The latest orphan drug designations and the Commission Communication on Regulation (EC) 141/2000

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Abstract

The implementation of Community Regulation on orphan medicinal products in the European Union in April 2000 has resulted in a deluge of applications for designation of medicinal products as orphan for rare diseases. By April 2004, the Committee for Orphan Medicinal Products had already given positive opinion on 63 per cent of the 316 applications considered by them. A significant number of these positive designations have already matured into full marketing authorisations. Three major reasons – failure to meet prevalence or significant benefit criteria or provide evidence of biological plausibility – have equally contributed to either the negative opinion on or the applicants withdrawing the remaining applications. In July 2004, the European Commission issued a communication setting out its position on certain matters relating to the implementation of the designation and market exclusivity provisions. The Commission, the European Medicines Agency (EMEA) and the Committee for Orphan Medicinal Products (COMP) continue to be proactive and provide as much guidance and incentives as practical, engaging themselves with sponsors, patient groups and academia. As experience builds up and issues are clarified, there are expectations that the Community Regulation on orphan medicines will prove to be a spectacular success.

Keywords: *biological plausibility, Commission Communication, orphan medicinal products, prevalence, protocol assistance, significant benefit*

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INTRODUCTION

The introduction of orphan drugs legislation in the European Union (EU) in April 2000 has witnessed great strides in the designation and approval of medicinal products for the treatment of orphan diseases. This review summarises the European experience in the first four years following the implementation of this legislation, focusing on some of the major deficiencies identified in the applications for designation, and on some complex issues regarding the criteria for designation that required clarification by the European Commission (EC).

There are two primary pieces of orphan drug legislation in the EU. The first is the Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16th December, 1999, on orphan medicinal products. This is concerned with the purpose, definitions, criteria for designation, establishing the Committee for Orphan Medicinal Products (COMP), procedures, provision of protocol assistance, access to centralised procedure without further justification for community marketing authorisation, market exclusivity and other incentives. The other is the Commission Regulation (EC) No. 847/2000 of 27th April, 2000, laying down the provisions for implementation of the criteria for designation and definitions of the concepts of 'similar medicinal product' and 'clinical superiority'. These regulations and other information with

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regard to orphan medicines are available from the EC website.[1]

Applications have far exceeded the expectations

The reader no doubt appreciates that it is the Committee that issues an Opinion and the Commission that issues the Decision that is binding on all the member states. Once the Commission issues a Decision designating a product as orphan, it qualifies for all the incentives provided for in the Regulation. Apart from ten years of market exclusivity (which may be reduced to six years if a member state can demonstrate that the product is sufficiently profitable not to justify the maintenance of market exclusivity), other major incentives provided by the legislation include fee waivers and access to other Community incentives. The fees waived or heavily discounted include fees for applications for protocol assistance, marketing authorisations and renewals and also for inspection.

Oncology, metabolic disorders and immunomodulators have dominated the field

The COMP held its first plenary meeting in April 2000. The number of applications for designation received and determined has far exceeded initial expectations. This unexpected surge of applications enabled the COMP to identify rapidly a number of complex issues that were not fully elaborated upon in the Regulation.

CURRENT EXPERIENCE

Small-to-medium sized companies have been the key players

Following its first plenary meeting in April 2000, the EMEA has received 261 and 344 applications for designation by April 2003 and April 2004 respectively, thus averaging about 86 applications per year. The outcomes of these applications are summarised in Table 1. The overall pattern of outcomes of the applications for designation during the fourth year was essentially similar to that seen during the first three years of the COMP operations.

Of the 147 medicinal products with positive opinion during the first three years, oncology (31 per cent), metabolic (13 per cent) and immunology (13 per cent) were the main therapeutic areas targeted by these medicinal products. Indications relating to musculoskeletal and nervous systems (both together 9 per cent) and cardiovascular and respiratory systems (9 per cent) were the next two largest categories. The average prevalence of the conditions was <1 per 10,000 in 61 per cent and between 1 and 3 in another 31 per cent of these applications.

Innovative products represented two-thirds of the applications and 50 per cent of the designations. The majority of the products applying for designation were of chemical origin and products originating from biotechnology (including gene therapy, antisense therapy, monoclonal antibodies and DNA-derived products) constituted about a third of the applications and designations. There were five products of animal origin, two of human origin and two of plant origin.

