Affordable orphan drugs

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Title: Affordable orphan drugs: A role for not-for-profit organisations

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Abstract

The success of the Regulation on Orphan Medicinal Products in the European Union is evidenced by the 127 orphan drugs that have had market authorisation since 2000. However the incentives aimed to stimulate research and development have had the unintended consequence of increasing drug cost, resulting in many orphan drugs not being cost-effective. Orphan drugs command an increasing share of the pharmaceutical market and account for a disproportionate amount of healthcare expenditure. Orphan drug ownership by socially motivated, not-for-profit organisations may facilitate access to more affordable orphan drugs, for the benefit of patients and healthcare systems alike. Using repurposed drugs as a paradigm, this review navigates the regulatory hurdles, describes the legal context and identifies funding opportunities, in a bid to facilitate and encourage not-for-profit organisations to lead on the development of affordable orphan drugs.

Introduction

The introduction of the Regulation on Orphan Medicinal Products in the European Union (EU) in 2000 [1] has been successful in making drugs for rare disorders commercially viable. Incentives associated with orphan drug status – principally the 10 years of market exclusivity – have facilitated the development of 127 orphan drugs to date. However, there remains considerable unmet need for the estimated 27 to 36 million people in the European Union affected by the 5-8000 rare diseases [2]. The International Rare Disease Research Consortium has set an ambitious objective to deliver 200 new therapies for rare disease by the year 2020, and with 1,404 active Orphan Designations currently in place, this target may be achievable.

Despite successes with the development of new medicines for rare diseases, orphan drug regulations have had the unintended consequence of high costs [3], allowing orphan drug manufacturers to profit excessively from the incentives on offer [4]. A number of orphan drugs are not deemed to represent good value for money [5], even with special allowance for exceeding conventional thresholds of cost-effectiveness [6]. A 2010 review of access to orphan drugs across Europe found that only 21 were widely available, 25 had limited availability and 14 orphan drugs were scarcely available [7]. The increasing cost of orphan drugs is a concern at a time when European countries face economic difficulties, and budget-constrained health care systems find it difficult to meet the escalating demand for treatments. Solutions are needed; not only to promote and sustain innovation, but also to ensure that patients with rare diseases can access effective and affordable medicines once Marketing Authorisation has been granted.

We propose a greater role for not-for-profit organisations to become market authorisation holders. Ownership of intellectual property (IP) rights by socially motivated organisations may facilitate access to more affordable orphan drugs, for the benefit of patients and healthcare systems alike.

Some of the barriers to ownership of orphan drugs by not-for-profit organisations are likely to result from financing, but also from unfamiliarity with the required procedures, uncertainty about the level of evidence required, lack of resources for applying for market authorisation and a lack of knowledge about the obligations to maintain registration [8]. Moreover, there may be a lack of clarity on patent or Intellectual Property issues and potential issues of liability.

The purpose of this review, therefore, is to provide an overview for public sector and not-for-profit organisations, of the processes and procedures for orphan drug designation and regulatory approval. The review is structured as follows: (i) ownership of orphan drugs by not-for-profit organisations, with repurposing of drugs for orphan indications as a paradigm; (ii) Cost of

repurposed orphan drug development; (iii) Business models for orphan drug development by not-for-profit organisations; (iv) Intellectual Property issues and opportunities that might arise; and (v) a step-by-step guide to the European regulatory process.

i. Ownership of orphan drugs by not-for-profit organisations

Public sector and other not-for-profit organisations are as entitled as biotech and pharmaceutical industries to be sponsors for orphan designations and become market authorisation holders of drugs, including orphans.

Clinicians and academics are already instrumental to drug development, and are an important source of innovative medicines in the European Union [9] but none are yet orphan MA holders. Commercial sector dominance in the orphan drug market is illustrated in Table 1, with 93% of orphan designations and 100% of products. The number of hospitals or universities that are named as sponsors for Orphan Designations in the EuOrphan database is only 26 (out of 1,110), with a further 31 sponsored by individuals and 19 sponsored by charities or patient groups. While many sponsors of orphan designations are outside the for-profit commercial sector, none are orphan drug market authorisation holders.

--- Insert Table 1 here ---

The greatest opportunity for not-for-profit organisations (including universities, health services, charities or philanthropic enterprises) to make a significant contribution to bring affordable orphan drugs to market is with repurposed (or repositioned) drugs. Kesselheim *et al* [11] described the roles of academia in rare disease drug repurposing in the USA, highlighting that many drugs or drug classes approved by the Food and Drug Administration between 1984 and 2009 were based on discoveries made by academic researchers who were supported by federal government funding. Far fewer medicines had originated solely within pharmaceutical industry research programmes. In fact, for-profit commercial sector involvement in repurposed drug development has been restricted by the lack of potential returns on investment. This is because the cheap generic drug can easily substitute for the branded repurposed medicine if method-of-use patents are difficult to enforce.

