in regulatory and trade laws, misappropriation of public funds, bias in reporting and many other irregularities all of which undermine the efforts for improving the present status quo and benefiting affected patients (Figure 1)^[20].

The present world trade and patent laws mostly benefit developed countries and affect the effective supply of sufficient food and drugs in the developing countries, where the resources are scarce and the appropriate technologies underdeveloped^[12,14]. This can be illustrated by the sale of drugs amounting to about 0.5 trillion USD per year by the first twelve richest multinational pharmaceutical companies situated in the United States and Western Europe (Table 2). Such revenues are mainly generated from drugs sold for major common diseases. Interest

in drug development for neglected tropical diseases and rare, orphan diseases is limited, unless pharmaceutical companies are convinced that such projects can result in substantial profit returns^[11]. The introduction of orphan drug legislation in developed countries has increased orphan drug development and global orphan drug sales which have steadily increased in the last few years and are now approaching 100 billion USD annually^[13].

Market and monetary conditions appear to be the major determinant in government health policy, public health budgets and health resource allocation, which affect, to a great extent, the treatment of patients worldwide. However, it was recently realised by governments in many countries that allowing market forces and the free economy to influence and determine health conditions and resource allocation will be very costly and detrimental to the overall treatment and safety of patients^[1,2,7,20].

Within this context, the institution of NICE in the United Kingdom and similar organisations elsewhere in developed countries is a limited step in the right direction, but does not address other major issues such as the pricing of drugs and the influence of pharmaceutical companies on governments, clinicians, pharmacists, regulatory authorities and other organisations. Similarly, it does not address many other problems such as pharmacoeconomic issues, literature bias and misinformation, transparency on drug efficacy and toxicity as well as development of generic drugs and nutraceuticals, and the availability of drugs at a lower cost than developing countries. One of the problems on drug selection and treatments is that NICE and similar organisations rely on published data, which are mostly biased due to the association with pharmaceutical companies and they are not generated by independent clinical investigators^[5,19,20,24,50,141].

It appears that as the world population expands and the global economic situation is worsening, financial health resource allocation will become more important and related issues will be discussed on a wider platform in the state authorities, the medical literature and elsewhere. Similarly, initiatives may be taken by government bodies at different levels to decrease or limit the expenditure on drugs and medical devices, without lowering patient safety or treatment standards.

The paradigm of drug design and development of L1, which was mostly the result of academic initiatives and procedures, may prove to be a suitable model for the design of orphan drugs for orphan and rare diseases. This model has been shown to be more successful in comparison to the model of development used by pharmaceutical companies for DFRA, since L1 has been shown to be less toxic and more effective. Furthermore, as a result of transparent procedures a number of prophylactic measures were introduced as soon as the toxic side effects of L1 were identified and reported in the medical literature^[17,127].

Transparency on the efficacy, toxicity and costs of the drugs is a major aspect of decision making for health policies and resource allocation. Despite the fact that such issues should be examined by expert public watch-

dog committees, most decisions rely on the pharmaceutical company's submission data and to a lesser extent on published data by independent investigators. Within this context, a relatively new science was developed, pharmacoeconomics, which is trying to address the cost of drugs and the impact on public health and society in general.

However, research reports suggest that there is evidence of publication bias with about 90% of pharmacoeconomics articles in most journals supporting the drug in question, compared to only 30% in the *New England Journal of Medicine*^[52,141]. Similar articles sponsored by Novartis have been published for DFRA suggesting that DFRA is better value for money than DF, which however took into account much higher daily and weekly doses of DF, excluded the DFRA cost of toxicity monitoring and treatment outcomes as well as other relevant parameters^[66,145]. Similar comparisons were also made by a different study sponsored by Apotex, one of the manufacturers of L1 in Western countries and by a company in Thailand, which showed much lower costs using L1 than other chelators^[146,147].