In roughly two-thirds of the cases, the sponsors of applications for designation have tended to be small-to-medium sized companies with a limited portfolio of products. A few applications have also originated from individuals or from academic institutions. Whereas most sponsors held only one designation, there were a few with more than three designations.

Table 1: Status of the applications submitted for designation

	3 years to April 2003	4 years to April 2004
Total number of applications submitted	261	344
Applications with positive COMP Opinion	147 (68%)	200 (63%)
Applications withdrawn	64 (30%)	111 (35%)
Applications with negative COMP Opinion	4 (2%)	5 (2%)
Under validation or evaluation	46	28

Percentages shown in parentheses represent proportion of all applications determined by COMP as positive or negative and those withdrawn (and not of the applications submitted to the Secretariat).

REASONS FOR WITHDRAWAL OF APPLICATIONS

Majority of applications withdrawn have failed on only one criterion

In order to avoid unwanted commercial publicity associated with a negative opinion, applicants have most frequently preferred to withdraw their applications when a negative COMP opinion is imminent. Although the rate of withdrawal of applications for designation was a little higher during the fourth year than in the preceding three years (35 versus 30 per cent), the reasons that led to their withdrawal were not substantially different during the two periods in qualitative terms, the differences being only quantitative.

Three leading causes of failure are prevalence, significant benefit and medical plausibility

Failure at validation results most frequently from inadequate or incomplete provision or documentation of all the components required. During the first three years, 13 (20.3 per cent) of the 64 applications withdrawn had failed during validation and 51 during evaluation by the COMP. During the four year period to April 2004, 21 (18.9 per cent) of the 111 applications withdrawn had failed during validation. This would suggest only a marginal improvement in the quality of submissions to the Secretariat. Of the remaining 90 applications, 84 had been withdrawn during first evaluation by the COMP, 5 during an appeal and 1 following a negative opinion. In order to improve the prospects of success in future applications, it is worth examining the main reasons that led the applicants to withdraw these applications during the two periods. The synthesis of these data has been a complicated process because issues are often multifactorial and interrelated but Table 2 summarises the essential information. It is evident that the proportion of medicines failing on single criterion diminished in the fourth year as the sponsors gained more experience with the Regulation.

The therapeutic areas that concerned the 111 applications withdrawn during the four year period were oncology (41 per cent), musculoskeletal or neurological (13 per cent), metabolic (8 per cent) and anti-infectives (7 per cent). The remaining 31 per cent concerned miscellaneous indications. Of these 111 applications, 13 were later resubmitted: 6 were successful with a positive opinion, 2 were given a negative opinion, 3 were withdrawn because of an imminent negative opinion and 2 were still under evaluation as of April 2004.

It is evident that the main reasons for failure are inability to fulfil the criteria for designation that include prevalence and assumption of 'significant benefit'. Another major reason is inadequate

Table 2: Reasons for withdrawal of applications for orphan designation

	3 years to April 2003	4 years to April 2004
Number of criteria	**Data available on 64* withdrawals**	**Data available on 84† withdrawals**
Only one criterion of designation	61%	39%
Two or more criteria of designation	36%	46%
Proof of concept	3%	7%
Other	–	7%
Specific criteria	**Data available on 51† withdrawals**	**Data available on 90‡ withdrawals**
Prevalence	59%	39%
Significant benefit	42%	31%
Medical plausibility	40%	30%
Life-threatening or debilitating nature of condition	6%	2%

* Includes all withdrawals (13 at validation plus 51 during evaluation phases).
† Includes withdrawals during evaluation by COMP.
‡ Includes 84 withdrawals during first evaluation by COMP *and* 5 on appeal and 1 following a negative opinion.

Seek protocol assistance early and frequently

demonstration of biological or medical plausibility – that is, providing adequate evidence on how the medicinal product proposed for designation acts and modulates the pathway of pathogenesis or may modify the outcome of the condition to be designated ('proof of concept').

