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Orphan Drugs for Adoption: The European Approach

Nigel Nicholls Postgraduate Student (Pharmaceutical Medicine)
University of Surrey, Egerton Road, Guildford, Surrey GU2 5XP, UK, and Product Affairs Manager, Orphan Europe (UK); email: nn.uk@orphan-europe.com

Abstract

This paper seeks to review the current situation in Europe with regard to orphan drugs in the light of some of the developments that have occurred in the USA in this area. The recently adopted EU legislation is discussed as is the impact this may have on the discovery and delivery of new and much needed drugs for orphan indications. The challenges facing the pharmaceutical industry and the opportunities and benefits to be gained are examined. A survey conducted by the author of a sample of pharmaceutical companies and their attitudes towards orphan drug developments suggests that much more still needs to be done if licensed treatments for orphan disorders are to become more commonplace.

Key words: Orphan drugs – Legislation – Europe

Introduction

It has been estimated that there are over 5000 conditions or diseases which can be defined as 'orphan' or rare[1,2]. However, although there are many orphan diseases, each has very small numbers of patients, so that traditionally a lower priority has been allocated by both academia and industry for the development of the drugs required to treat these diseases. Legislation was first implemented in the USA in 1983, and 10 years later in Japan, to encourage pharmaceutical manufacturers to become more involved in orphan drug development[3]. In the USA an orphan drug is one which is intended for the diagnosis or treatment of diseases with a prevalence of up to 200 000 persons. The legislation has been highly successful in terms of stimulating marketing and development of orphan drugs. As of October 1999, 16 years after the start of legislation, there are over 190 orphan drug products on the US market. It was estimated, in a presentation by Dr Haffner of the FDA, that some nine million people have benefited as a direct result of the legislation (meeting on Orphan Drugs: Research, Development and Registration, Madrid, 2–3 December, 1999).

European legislation for orphan medicinal products, in discussion since the mid-1980s, was finally ratified by the European Parliament on the 16th December 1999. It came into force having been published in the Official Journal on the 22nd January, 2000[4]. The question remains as to how the European pharmaceutical industry and regulators respond to the challenge presented by this legislation. Will orphan drugs be developed at sufficient speed to ensure patient groups receive treatments that are urgently needed, at the same time ensuring that these treatments are properly tested and regulated?

Background

The EU Orphan Drug Regulation covers any medicinal product to treat, diagnose or prevent a disease which fits the definition of 'orphan'. While acknowledging that orphan medicinal products could be defined using either epidemiological or economic criteria (i.e. in the latter case, products with a low likelihood of recouping the costs of development), the decision in the Regulation has been '*that an epidemiological criterion, based on prevalence, be used initially*'. The low prevalence definition for an orphan drug in the Regulation is proposed as meaning a drug for a disease affecting less than 5 per 10 000 persons in the European Community.

The Regulation's main aim is to encourage the EU pharmaceutical industry to become more involved in developing orphan products for rare disorders. It hopes to achieve this by providing the incentives outlined in Table 1.

Table 1. Incentives for manufacturing orphan medicinal products in the EU	
Incentives in the EU Regulation	**Manufacturers' entitlement**
Designation as an orphan medicinal product	Entitles the holder to all incentives and registration in the Community Register of Orphan Medicinal Products
Protocol assistance	Advice can be requested on the various tests needed to demonstrate quality, safety and efficacy. Should ensure that the product is approved in a more timely manner
Access to the centralised regulatory procedure and possible fee waiver	Assessment of the product by the centralised procedure should allow the product faster approval in all EU countries than approval by the mutual recognition system. Fees for assessment of products may be waivered in part or whole
10 years' marketing exclusivity	No other marketing authorisation for the product's registered indication will be granted or allowed within a ten-year period. A review will take place at the end of year five to ensure the criterion the product was granted the designation for are still being met

In recognition that this has been a much-neglected medical area, with small numbers of patients in each of a large number of disorders, the EU Orphan Drug Regulation does not attempt to sub-classify the diseases in any way. It is, nevertheless, interesting to note that around 80% of the known orphan diseases have a genetic component and that clinical symptoms are often displayed in early childhood[1]. The development of orphan medicines in the EU therefore has the potential to effect the greatest good in the treatment of children, where there is a lack of licensed medicines for many orphan metabolic diseases. In some cases treatments have been discovered which have never been fully developed. Often chemicals, which are not of pharmaceutical grade, that have had no toxicological testing or any formal clinical studies performed, are used. Examples of these, together with the chemical used (in parentheses), include: Menke's disease (copper histidine), tetrahydrobiopterin synthesis defects (tetrahydrobioptrin) and lactic acidosis due to dehydrogenase complex defects (dichloroacetate). The EU Orphan Drug Regulation may be the spur that ensures that further research is now undertaken in these neglected areas.

