Increasing the use of orphan drugs in clinical practice

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Orphan drugs enable people suffering from rare diseases to access well-tolerated, effective drugs. This article reviews the legislation supporting orphan drugs and factors driving their increasing importance in clinical practice, as well as highlighting some medicolegal issues.

Over the last 21 years, the USA's Orphan Drug Act 1983 has enabled millions of people suffering from rare and life-threatening diseases to access relatively well-tolerated, safely formulated and effective drugs, leading the act to be considered 'one of the most successful US legislative actions in recent history' (Haffner et al, 2002). The European Union (EU) enacted orphan drug legislation in 1999 and it is expected that orphan drugs will be increasingly adopted into everyday clinical practice – not least as the genomic revolution leads to increasing stratification of diseases into distinct molecular subtypes. Against this background, this review introduces the concept of orphan drugs, the reasons these agents require specific legislation and the factors driving their increasing importance in clinical practice.

THE ORPHAN DRUG CONCEPT

The US Orphan Drug Act 1983 was established to encourage research into rare diseases in which the return on investment from the usual market was inadequate. The approach proved a resounding success. In the decade before the act became law, ten products were approved for rare diseases, defined as those conditions affecting fewer than 200 000 people in the USA. Since 1983, around 1100 drugs and biological products have been designated as orphan products for the purposes of research and development (R&D) and more than 230 of these have received Food and Drug Administration (FDA) marketing approval.

As a result, some 11 million patients in the USA have received treatment for an orphan disease (Haffner et al, 2002), thereby meeting clear and significant clinical needs. Approximately 85% of orphan drugs treat serious, life-threatening and usually chronic diseases. Indeed, 31% of orphan drugs treat rare neoplasms, such as ovarian cancer or hairy cell leukaemia. Metabolic disorders account for a further 11% of orphan drugs (Haffner et al, 2002). It is likely that few of these products would have been marketed without the benefits conferred by the Orphan Drug Act 1983.

The success of the US Orphan Drug Act 1983 inspired other countries to enact specific legislation to encourage research into diseases considered commercially unviable. For example, Japan and the EU (European Parliament, 1999) passed orphan drug laws in 1993 and 1999 respectively (Haffner et al, 2002). The European orphan drug regulations are based on a disease prevalence of 5/10 000 of the population (Pabst, 2001). The World Health Organization defines a rare disorder as affecting between 0.65 and 1 of every 1000 inhabitants (Lavandeira, 2002), whereas Japan and Australia sets the limit at 50 000 and 20 000 patients respectively in each country (Japanese population is about 127 million, Australian population is about 20 million) (Lavandeira, 2002). Based on this, there are around 5000 rare diseases (Haffner et al, 2002).

However, epidemiologically rare diseases are not necessarily either medical curiosities or commercially unviable. For example, haemophilia and other congenital coagulation disorders are rare disorders according to the above definitions, but research into new treatments for haemophilia is profitable for pharmaceutical companies (Lavandeira, 2002). Thus haemophilia is not an orphan disease. In other words, an orphan disease needs to fulfil two criteria. First, it is a rare

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condition in which there is currently no effective or well-tolerated treatment on the market. Second, the development of a new agent for the disease is not economically viable in the normal commercial context (Haffner et al, 2002).

The commercial context

The cost of bringing a drug to market is increasing rapidly (*Table 1*). DiMasi et al (2003) estimated that the 'out-of-pocket' costs for bringing a drug to market were US$403 million at prices for the year 2000. Development takes, on average, 90 months. So the capitalized cost, which included a discount rate of 11% to allow for the development time, was US$802 million. This is 2.5 times higher than the figure from a previous study from the same group published in 1991 (DiMasi et al, 1991) (*Table 1*).

Moreover, pharmaceutical R&D costs are growing at 7.4% annually above general inflation. This increase suggests that during 2001 out-of-pocket and capitalized pre-approval costs could be US$540 million and US$1.1 billion respectively (DiMasi et al, 2003). Such figures allow for 99.9% of drugs that fail either in the laboratory or during clinical trials (Anonymous, 2002).

The escalating cost partly reflects pharmaceutical companies' increasing emphasis on developing drugs to treat chronic and degenerative diseases (DiMasi et al, 2003). Traditional paradigms – for example, the over-secretion of gastric acid leading to ulcers – are giving way to multifaceted conditions, e.g. Alzheimer's disease and schizophrenia, which are driven by complex and dynamic interactions between genotype, phenotype and environment. Indeed, scientists' growing appreciation of the genetic determinants of disease encourages differentiation into molecularly defined subtypes, one factor driving the increasing importance of orphan drugs in clinical practice (Haffner et al, 2002). This will be discussed in more detail later.

Partly as a response to increased R&D costs, pharmaceutical companies increasingly concentrate on investigating potential 'blockbusters' – drugs that potentially generate over $1 billion in peak sales each year. Thus, pharmaceutical R&D tends to focus on common diseases. Just one in ten drugs becomes a blockbuster. Nevertheless, industry analysts believe that blockbuster drugs account for only around 30% of total drug sales (Milne, 2002). These drugs help support the other agents that do not make these types of return on investment. Approximately 90% of drugs generate less than $180 million a year, for example (Milne, 2002). As expected from the epidemiology, the return on an orphan drug is even less. The average US sales for biological products approved first as orphan drugs averaged $103 million (Milne, 2002).