ORPHAN PRODUCTS APPROVED BY CHMP

Following designation, applicants are commonly encouraged by the COMP to seek protocol assistance so that these medicines are developed in a systematic and scientific manner, thereby maximising their prospects of approval by the European Committee for Medicinal Products for Human Use (CHMP). In order that the issues raised by the COMP are fully addressed during requests for protocol assistance, the COMP is represented on Scientific Advice Working Party by at least two of its members. Of the 200 medicinal products that had received positive opinion by the COMP as of April 2004, 41 had matured to the point of submission of applications for marketing authorisations and the CHMP had given positive opinion for grant of marketing authorisations to 17 applications (Table 3) and an additional 17 were under evaluation. A further 7 applications for marketing authorisations were either given a negative opinion or withdrawn by the applicant.

Data sets for marketing authorisation applications have ranged widely

The 17 applications that had been approved by the CHMP as of April 2004 had included data sets ranging from as few as 12 to as many as 1,064 patients for efficacy analysis and from as few as 20 to as many as just over 4,600 patients for safety analysis. The normal standards of safety, quality and efficacy that prevail for non-orphan medicinal products have not been compromised in a rush to approve these orphan products. However, highly promising or efficacious products have been approved subject to various post-approval commitments for additional data. This is an important point to emphasise since patients with rare diseases are just as entitled to medicines tested to the normal highest standards.

For the record, three additional products have also received positive CHMP opinions as of December 2004. These are WILZIN for the treatment of Wilson's disease, PRIALT for the

Table 3: Orphan medicinal products given positive opinion by CHMP (to April 2004) following introduction of the EU orphan medicinal products regulation

Product	Active ingredient	Route of administration	Summary indication
Fabrazyme	Agalsidase beta	IV infusion	Fabry's disease
Replagal	Agalsidase alpha	IV infusion	Fabry's disease
Glivec CML	Imatinib mesilate	Oral	Chronic myeloid leukaemia
Trisenox	Arsenic trioxide	IV infusion	Acute promyelocytic leukaemia
Tracleer	Bosentan monohydrate	Oral	Pulmonary arterial hypertension
Zavesca	Miglustat	Oral	Gaucher's disease
Somavert	Pegvisomant	SC injection	Acromegaly
Carbaglu	Carglumic acid	Oral	Hyperammonaemia due to *N*-acetylglutamate synthase deficiency
Busilvex	Busulfan	IV infusion	Haematopoietic progenitor cell transplantation
Aldurazyme	Laronidase	IV infusion	Mucopolysaccharidosis
Ventavis	Iloprost	Inhalation	Pulmonary arterial hypertension
Xagird	Anagrelide hydrochloride	Oral	Essential thrombocythaemia
Onsenal	Celecoxib	Oral	Familial adenomatous polyposis
Litak	Cladribine	SC injection	Hairy cell leukaemia
Photobarr	Porfimer sodium	IV infusion	Barrett's oesophagus
Lysodren	Mitotane	Oral	Adrenal cortical carcinoma
Pedea	Ibuprofen	IV infusion	Patent ductus arteriosus

SC = subcutaneous, IV = intravenous.

treatment of chronic pain requiring intraspinal analgesia and ORFADIN for the treatment of type 1 tyrosinaemia.

COMPLEX ISSUES FOR CLARIFICATION

Arising from the unexpected surge of applications, the COMP was able to identify rapidly a number of complex issues that required further clarification. These included determining:

COMP has identified many complex issues

- the prevalence of recurrent conditions (recurrent episodes of a condition in the same patient);
- the prevalence of a condition when the medicinal product is intended for diagnostic or preventive purposes (for example a product for imaging purposes or for immunisation);
- whether an indication claimed by two products is the 'same' when the wording differs only slightly and what criteria does one apply to conclude that the two indications are the same;
- whether two medicinal products act by the same mechanism of action;
- whether two medicinal products contain a similar active substance;
- the level of evidence ('proof of concept') required to support the biological or medical plausibility of the activity of a medicinal product in the condition to be designated;
- the practice and the validity of fragmenting or subsetting a major disease into a large number of entities (so-called 'salami slicing'), each subset thereby fulfilling the criterion of low prevalence set by the Regulation – these practices are often not well supported and have lacked any scientific credibility;

Salami-slicing needs scientific credibility

- pursuant to Article 3(1)(b) of Regulation (EC) No. 141/2000, the criteria for 'significant benefit' when there are a number of existing authorised therapies but no widely accepted 'gold standard';
- an application for orphan designation of a medicinal product when its active ingredient has been approved in only a few member states of the Community. In brief, what constitutes a satisfactory method authorised in the Community?