Repurposing off-patent drugs overcomes numerous challenges associated with the research and development of new drugs [12]. The opportunities offered are that they have already been well characterised in terms of pre-clinical toxicity, ADME (absorption, distribution, metabolism and excretion) and safety, as well as having established processes for production. The data requirements for licensing a repurposed drug are also less, especially with respect to the demonstration of safety,

and developers may utilise an alternative legal basis for a market authorisation, taking existing knowledge into account, and requiring fewer pivotal trials to satisfy the requirements of the regulatory authorities. Bibliographic evidence is permitted to support market authorisation applications [13]. Consequently, repurposed drugs come to market quicker and are more likely to be approved than new drugs [14-17]. EMA-approved repurposed (and rediscovered) drugs with orphan indications represent just 20% of all orphans, indicating a lost opportunity which industry neglects.

ii. Cost of repurposed orphan drug development

While the cost of developing a new drug is very high [18,19], the costs of bringing repurposed drugs to market are significantly lower [12], particularly after discounting the cost of discovery [20]. The not-for-profit organisation Drugs for Neglected Diseases initiative, for instance, has earned approval for six treatments over a period of 10 years, and put another 26 drugs into development, all for US$290 million [21].

Notwithstanding any clinical studies, there are costs involved in applying for patents, product manufacture, marketing, promotion, distribution, sales, and supply [22]. But these may be limited: the cost of marketing and advertising orphan drugs, especially for the rarest diseases, is comparatively small because the target populations of physicians and patients are themselves so small [14]. Agreements with for-profit pharmaceutical companies may be necessary for manufacture, distribution and supply [23]. This represents a potential threat to achieving the aim of low cost medicines and there are numerous recent examples of generic drug 'price gauging', where cheap products are priced above market rates under conditions of monopoly [24]. However, alternative models are available. The not-for-profit pharmaceutical company OneWorldHealth (http://oneworldhealth.com/), as one example, is partnering with the International Dispensary Association, a not-for-profit drug supplier based in The Netherlands, to manufacture the off-patent aminoglycoside antibiotic paromomycin, in India in order to maintain a pricing structure at US$10 per adult and US$5 per child [23].

iii. Business models for orphan drug development by not-for-profit organisations

A key challenge for non-for-profit development of orphan drugs is in their financing. Despite the savings possible through repurposing old drugs, there remain significant costs which may be financed in different ways [20].

Though not repurposed, ivacaftor is the first orphan drug developed through "venture philanthropy"—a partnership between a charity and a drug company. This model provides a

mechanism for non-profit organisations (in this case, the Cystic Fibrosis Foundation) to help finance the development of a treatment in return for a share in profits that can be re-invested in other new treatments [25]. The converse is needed for public or other not-for-profit ownership of repurposed orphan drugs—that is, a model for the private, public or charitable (including philanthropic) financing of drug development by not-for-profit organisations.

One option is for the public sector to (co-)fund research and development activities, and then own or share ownership of the orphan medicinal product. Across Europe, more than €620 million in funding was awarded by FP7 to over 120 research projects on rare diseases and orphan medicinal products [26]. Horizon 2020 and the Innovative Medicines Initiative have maintained a strong commitment to fund research in rare diseases, and represent important funding opportunities, which may have wider societal benefits if orphan drugs resulting from these investments are ultimately affordable to healthcare systems. Example schemes in the UK include the National Institute for Health and Research (NIHR) Invention for Innovation (i4i) and the Health Innovation Challenge (HIC) Fund which support translational research to advance interventions for increased patient benefit. The NIHR's Rare Disease Collaboration is supported by a £20m investment and includes pharmaceutical industry partners for developing repurposed drugs for orphan diseases.

Alternative models of financing include Social Impact Bonds, which are arrangements between one or more government agencies and an external organisation, where the government specifies an outcome and promises to pay the external organisation a pre-agreed sum if it is able to achieve the outcome. The UK charity Findacure (http://www.findacure.org.uk/), for example, secures funding for phase II clinical trials of generic drugs repurposed for rare diseases that have a high cost of care to the NHS. Successful trials lead to off-label prescription in the NHS, and reduce the healthcare cost of patients. The NHS then pays a proportion of their savings back to the charity as a success payment. The Fair Medicine foundation (http://fairmedicine.eu/) aims to offer sustainable and affordable access to medicines in the Netherlands and is centred on partnerships to share responsibilities, risks and rewards, and funding from the Ministry of Public Health, Welfare and Sport.

Other initiatives include Cures Within Reach (http://www.cureswithinreach.org/), which repurposed the generic drug sirolimus for autoimmune lymphoproliferative syndrome, and Amadeus Capital Partners who are financing the Cambridge start-up company Healx (http://healx.io/) to help progress its work in the field of repurposing existing medicines for new rare diseases.