Children are not only the most affected group for rare diseases but are also often effectively 'therapeutic orphans' for other reasons, as was discussed by Turner *et al*. in 1997[5]. The development of drugs for the more common diseases, which affect large numbers of the population, traditionally follows a route of primary development for adults. If children are a much smaller market, companies are actually loathe to continue the formal development work to include the studies required to show that the drug is safe to use in children.

In response to this situation, paediatricians and pharmacists formed a working party in 1991 under the direction of Professor Sir David Hull. The group has striven for the appropriate development, monitoring and marketing of drugs for children; both those for orphan diseases and those required to treat children which have only been fully tested in adults. As a result of this campaigning role, *Medicines for Children – A Paediatric Formulary* was published in July 1999[6]. The hope is that this will be a guide to best practice in this area, thereby encouraging more uniform treatment of certain diseases and identifying key drugs that are worthy of further research work.

Despite these efforts, it is unlikely that any significant progress will be made without industry playing its full part in the development of orphan drugs. It is encouraging that US pharmaceutical manufacturers are now required to justify to the FDA why children are not included when developing a new chemical entity which could also treat children[7]. Within the rare diseases field the tide is slowly changing but much remains to be accomplished. Currently of the 1425 trials registered by the Rare Diseases Alliance in the USA, only 194 were being sponsored by industry.

Industry Involvement

The main thrust of the EU Orphan Drug Regulation is to encourage industry to develop drugs for rare disorders. In order to aid this process, various incentives have been incorporated into the legislation. In order to gain an impression of the preparedness and enthusiasm of the UK pharmaceutical industry for this legislation, a survey of 40 pharmaceutical companies in the UK was undertaken. The survey also attempted

to establish whether any differences in attitude towards orphan drug development exists between the traditional pharmaceutical companies and the emerging biotech companies.

Evaluating Orphan Drug Development in the UK

A Likert type, self-administered questionnaire was devised as the research instrument to poll a number of companies to gauge how much orphan drug development was taking place in the UK. The questionnaire was closely modelled on a similar survey conducted in the USA in 1986[8]. Forty companies were randomly chosen: 20 from the 'mainstream' and 20 from the 'biotechnological' sector in the UK.

The questionnaire sought to ascertain whether the companies surveyed were currently involved in orphan drug development, to what stage that development had progressed, and the number of products being researched. Of those companies not involved in any development, the survey attempted to find out the reasons behind that decision. It was felt important to establish whether this was because of lack of resources, both manpower and fiscal, or whether it was thought to be strategically undesirable. The final questions of the survey dealt with the proposed incentives in the EU Orphan Drug Regulation and the impact these might have on the companies' attitudes to orphan drug development.

Results of the Survey

The response rate to the questionnaire was 26/40 (65%): 15 from biotech and 11 from mainstream companies.

When questioned about development, 9 of the 26 (35%) respondents were engaged in orphan drug development while the remaining 17 (65%) were not. The results for biotech and mainstream companies are shown in Figure 1.

Although no statistical validity can be attached to the figures, it is interesting to note that a greater proportion of biotech companies 6/15 (40%) to mainstream companies 3/11 (27%) were engaged in orphan drug development.

The reasons for not developing orphan medicines were elicited in question two of the survey. Of the 17 companies who stated they were not developing orphan drugs, two gave no reason for this and were therefore not included in the results which are presented in Figure 2.

The majority of both biotech and mainstream companies reported that it was not part of their mission statement to develop such medicines. Rather surprisingly, more mainstream companies than biotech companies put lack of company resources and poor profitability of the medicines as key factors.