As a result, orphan drug legislation encourages R&D with a number of financial and other incentives. For example, the FDA will not approve an application for a drug for the same indication by a different company for 7 years, protecting the orphan indication from generic competition. Indeed, agents not normally covered by patents, such as generics, can be designated as orphan drugs for specific indications (Haffner et al, 2002). Similarly, the EU awards grants, national or community fiscal support, lower or cancelled registration fees, exclusive rights for 10 years and a number of other initiatives to encourage research into orphan diseases (Pabst, 2001).

PAEDIATRICS AND ORPHAN DRUGS

Around half of orphan drugs are for children (Haffner et al, 2002), reflecting in part ethical and logistical problems associated with paediatric clinical trials, which have traditionally occurred late in drug development. The principles of clinical drug trials in adults are similar to those for paediatric patients, however, specific issues such as those related to growth and development need to be addressed in paediatric trials. Pharmacokinetics, pharmacodynamics and toxicity are often different in newborn infants from older children and adults. Moreover, liquid formulations are required for toddlers, while poor compliance can be a particular problem among adolescents. To complicate matters further, future EU directives covering informed consent in clinical trials will require both the child's and parent's assent.

The relative absence of paediatric clinical trials and specially approved medications encouraged the use of unlicensed and off-label drugs in children's wards worldwide (Nahata, 1997; Turner et al, 1997). More recent changes, such as the US Pediatric Rule 1998, which demands that paediatric data are collected for labelling purposes, as well as changes to the US FDA Modernisation Act 1997, might redress the balance. The challenge for the pharmaceutical industry is to develop child-friendly protocols that allow the sponsor to collect high-quality data.

TABLE 1.
Trends in costs per approved new drug

	Cost (US $million)*		
Year	**Preclinical**	**Clinical**	**Total**
1979	84	54	138
1991	214	104	318
2000	335	467	802

Adapted from DiMasi et al (2003). * prices from year 2000

Use of unlicensed medications in paediatrics

In the meantime, the level of use of unlicensed medications among paediatric patients is becoming the focus of increasing academic research and media attention. In neonatology, for example, up to 90% of newborn infants who require treatment may receive unlicensed medications (Conroy et al, 1999). Overall, 67% of drugs received by young children may be unlicensed (Conroy et al, 2000).

Since 1997, the FDA has suggested various initiatives to increase regulation of paediatric medication. European authorities have been much slower in introducing such legislation. Nevertheless, in 2002 the European Commission published a consultation document *Better Medicines for Children* (European Commission, 2002) to regulate the development of medicines for use in paediatrics and to ensure that the highest ethical criteria are met to protect children. By February 2002, only 50 drugs had been granted paediatric exclusivity, which is a small number compared to the number of agents launched by the pharmaceutical industry.

Nevertheless, the new legislation should encourage more paediatric drugs to reach the market. For example, the US Best Medicines for Children Act 2001 proposes establishing a $200 million fund for the study of off-patent drugs. The European Commission also proposes incentives for research, citing orphan medicines legislation as an example of an effective incentive. They also advocate an additional period of market exclusivity could be added to existing patent protection for drugs validated in children. Meanwhile, orphan drugs continue to help clinicians treat serious paediatric diseases.

TABLE 2.
Biotechnological products in development and approved: US data

Indication	Number of approved biopharmaceuticals	Number of biopharmaceuticals in development
AIDS/HIV	1	21
Autoimmune disorders	7	26
Blood disorders	16	3
Cancer and related	16	178
Diabetes	2	10
Growth disorders	10	4
Heart disease	7	15
Infectious diseases	28	47
Infertility	3	2
Transplantation	3	6
Other	10	113

AIDS/HIV = acquired immunodeficiency syndrome/human immunodeficiency virus.
Adapted from Walsh (2003)

REASONS DRIVING INCREASED USE OF ORPHAN DRUGS

Orphan drugs have already made a considerable clinical impact in specific conditions and are likely to be increasingly adopted into medical practice over the next few years for several reasons. First, biopharmaceuticals are becoming increasingly important sources of new medicines and many of these receive orphan drug designation. Indeed, over a quarter of new medicines approved in the major pharmaceutical markets since 2000 have been biopharmaceuticals. Moreover, some 500 new biopharmaceuticals (*Table 2*) are in development, many for cancers (Walsh, 2003) which are notable orphan diseases.

Around a fifth of orphan drug designations are for biotechnology products, with almost half of the biological products approved in the USA since 1982 being orphan products. For example, monoclonal antibodies represent around 5% of designated orphan products. These are used in the diagnosis and management of a range of cancers and autoimmune disorders. More recently, tissue-engineered products and gene therapy received orphan drug status (Haffner et al, 2002). The number of orphan biopharmaceuticals is set to grow, driven by advances in molecular biology.

Second, pharmacogenomic advances should also encourage orphan drug development. In theory, at least, pharmacogenomics allows the development of pharmaceuticals tailored to each patient's genetic profile as well as increasing stratification of diseases into distinct molecular subtypes. Certainly, understanding a patient's pharmacogenomic profile should allow researchers to predict those patients most likely to suffer an adverse event from certain drugs or those most likely to respond well to others. Furthermore, classification of disease subsets yields new molecular drug targets. This might mean that clinically homogenous conditions could be deconstructed into several orphan diseases (Haffner et al, 2002), each requiring specific treatment, with improved outcomes.

Third, there is a growing recognition that current research priorities do not adequately reflect true clinical need worldwide. According to the Global Forum for Health Research (Lee and Mills, 2000), less than 10% of research funds are directed to conditions that account for 90% of the global disease burden. Orphan drug legislation might provide an incentive for further research into tropical diseases, including malaria and schistosomiasis. Millions of people worldwide suffer from these conditions, but in developed countries they qualify as orphan diseases (Milne, 2002). The research will still fall under the legis-