More issues will no doubt emerge in the future as the nature of active substances and the conditions to be designated assume greater complexity. With regard to determining whether two products contain similar active substance, act by the same mechanism of action or have the same therapeutic indication, the Commission has issued a draft guidance note for public consultation. This can be accessed at the EC website.[1]

As stated earlier, the three main reasons for failure of an application for designation concern prevalence, assumption of 'significant benefit' and biological or medical plausibility.

Prevalence

Applicants are required to show that the condition affects no more than 5 per 10,000 of the Community population or provide evidence of insufficient return to justify the investment necessary to develop a product regardless of the prevalence of the condition.

The fundamental problems, identified by the COMP to adversely affect prevalence calculations, arise from:

- Poor characterisation of the condition to be designated and therefore of the potential target population. For example, this has frequently been the case when the condition to be designated is a lymphoma, convulsive disorder, organ-specific malignancy, specific stage of a malignancy or genetically and biochemically distinct subset of a clinically heterogeneous disorder.

- Failure to distinguish between prevalence and incidence; for example, when a patient experiences more than one episode of a condition.

- The source of the epidemiological data from which prevalence is calculated. The preferred option is the EU data, although the use of non-EU data may be acceptable if justified. In addition, problems frequently arise when the Committee is not content with the statistical treatment of the (usually published) available epidemiological data on prevalence.

Calculation of prevalence is critical – consult the guidance

The calculation of prevalence is complicated when orphan designation is sought for a medicinal product that is intended for diagnosis or prevention (as opposed to treatment) of a condition. The target population in these circumstances needs to be carefully delineated. The Committee is especially reluctant to accept as a distinct condition a combination of two discrete diseases (each of a completely different aetiology) that simply co-exist more frequently; for example, hepatitis C in patients with HIV disease or tuberculosis in patients with diabetes.

In order to assist applicants, the Committee has now adopted a document entitled 'Points to consider on the calculation and reporting of prevalence of a condition for orphan designation'. This and other information with regard to orphan medicines can be accessed under 'Orphan Medicinal Products' at the EMEA website.[2]

Assumptions of significant benefits are closely scrutinized by COMP

With regard to applications for orphan medicinal product designation based on insufficient returns to justify investment, the COMP has on a rare occasion witnessed some unconventional practices of calculating costs and revenues. It may be helpful to remember that although the COMP is essentially a scientific advisory committee, it does have access to, and is able to draw on, the expertise of, highly competent accountants, commerce lawyers and pharmaco-economists. To date, no drug has received a positive designation on the basis of insufficient return. One single application that was submitted was later withdrawn.

Significant benefit

The notion of 'significant benefit', enshrined in Article 3(1)(b) of Regulation (EC) No. 141/2000, embraces 'a clinically relevant advantage or a major contribution to patient care'. A clinically relevant advantage may include improved efficacy and/or safety, a claim most frequently made by applicants based on a novel mechanism of action. Among other factors, a major contribution to patient care could include a new route of administration, a new formulation and potential for self-administration by the patient. During the first three years, assumption of 'significant benefit' over existing therapies had been included in about two-thirds of the applications. In nearly 20 per cent of these, 'significant benefit' related to a major contribution to patient care.

Regardless of whether the arguments have been convincing enough for a positive opinion by COMP, it is acknowledged that the majority of applicants have presented well-thought-out arguments (at least as they perceive them) to support their assumptions of 'significant benefit'. However, the applicants have not infrequently also presented rather esoteric or spurious arguments. Some sponsors have made claims of 'significant benefit' from enhancement of the pharmaceutical quality of a product even when this is only in compliance with the relevant CHMP guidelines. Others have presented arguments of supposedly improved safety of recombinant products relative to plasma or blood-derived products even when there are no documented safety concerns with the latter. The COMP has rejected such arguments when real (as opposed to hypothetical) safety concerns have not been, or cannot be, documented.

When the criteria for prevalence and

A wide range of established scientific data can support biological or medical plausibility

the life-threatening or chronically debilitating nature of the condition are met, a medicinal product may be designated as orphan without any further burden on the applicant if there exists no 'satisfactory' method authorised in the Community. It should be evident, therefore, that the notion of 'significant benefit' applies only when there is a 'satisfactory' method that has been authorised in the Community. Although the Regulation does not define what constitutes 'satisfactory' method, it explicitly excludes 'off-label use' when it uses the term 'authorised'.

