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Quantifying emerging drugs for very rare conditions

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Summary

Background: EU legislation is encouraging pharmaceutical companies to develop drugs for rare conditions, but their often high cost, and potential for long-term administration has led to debate about their affordability and cost-effectiveness.
Aim: To investigate how many drugs are in development for very rare conditions.
Methods: We defined very rare conditions as having a prevalence of <1:50 000, and identified pharmaceuticals in phase II, phase III trials or pre-registration for these conditions using commercial databases.
Results: We identified 42 very rare conditions with at least one drug in late-stage clinical development, with a total of 113 drugs in development (17 for at least two indications). Sixteen drugs were pre-registration, 29 were in phase III development, 65 were in phase II development, one drug was both pre-registration and phase II for different indications and two drugs were in both phase II and phase III trials for different indications.
Discussion: Not all the drugs in development will reach the market, but it is likely that a significant number will do so. Affordability and methods to assess cost-effectiveness will need debate and clear national policy for decision-makers to follow.

Introduction

The EU defines an 'orphan' medicinal product as intended for the diagnosis, prevention or treatment of a life-threatening or very serious condition with a population prevalence of five cases or fewer per 10 000 population (⩽25 per 50 000). Within this category, a new sub-group has been suggested of 'ultra-orphan' products, for very rare conditions with a prevalence of <1 per 50 000 population.[1] In response to difficult development and marketing conditions, the Orphan Drug Act (ODA) was introduced in the US in 1983, with the EU following with similar regulations to offer pharmaceutical companies incentives to develop drugs for rare conditions in 2000 [http://www.emea.eu.int/]. Up to April 2005, 458 applications for orphan designation had been submitted to the European Agency for the Evaluation of Medicinal Products (EMEA), 381 had been designated as orphan products as of December 2006 and 35 orphan medicinal products had received a positive opinion from the EMEA Committee for medicinal products for human use by December 2006.[2–4]

With increasing emphasis on evidence of cost-effectiveness for all major new drugs entering health services, a process often called the fourth hurdle,[5] an important question is whether any exceptions should be allowed for potentially non cost-effective drugs. The 'rule of rescue', defined as the imperative to rescue identifiable individuals facing avoidable death, notwithstanding the potentially high opportunity cost of doing so,[6] has been used to make a special case for funding expensive drugs for very rare diseases such as enzyme replacement therapies for lysosomal storage disorders. The rule of rescue can conflict with the aims of cost-effectiveness analysis, and applying the rule could potentially channel an unequal proportion of resources to a few patients in desperate

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circumstances, at the expense of others.[7] The awarding of higher values to the health outcomes of those with rare disorders in economic analyses has been argued to be inequitable and unjust.[8] Furthermore, in taking isolated commissioning decisions, opportunity costs may be obscured, leading to inefficient decisions for the population as a whole.[9]

Just over half of the Citizen's Council of the National Institute for Health and Clinical Excellence (NICE) voted to pay premium prices for drugs to treat patients with very rare conditions.[10] The council went on to examine the balance between rescue and quality of life for all, reporting a majority decision that the rule of rescue should be applied in some situations.[11] Options for funding policies for rare diseases have been debated,[12,13] yet clearly the overall affordability of a policy favouring ultra-orphan conditions and the drugs to treat them will depend on the number of products in development.

Although there are no validated databases of rare conditions, of the 30 000 diseases known to the World Health Organization (WHO), estimates of the number classified as rare are as high as 6000.[14] Given that there are only 35 orphan drugs with positive opinions within Europe, there is great potential for the number of licensed orphan drugs to increase in the future, and for policy makers to be faced with increasing numbers of difficult decisions about funding these drugs. We explore whether there are sufficiently few drugs in development for very rare conditions to consider making special cost-effectiveness exceptions allowable. Our research focuses on drugs for very rare diseases, defined by an incidence or prevalence of <1 in 50 000, rather than orphan drug designation for non-profitability or for disease severity.

Methods

The process we used to identify very rare conditions with drugs in development is outlined in Figure 1.