Publication bias, misinformation, lack of transparency, selective reporting and other issues surround the publications sponsored by pharmaceutical companies, their academic consultants and medical writers^[20,52,141]. Pharmaceutical company sponsored publications usually make excess claims on drug efficacy in contrast to toxicity, which is usually omitted or is scarce. Other marketing methods include misinformation reports on reduced efficacy, high toxicity and high cost of generic and other new competing drugs. Similar strategies, may involve the highlighting of reports of clinical studies using ineffective doses of generic and other new competing drugs or by making false claims on their toxicity.

Publication bias is also the responsibility of the editorial boards of journals, where the risk/benefit assessment for drugs is overtaken by other issues, which may ultimately influence patient treatments. In the case of L1 for example, an editorial dealt with a conflict between an academic and a pharmaceutical company (Apotex) without questioning the motives of the academic or the risk/benefit assessment on the treatment of the thalassaemia patients in developed and developing countries^[76]. The same journal ignored its own earlier publications on the efficacy of L1 and its impact on the treatment of thalassaemia patients, probably because L1 was used under its chemical name and before the INN name Deferiprone was registered^[69]. This conflict delayed the registration of L1 in the USA and Canada for more than twelve years, which may have resulted in many fatalities related to congestive cardiac failure, since L1 is known to effectively remove iron from the heart and reverse or prevent this form of iron toxicity^[50,60,75,92].

There are many other examples of pharmaceutical company marketing policies for driving the market to adopt their product in addition to academic journals, such as the recruitment of patients in seeding trials, who eventually will remain on the treatment with the new drug after the trial, also in swinging opinion in support

of their new drug through conferences, through bribery and other methods (Figure 1)^[130-133]. Such methods can influence patient treatments costing the health services billions of dollars, such as in the case of renal dialysis for end-stage renal diseases (ESRD). Emphasis on the prevention of progression of diabetic nephropathy *via* generic drug therapy may minimise such costs^[148].

Despite the influence of pharmaceutical companies on public health resource allocation, recently there have been an increasing number of initiatives to change the status quo and overall improve public health care, including the prospect of orphan patient treatments in developing and developed countries. Examples include the successful lobbying by patient organisations for the introduction of L1 in the United States, the court ruling for cheaper imported drugs in India to help local patients and the clinical evaluation of EDTA by NIH in the United States for possible use in patients who suffered myocardial infarction and diabetes^[55,149-151]. Further improvements can include the introduction of nutraceuticals, generic drugs and drug combinations in many orphan, rare and other diseases. For example, zinc has been suggested for use as adjunct treatment in infants with serious bacterial infections, which is one of the top causes of global mortality^[152]. Similarly, the wider application of L1 and other generic drugs as main, alternative and adjuvant therapies in many conditions may result in more effective and less costly therapeutic options for many categories of orphan and other patients^[55].

NEW POLICIES FOR IMPROVING DRUG AND HEALTH DEVELOPMENT

There are increasing prospects of reducing the rate of global mortality and morbidity by adopting specific policies that can have direct effects on many diseases including orphan, rare and tropical diseases. Improvement of food and health resources, better sanitation and drinking water purity, sex education and family planning are some of these policies which can play a major role in such efforts, especially in developing countries^[1-3,153]. Similarly, the availability of drugs for the treatment of diseases is another major factor affecting the rate of global mortality and morbidity, especially patients in developing countries.

In contrast, different health policies can be introduced to reduce the rate of mortality and morbidity in the developed countries. Such policies can reduce, for example, environmental pollution, bad dietary habits, excess alcohol consumption and smoking which have been shown to lead to obesity, cancer, cardiovascular and other diseases. A similar policy is to tax such unhealthy habits similar to cigarettes and the relevant tax revenues to be used for subsidizing food supplies for malnourished people, vaccines, medicinal drugs and improve health education.