Biological or medical plausibility

Since orphan diseases are rare, it is vital that scarce clinical trial resources are utilised effectively during the development of an orphan medicinal product. This requires the applicant to secure a positive opinion for designation as early as possible in order to take advantage of the facilities of scientific advice and protocol assistance at heavily discounted rates. The downside of this apparently pragmatic approach is that an application may be too premature. There may not be adequate documentation of the mechanism of action of the medicinal product and how this mechanism fits into the pathway of pathogenesis of the condition and/or the pharmacological modulation of its outcome ('proof of concept').

Apply early but avoid premature applications

The COMP has accepted a wide variety of data and arguments to support biological plausibility. These range at one extreme from purely intuitive arguments based on robust data on the mechanism of action of a drug and how this mechanism may modify the disease to *in vivo* clinical data in a sizeable number of patients at the other extreme. When the pathogenesis of a condition to be designated can be pinpointed to dysfunction of a discrete pharmacological target as, for example, in many metabolic diseases, arguments based on mechanism of action may be sufficient. In contrast, when little or nothing is known about the mechanism of action of the drug, the pathogenesis of the condition or when the scientific rationale that supports the application is at an embryonic stage without a precedent as, for example, in many cancers, successful applications have relied on more convincing arguments based on robust non-clinical (*in vitro* but preferably *in viv*o) or early clinical data.

The Committee is currently preparing a guidance note to assist the sponsors with regard to the level of evidence that it considers desirable to support biological plausibility and claims of 'significant benefit' when submitting applications for orphan medicine designation.

COMMISSION COMMUNICATION

In July 2003, the Commission issued a Communication (2003/C178/02) with the intention of setting out its position on certain matters relating to the implementation of the designation and market exclusivity provisions of Regulation (EC) No. 141/2000 of the European Parliament and of the Council. This Communication provides guidance to the European Medicines Agency (EMEA), the member states, the pharmaceutical industry and other interested parties and clarifications in several areas in order to avoid a departure from the spirit of the Regulation. It considers issues in relation to Articles 3 (criteria for designation), 5 (procedure for designation and removal from the register), 7 (Community marketing authorisation) and 8 (market exclusivity) of the Regulation. Only the clarifications relating to Article 3 (criteria for designation) are summarised below. Interested readers should refer to the full text of the Communication for other details.[3]

Prevalence in the EU

With regard to the criteria envisaged for designation of an orphan medicinal product, the terms of the Regulation do not distinguish between treatment and

For products intended for diagnosis or prevention, consider the population expected to be administered the product on an annual basis

diagnosis or prevention of a condition (eg vaccines). In the case of a medicinal product intended for the diagnosis or prevention of a condition, the population 'affected by' the condition may be interpreted in several ways. If a product for the diagnosis or prevention of a condition is effective, this may result in a decrease in the population actually suffering from the disease or condition to fewer than 5 in 10,000 persons in the EU.

The objective of the Regulation is to provide incentives for the development of orphan medicinal products where such incentives are needed. Therefore, in the case of medicinal products intended for diagnosis or prevention, the Commission considers that the prevalence calculation of those persons affected by the condition shall be based on the population to which such a product is expected to be administered on an annual basis. For example, following successful vaccination campaigns, although the vaccinated population is very large, the prevalence of the condition in question may be very low. The prevalence calculation in these cases shall be based on the population vaccinated on an annual basis. It may be pointed out at this stage that the high prevalence of a condition in a handful of member states (eg a haemoglobinopathy or porphyria) is of no consequence in calculating the prevalence *in the Community* as a whole.

It is the prevalence in the EU that matters

Prevalence outside the EU

Identify all products authorised anywhere in the EU when claiming significant benefit

Article 3(1)(a) of the Regulation requires that a condition may be considered as orphan if it affects 'not more than five in 10 thousand persons *in the Community*'. Consequently, the prevalence of the disease or condition outside the Community has no influence on the interpretation of the prevalence criteria. A medicinal product intended to treat a condition that affects a large number of people in certain countries but that has a low prevalence in the EU, is therefore eligible for designation as an orphan medicinal product with respect to the prevalence criterion, and if all other criteria are met, eligible for the benefits set out in the Regulation.