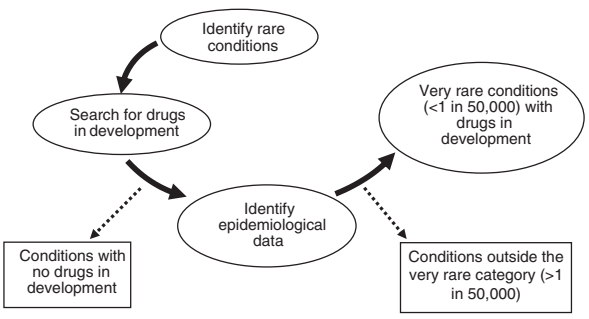

Figure 1. Identification of very rare conditions and drugs in development

A list of purported rare conditions was developed from the EU orphan drug register (as of August 2004), the USA National Organization for Rare Diseases ([http://www.rarediseases.org], accessed August 2004), the National Horizon Scanning Centre (NHSC) reports ([http://www.pcpoh.bham.ac.uk/publichealth/horizon/technology.htm], accessed August 2004) and the National Specialist Commissioning Advisory Group list of specialized services ([http://www.advisorybodies.doh.gov.uk/NSCAG/Services.htm], accessed February 2005). For each condition identified, any pharmaceuticals in late-stage clinical development (phase II or phase III clinical trials or where an EMEA licence application had been filed, i.e. pre-registration) were identified from the PharmaProjects database ([http://www.pjbpubs.com/pharmaprojects/index.htm], searched October and November 2004) and Adis R&D Insight databases ([http://www.adis.com/], searched November 2004 and April 2005).

For each condition with at least one drug reported in late-stage clinical development, prevalence data were identified for England and Wales using NICE outputs, NHSC reports, Clinical Evidence,[15] the Health Protection Agency [http://www.hpa.org.uk/], Cancer Research UK,[16] MEDLINE and Internet searches. If prevalence data could not be found, incidence data were used and the prevalence inferred. If epidemiological data were not found for England and Wales, data from the UK or countries with potentially similar epidemiology were used. Conditions with a prevalence of <1 per 50 000 population were categorized as very rare, and drugs in late-stage clinical development for these conditions were included.

Results

We identified 1095 purportedly rare conditions, finding 189 with at least one drug in late stage clinical development. Using epidemiological data, we identified 42 conditions in the 'very rare' category with at least one drug in late-stage clinical development (Table 1). For 26 conditions, no epidemiological data were identified, leaving these unclassified.

One hundred and thirteen drugs were in development for the identified conditions. Of these, 14 were in development for two indications and three were in development for three indications. Excluding drugs in development for multiple indications, 16 drugs were pre-registration, 29 were in phase III development and 65 were in phase II development (Table 2). One drug was both pre-registration and phase II for two different indications,

Table 1 The number of very rare conditions with drugs in late-stage clinical development

Category	Prevalence	Patients in England and Wales	Conditions with drugs in development	Total number of drugs
Very rare condition	<1 per 50 000 population	<1000	42	113

Table 2 Very rare conditions with drugs in development

Disease/disorder	Prevalence per 50 000 population	Incidence per 50 000 population	Origin of epidemiological data (country)	Number of drugs in development		
				Phase II	Phase III	Pre-registration
Acute lymphoblastic leukaemia		0.6	England and Wales	9	5	1
Amyloidosis		0.6	Unspecified	1	1	0
Anthrax		0.002	England and Wales	0	0	1
Aplastic anaemia		0.1	UK	1	0	1
Aspergillosis		0.5–1	USA	2	1	1
Becker muscular dystrophy	0.3–0.4		Canada, Italy, Norway, Yugoslavia	1	0	0
Bronchopulmonary dysplasia		0.9	USA	1	0	0
Brucellosis		0.02	USA	0	0	1
Carcinoid syndrome		0.75	Unspecified	0	1	0
Cholera		0.01	England and Wales	0	1	2
Chronic granulomatous disease	0.01–0.04		USA, Australia, Sweden	0	1	0
Chronic inflammatory demyelinating polyneuropathy	0.95		Australia	1	0	0
Chronic myelogenous leukaemia		0.5	England and Wales	21	4	1
Eosinophilic pneumonia		<0.05	Unspecified	1	1	0
Fabry disease	0.08–0.19		England and Wales	1	0	0
Fukuyama muscular dystrophy	<0.39		Italy	1	0	0
Gaucher's disease	0.19		England and Wales	1	0	0
Hairy cell leukaemia		0.15	England and Wales	0	0	1
Hermansky-Pudlak syndrome	0.05–0.1		International	1	0	0
Hunter's syndrome	0.06		England and Wales	0	1	0
Hyperoxaluria	0.05		Unspecified	1	0	0
Idiopathic myelofibrosis		0.2	Sweden	1	0	0
Idiopathic thrombocytopenic purpura		0.08	England and Wales	3	0	0
Legionnaires' disease		0.3	England and Wales	0	0	1
Leishmaniasis		0.06	England and Wales	0	2	3
Leprosy		0.03	England and Wales	0	2	1
Mantle cell lymphoma	0.15–0.77		England and Wales	8	1	0
Maroteaux-Lamy syndrome	0.01		England and Wales	0	0	1