Health resource allocation can also be improved by reducing public health spending on drugs and diverting resources to other health areas which have an impact on the rate of global mortality and morbidity. This can

be achieved through the adoption of policies that can limit excess profits made by multinational pharmaceutical companies and also through other measures that may facilitate the use of the best, safest and less costly treatments for the benefit of patients globally. Such measures and policies may include the sale price of drugs in developing countries to be adjusted as to the per capita ratio of developing to developed countries.

Transparency on the efficacy, toxicity and costs of manufacturing and sale of drugs including orphan drugs is essential for the development, application and safety of drugs in all diseases^[66]. Within this context, the risk/benefit assessment of different drugs for each condition should be independently assessed and not rely only on published data, especially on studies sponsored by pharmaceutical companies. Identification of the therapeutic index of new and generic drugs and their impact on the treatment of each condition is also important for decreasing patient morbidity and mortality. Similarly, the implementation of drug safety measures is paramount for patient survival and well-being. In addition to the identification of toxic side effects, research on prophylactic measures and identification of drug antidotes can increase patient safety and survival.

The development of personalised medicine based on ADME, toxicity and other parameters is a further step in the achievement of improved therapeutic interventions^[154]. Within this context, randomised clinical trials may not necessarily be the only tool of comparison for competing drugs in each condition. This is particularly important for generic drugs, where it may not be feasible to carry out such studies due to insufficient funding. The most important parameter for comparison in drug application in all diseases is whether the drug in question achieves a full treatment with acceptable level of toxicity. In cases where full treatment cannot be achieved, the effects on morbidity, mortality and cost of the drug under investigation should be compared to other drugs used for the same condition.

The paradigm of the development of L1 and other orphan drugs, which was based on academic and patient initiatives and efforts, appears to be a more successful, less costly and safer method in comparison to the monetary approach of pharmaceutical companies on orphan drugs. In such cases there are transparent procedures and scrutiny by academic peers with ethical instead of monetary motives. Similar academic initiatives involve the institution of drug combination treatments, which are studied and developed by academics independently of pharmaceutical companies and monetary motives^[90-93,115]. Generic drug research and applications in other conditions such as the use of EDTA in many non-metal toxicity conditions by thousands of clinicians worldwide in millions of patients is another example of drug development independent of the pharmaceutical companies^[55,64,150,151]. The development of other generic drugs and nutraceuticals is also increasing, especially in conditions where treatments are not successful or very expensive. Such approaches in-

clude the development and use of medicinal products in alternative and Chinese medicine.

The role of pharmaceutical companies is essential in manufacturing and developing drugs against diseases. This is a major contribution to society since it helps the treatment of billions of people every day. However, like any other business their main aim is profit and ethical considerations are secondary or absent in their agenda and policy planning. Within this context, their efforts are based on ways to maximise the income from the sale of their drugs. Unless government and regulatory authorities are vigilant and their medicinal drug policies are sufficiently effective, the treatment and safety of patients may be compromised by the activities of pharmaceutical companies including the exploitation of loopholes in regulatory and marketing procedures^[20]. Similarly, the development of orphan drugs by pharmaceutical companies is not of major interest unless major financial benefits are clearly secured. Such policies and activities affect health resource allocation and especially orphan patients with orphan or rare diseases.

Drug selection and availability to patients in many cases resembles the sale of a market orientated product, like a chocolate brand or other food commodities. This can be observed for example in chelation therapy, where the drugs used for treatment are related to the marketing success of the manufacturing company and not the patient needs. The responsibility for allowing the manipulation of the drug market by pharmaceutical companies, which affects patient treatment outcomes and safety, lies exclusively with the government, the regulatory authorities and the clinicians. There are many recent examples of commercial company manipulations and government interventions, which may influence health resource allocation and outcomes. Such interventions include fines to settle civil and criminal investigations by the United States government in relation to sales and practices of various drugs by Pfizer totalling 2.3 billion USD, and a 3.0 billion USD fine for similar activities by Glaxo Smith Kline^[155,156].