Satisfactory method authorised in the Community

Article 3(1)(b) requires that the sponsor has to establish 'that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the Community'.

The Commission has now clarified the notion of 'satisfactory' method. In this context, Commission Regulation (EC) 847/2000 asks the applicant to provide details of the 'existing methods, which may include authorized medicinal products, medical devices or other methods of diagnosis, prevention or treatment which are used in the Community.' A treatment for a particular disease or condition may be associated with certain risks. These risks are balanced against the expected benefits when considering whether to grant or refuse a marketing authorisation in accordance with the criteria of safety, quality and efficacy as laid down in Directive 2001/83/EC. A marketing authorisation is granted if the risk/benefit assessment is positive. Therefore, at the time of the grant of a marketing authorisation in accordance with EU legislation, the authorised medicinal product is considered to be a satisfactory method as referred to in Article 3(1)(b). Therefore, the applicants for orphan designation should seek to show an assumption of 'significant benefit' over any existing authorised medicinal product in accordance with the second part of paragraph Article 3(1)(b), rather than seeking to show that an existing authorised medicinal product is not a satisfactory method.

Even if a product is authorised in only one of the member states, it is deemed to fulfil the criteria of 'authorized in the Community'. It is neither necessary for the product to have a Community authorisation nor does it have to be authorised nationally in *all* the member

Remember – EU now means 25 Member States

states for it to be considered as 'authorized in the Community'. Effective from 1st May, 2004, 'authorized in the Community' also includes authorisations in any of the 10 new accession countries. The Commission has reiterated that any reference to an already authorised medicinal product can refer only to the terms of the marketing authorisation. Consequently, any 'off-label use' outside the terms of approved Summary of Product Characteristics (SPC) is excluded when defining 'satisfactory'.

Commonly used methods of diagnosis, prevention or treatment that are not subject to marketing authorisation (eg surgery, medical devices) may be considered satisfactory methods if there is scientific evidence as to the value of such method(s). The assessment as to whether a particular method may be considered satisfactory shall take into account the (*clinical*) experience with the method in question, documented results, and other factors including whether or not the method is invasive and/or requires hospitalisation.

Significant benefit can stem from a number of clinically relevant advantages

Significant benefit

The Regulation requires that when there exists an authorised satisfactory method of diagnosis, prevention or treatment of the condition, the sponsor has to establish that the medicinal product to be designated will be of 'significant benefit' to those affected by that condition. 'Significant benefit' is defined in Commission Regulation (EC) 847/2000 as 'a clinically relevant advantage or a major contribution to patient care.' The applicant is required to establish 'significant benefit' compared with an existing authorised medicinal product or method at the time of designation. Since there is unlikely to be any clinical experience with the medicinal product seeking orphan designation, the justification for 'significant benefit' is likely to be assumptions of benefit by the applicant. In all cases, the COMP is required to assess whether or not these assumptions are supported by available data/evidence supplied by the applicant. The Committee assesses these assumptions without being so strict that the development of innovative products with potential significant benefits is deterred or held back. These data must be considered in the light of the particular characteristics of the condition and the existing methods. Thus different considerations, such as ease of self-administration, may be considered a benefit if the patient is ambulant, but may not be considered a benefit if the patient is likely to be hospitalised during treatment.

If the argument for 'significant benefit' is based on an increase in supply/availability of the method, the sponsor must provide details of the supply/availability problem and explain why this results in satisfying the unmet needs of patients. All claims should be substantiated by qualitative and quantitative data or acceptable references. If the supply of existing methods is sufficient to meet patients' needs in the orphan indication, an increase in supply will not be viewed as a 'significant benefit'.

With respect to potential availability of the product to the Community population, a medicinal product that is authorised and available in all member states may constitute a 'significant benefit' compared with a similar product that is authorised in a limited number of member states only. In this context, it is emphasised that the supply problems arising from manufacturing process limitations should be differentiated from those that arise from other reasons such as cost limitations or healthcare policy. Supply/availability problems must be long term or recurring and not of a transient nature. Since this is a normal obligation of every marketing authorisation holder, enhancement of the pharmaceutical quality of a product in compliance with the relevant CHMP guidelines does not constitute a basis for the assumption of 'significant benefit' in the context of orphan medicinal product designation.