(continued)

Table 2 Continued

Disease/disorder	Prevalence per 50 000 population	Incidence per 50 000 population	Origin of epidemiological data (country)	Number of drugs in development		
				Phase II	Phase III	Pre-registration
Medulloblastoma		<0.02	England and Wales	2	1	0
Motor neuron disease		0.95	Europe	5	1	0
Niemann-Pick disease	0.02		USA	0	1	0
Osteosarcoma		0.45	England and Wales	5	3	0
Paediatric cardiomyopathy		0.57	USA	2	2	0
Pemphigus	0.16		England and Wales	1	1	0
Pompe's disease	0.04		Netherlands	0	0	1
Primary pulmonary hypertension		0.05–0.19	England and Wales	2	2	2
Pulmonary alveolar proteinosis	0.5		USA	1	0	0
Severe combined immunodeficiency	0.66–1		USA	1	0	0
Sydenham's chorea		0.25–1	USA	3	0	0
Tay-Sachs disease	0.25		Australia	0	1	0
Thrombotic thrombocytopenic purpura		0.11	UK	3	0	0
Xeroderma pigmentosum	0.2		International	1	0	1

and two drugs were in both phase II and phase III trials for six different indications. Of the 42 very rare conditions, 15 conditions had drugs that were pre-registration, 20 conditions had drugs in phase III trials and 28 conditions had drugs in phase II trials.

Discussion

We identified 42 very rare conditions with at least one drug in late-stage clinical development, and a total of 113 drugs in clinical development, 17 of which were in development for several indications.

A major limitation of work in this area is in the categorization of very rare conditions. From our epidemiological searches, it was apparent that the lists of purported rare diseases were not always accurate, as some diseases were more common, with a prevalence greater than the European orphan definition. The lack of up to date, good-quality prevalence data for England and Wales for some conditions may have led to some misclassification. Twenty-four of the 42 very rare conditions had to be categorized using incidence rather than prevalence data. In the case of chronic myelogenous leukaemia, due to its chronic nature, the prevalence would be expected to be much higher than the incidence of 0.5 per 50 000 population, placing it potentially outside the very rare category. This may hold true for other chronic diseases categorized by incidence. For a further 26 conditions, no epidemiological data were identified, leaving these conditions unclassified. Some of the 26 conditions may fall within the very rare prevalence range.

Of the 42 very rare conditions with drugs in development, over a third are either lysosomal storage disorders, cancer or cancer-related diseases. There are seven lysosomal storage disorders (LSDs), with a combined potential patient group size of between 690 and 810 patients in England and Wales. Of the seven treatments in development for the LSDs, four are emerging enzyme replacement therapies (ERTs), a drug class which has been the focus of recent debate about ultra-orphan drugs, due to their premium prices.[9] Assuming these ERTs have an annual cost of about £100 000 per patient per annum,[8] and that there are an estimated 320 patients with the relevant LSDs, treating these patients with emerging ERTs could cost the NHS over £32 million per year. If all LSDs were to have ERTs developed, the cost to the NHS could be much higher.

There are eight cancer or cancer-related diseases potentially within the very rare category with technologies currently in development. Two treatments have been recently registered for two of these cancers. Imatinib (Glivec) is registered for chronic myelogenous leukaemia (CML) and costs between £1560 and £3110 per month (£18 950 and £37 900 per patient per annum) for as long as the patient continues to benefit.[17,18] Clofarabine (Evoltra), registered for treatment of acute lymphoblastic leukaemia in children, costs between £7200 and £18 000 for three cycles. Assuming a total patient population for the eight cancer and cancer-related conditions with drugs in late-stage development of between 3010 and 3670 in England and Wales, and assuming any new rare oncology products for these conditions have a similar cost to imatinib and clofarabine, treating these patients with new products could cost the NHS between £21.7 million and £139.2 million per year. This cost may be additional, or may be offset by reductions in the use of other treatments.

This research highlights that there are potentially at least 113 drugs for very rare conditions nearing the market. Of the 42 very rare conditions with at least one drug in late-stage clinical development, some of these conditions may potentially fall within the orphan category defined by non-profitability or disease severity, in addition to having a prevalence of less than 1 per 50 000. Although very rare conditions individually equate to small patient numbers, there are cumulatively a large number of patients with these conditions. The potentially high cost of new drugs for rare conditions could result in a disproportionately large impact of these conditions on health service budgets. In the long term, blanket acceptance of these high costs without detailed debate around the rule of rescue and relative cost-effectiveness could set a precedent which is difficult to sustain. If the case for special treatment for orphan conditions is to be made, it must be fully informed of these risks and open to long-term re-evaluation.

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