Several other measures and suggestions can also be considered in order to minimise the influence of pharmaceutical companies on patient treatment outcomes and safety and in reducing drug costs. For example, marketing expenses should not be included in the cost estimation and sale price of drugs. Similarly, the entry of pharmaceutical company marketing representatives should not be allowed in public hospitals for drug lobbying purposes, unless transparent procedures are followed and the time used for consultations is outside normal working hours. Manipulation of the drug market and prices and lack of transparency on safety, efficacy and costs should be penalized by the government authorities as shown in the United States, or where there are ineffective or corrupt regulatory authorities these can be replaced as shown, for example, in France^[156,157].

The influence of pharmaceutical companies on academia including publications should be more transparent and the publication of studies sponsored by pharma-

ceutical companies should be cited as advertisements. Similarly, academics associated with pharmaceutical companies or the employees of pharmaceutical companies should not be used as referees or in editorial boards for drug related topics.

Members of public hospitals, local and international health authorities should be prevented from acting as consultants for private pharmaceutical companies unless such activities are through transparent procedures and commercial involvement is outside public service responsibilities. The support received by clinicians from pharmaceutical companies including participation in conferences and clinical trials should also be through transparent procedures. Similarly, results from clinical trials on drugs should be independently reported and not controlled by medical writers and others belonging to the proprietor pharmaceutical company. Public expenditure in relation to doctors' absences for conferences organised or sponsored by pharmaceutical companies should not be considered as further education activities, unless these are organised by independent academic societies or non-profit academic organisations.

These and many other policies and measures may help to decrease the expenditure by health authorities on drugs both in developed and developing countries. Similarly, it may also help in the adoption of more transparent procedures and the improved allocation of health resources which may lead to better patient treatment outcomes and better safety. In the meantime, many research challenges are continuously emerging in many orphan, rare and other diseases which may influence health outcomes, morbidity and mortality as shown by L1 and other drugs^[158-162].

The world efforts for better redistribution of global wealth may be the answer to health resource allocation, since the major cause of mortality at present is associated with poverty, malnutrition and starvation. Present estimates suggest that 1% of the world population owns 50% of the global wealth and that more than 3.5 trillion USD are deposited in tax heavens by rich individuals and commercial companies.

CONCLUSION

World health developments including morbidity and mortality outcomes are a reflection of many factors which are affected by health policies in individual countries and globally. Food availability, health provision and education, family planning, disease prevention, nutrition, environmental and monetary influences, genomic and psychological aspects are some of the factors which are in dynamic equilibrium and can influence health levels and outcomes in each country. There is scope for substantial improvements in world health policies and many ethical dilemmas and issues related to health strategies need to be prioritised, readdressed and resolved in each country and also globally. The disease profile and health policies between developed and developing countries are different, with profound financial resource insufficiencies in the latter.

The availability and cost of generic and new medicinal drugs are among the major areas affecting the level of global health care. Monetary, ethical and other issues affect the supply of medicinal drugs for different categories of patients in each country. Health policies, regulatory and marketing procedures can variably influence the risk/benefit assessment, patient safety, drug availability and drug treatment outcomes in each country. Public health and overall national spending are also influenced by such procedures. Reassessment of drug pricing and of regulatory procedures with major emphasis on the development of orphan drugs based on a risk/benefit assessment may help in the treatment of many categories of orphan and rare diseases and millions of orphan patients globally. The criteria for drug development and use and of price levels in each condition should be readdressed and modified to improve patient treatments, drug safety and minimise costs.

The implementation of improved policies on health resource allocation and drug development can lead to the realisation of many major health aims such as the introduction of worldwide and universal health care. Similarly, advances in medical research can lead to the elimination and improved treatment of many diseases, to an overall reduction in the morbidity and mortality rates and an increase in the quality of life for patients worldwide.

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