Differentiate supply problems from access problems

The Communication goes on to

Enhancing quality in compliance with GMP guidelines does not constitute a significant benefit

provide a number of examples of assumptions on which 'significant benefit' may be based but which must be supported by scientifically credible arguments. Some of these examples are summarised in Table 4.

Finally, given the spirit of the Regulation, the Commission has emphasised that tactical applications for marketing authorisations and marketing practices will not be allowed to undermine the process. The Commission has also stated that the imminent expectation of a Community authorisation as compared with the existence of a national authorisation in one or a limited number of member states may be sufficient to maintain an assumption of 'significant benefit'. In this situation, the designated orphan medicinal product will be maintained in the register, provided that the criteria are still met. A question is often asked regarding the fate of the national authorisations following a centralised marketing authorisation for the orphan product. These national authorisations continue to remain in force and the centralised marketing authorisation has no effect whatsoever.

Community legislation on orphan medicinal products has the potential to be a spectacular success

CONCLUSIONS

Commensurate with its policy advisory functions, the COMP proposes to submit to the Commission a review of the entire process and its activities over the first five years to April 2005 and to recommend changes in specific aspects of the Regulation. As a result of these changes, the COMP should be able to promote the development of a wide range of orphan medicines more effectively and with greater equity. Indeed, the Commission Communication issued in July 2003 is a step in this direction.

Following the introduction of the Orphan Drugs Act in the USA in 1983, the number of active substances designated as of 2004 is 1,422, with an average of 68 per year. Of these, 262 (18.4 per cent) have received marketing authorisations (12.5 per year). The average number for the EU is 50 designations per year and 8.5 per cent of the 200 designations have received marketing authorisations. These figures have to be seen in the context of differences between the USA and the EU in threshold and other criteria for designation. There is little doubt that the Community Regulation on orphan medicines has the potential to be a spectacular success.

The Committee is proactively encouraging the development of orphan medicinal products. When the decision on the designation of a product is borderline, the COMP has invariably given the benefit to the applicant. Within a very short space of time, a large number of medicinal products have been given a positive opinion after rigorous examination of the criteria for designation and of the biological plausibility for their potential benefit in the condition designated. The establishment of a dedicated Secretariat that services the COMP has been one important factor behind this success. The representation of

Table 4: Examples of potentially valid assumptions of 'significant benefit'

- Benefits in a subset of patient population, eg those resistant to existing therapy.
- A new source of existing therapy that has hither to been sourced from blood and plasma at risk of viral or transmissible spongiform encephalopathy (TSE) transmission. The alleged risks must be more than theoretical and be balanced against the inherent risks related to the new source.
- Clinically relevant improved safety.
- More favourable and clinically relevant pharmacokinetics.
- More convenient formulation or route of administration.
- Limitation in availability of authorised product owing to extreme storage conditions.
- Insufficient quantity of authorised product on the market.
- Limitation in scale of manufacturing process (eg fermentation).

the patient groups as well as EC on the COMP and the willingness of experts, drawn from almost all the member states, to assist the COMP have also been pivotal. Informal and formal meetings of the COMP with CHMP and its various expert working parties, patient organisations, academia and the industry continue to vitalise the process.

COMP, EMEA and EC are all enthusiastic and proactive but sponsors must play their role too

The sponsors of active substances for designation can greatly improve their prospects of success by following some basic principles and paying due attention to the data to be submitted and the arguments presented. The Secretariat welcomes pre-submission meetings to assist the sponsors to help them with this process. Apart from providing adequate data on prevalence, the important issues that determine success are biological plausibility, assumptions of significant benefit (if appropriate) and especially when the science is too fanciful, some preliminary data on the activity of the substance on which the COMP can confidently issue a positive opinion.

Assessment of orphan medicinal products has become a significant part of the activities of CHMP and its expert working parties. It is anticipated that the development programmes of many of the medicinal products designated to date will have matured enough over the next few years, resulting in availability of medicinal products for the diagnosis, prevention or treatment of an even wider range of orphan diseases. Patients treated by these medicines can rest assured that these have been tested and assessed to the highest standards.

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