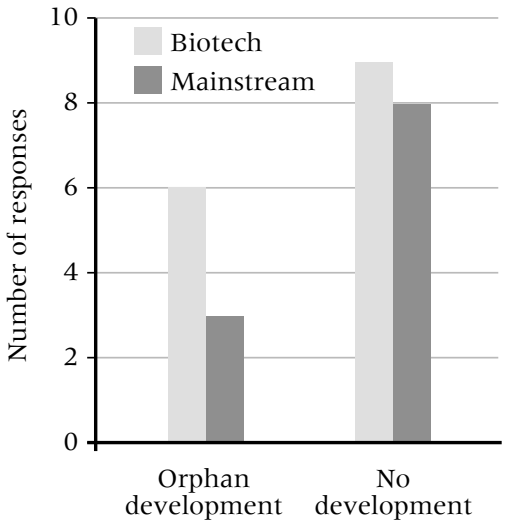

Figure 1. Orphan drug development

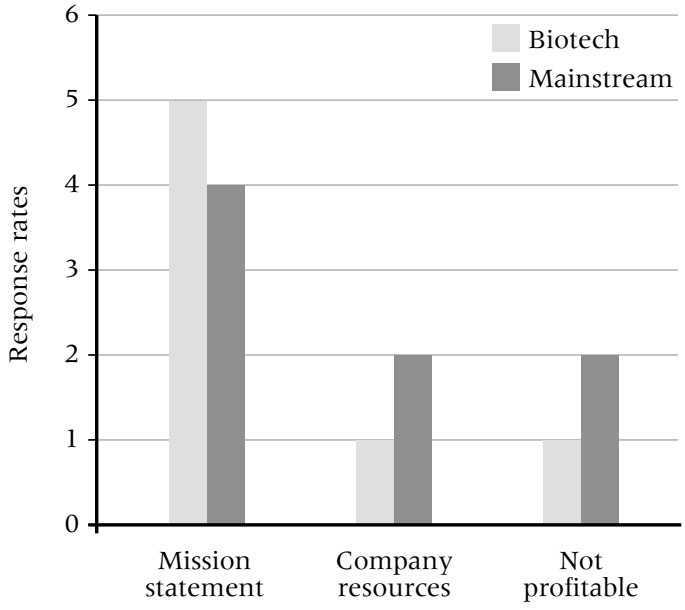

Figure 2. Reasons given for not developing orphan drugs

Discussion

Although awareness has been increased in the EU to stimulate research into rare diseases, much of the effort has come from patient groups and non-governmental bodies representing childhood diseases. In the UK particularly, the organisations 'Children Living with Inherited Metabolic Diseases' (CLIMB, formerly RTMDC) and 'Contact-a-Family', deserve special mention in this regard (Table 2). However, in order for more treatments to be developed, the pharmaceutical industry in the EU must be woken up to the challenges and opportunities ahead.

The brief survey outlined above paints a picture of indifference in some quarters, but also gives encouraging signs that some companies are taking, and it is hoped, will continue to take, practical steps to ensure that orphan drugs are developed in the EU. The challenge remains to convince more companies to recognise the gains that they can accrue, in terms of both increased and improved public image, and also in monetary returns from participating in orphan drug production. The challenge is a difficult one. The orphan drug sector is seen as being inherently unprofitable and much work needs to be done to counter this argument.

It may be that many of the larger pharmaceutical companies will continue to find orphan drug development unattractive, despite the incentives outlined in the EU Orphan Drug Regulation. Although the biotech sector within the EU is not yet as established and as profitable as in the USA, it is growing rapidly. Such companies may find that there are now more opportunities offered to them to explore orphan drug development. The opportunities may arise not only because of the incentives proposed in the EU Orphan Drug Regulation but also by larger pharmaceutical companies licensing or selling 'unpromising' drug candidates.

Whether the legislation will be effective within the EU remains to be seen. There can be little doubt, however, that there are many orphan diseases ready for adoption by pharmaceutical companies if only some momentum can be brought to the cause. To extend the analogy of real life, adoption of pharmaceuticals may not be too far-fetched when it is realised that legislation only is not enough, but that a change of hearts and minds towards orphan drug development is required.

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Table 2. Contact addresses

CLIMB	**Contact-a-family**
The Quadrangle Crew Hall Weston Road CREWE Cheshire CW1 6UR Tel.: 01270–259375 Fax: 01270–250244	170 Tottenham Court Road LONDON W!P 0HA Tel.: 0171–383 3555 Fax: 0171–383 0259