Capital raised through crowdfunding represents a new approach to financing biomedical research and development. In one study, potential donors stated an overwhelming preference for projects

conducted by non-profit research organisations and for projects that have the potential to yield a curative therapy in paediatric diseases [27]. However, preferences for donation were higher for common diseases than for rare diseases.

iv. Intellectual Property issues and opportunities

Although not an intrinsic part of the regulatory evaluation process, due thought and consideration must be given to the intellectual property aspects of repurposed orphan drug development both to understand the existing intellectual property landscape and to determine whether any protection is available. This key step involves a search of patent registers to find any existing patents or patent applications which cover the drug in question.

A check for supplementary protection certificates (SPCs) should also be carried out. Sometimes referred to as "patent extensions", an SPC does not technically extend the life of the patent; instead a "new" right is granted which protects an authorised product which is protected by the patent. An SPC is granted to provide an additional period of protection after patent expiry to a patent holder who "lost" part of the patent term due to the length of time taken to get regulatory approval and get their medicinal product on to the market. SPCs are granted on a national basis.

Even if the patent covering the compound itself has expired, there may be patents which protect the use of the compound for a particular indication or protect a particular route of administration or dosage regimen.

If the proposed orphan drug is to be given a brand name (as opposed to using the trade or generic name) then trademark registers should be searched to ensure the brand name is not identical or similar to any existing trademarks.

Finally, it is important to confirm that the original regulatory data exclusivity period for the drug in question has expired. In the EU, there is a data protection and market exclusivity period for nationally or centrally authorised products. Known as the "8+2+1 formula", the market authorisation holder is granted eight years of data protection (which means that third parties are prevented from referring to the registration dossier of the reference medicinal product) followed by a two-year period during which a generic product cannot be placed on the market. This period can be extended by up to one additional year if an authorisation for a new therapeutic indication is granted.

An orphan drug is entitled to market exclusivity for a period of 10 years (or 12 years in the case of a paediatric orphan disease). This was confirmed in a recent decision of the Court of Justice of the European Union [28].

Once the IP landscape has been established, the timeline for development should be considered. Ideally, the drug in question will already have become generic and there will be no existing patents to consider. Even if patents do remain in force, it is possible to carry out certain types of clinical trials using the product as there is a defence to patent infringement in the UK (and most European countries) which covers such trials. However, any product which is to be commercialised as a result of the trials cannot be marketed until the relevant patents have expired. As clinical trials are expensive and time-consuming, carrying them out during the life of an existing patent at least puts the orphan drug developer in an advantageous position to commercialise the orphan drug as soon after patent expiry as possible.

With regards to protecting intellectual property in the new indication, the first consideration is whether there is any desire on the part of the developer/ market authorisation holder of the orphan drug to prevent existing manufacturers of that drug from selling it to treat the new orphan indication.

Existing manufacturers of the drug could apply for a new indication to be included in a second market authorisation to cover the new orphan indication should they wish to sell the drug for that indication (orphan and non-orphan indications cannot be included in the same market authorisation). This would need the orphan holder to consent. If the developer/ market authorisation holder of the orphan drug is willing to allow third parties to rely on the data in their market authorisation application for the orphan indication and to be free to sell the drug for the treatment of the new orphan indication then there is no need to consider seeking patent protection (and the developer will not take advantage of the market exclusivity period). Equally, the other generic products may be used to treat the orphan indication off-label.

However, if the developer does want to prevent anyone else selling the drug for the new orphan indication then they should consider whether the new indication is one which is a patentable invention. In order for something to be patentable, it has to be new and inventive. It is an often misunderstood concept that exploiting old drugs for new uses is not novel drug discovery. However, patents can be (and are) granted for so-called second medical uses. This is in recognition of the fact that developing new uses for known compounds can involve a great deal of time, effort and research and provides significant benefit to society. Patents can also be granted for novel routes of administration or novel dosage forms.

Applying for a patent for the first time can be a daunting process and it is advisable to engage the services of a patent attorney both to explain the process and to draft the application. It is important

not to discuss the invention with anyone before a patent application has been filed unless that person has signed a confidentiality undertaking. This includes publications and presentations in conferences. This is to ensure that the novelty and inventiveness of the idea is preserved until the patent has been filed. In Europe, it is possible to file one patent application at the European Patent Office and to request that it is validated in all 38 countries in Europe which are members of the European Patent Organisation. Alternatively, individual national applications can be made in each country where patent protection is desired.

It can be a relatively expensive process to file a patent application and to prosecute it through to grant. As well as patent attorney fees, there will also be filing fees (and if the patent is granted, annual renewal fees which increase through the life of the patent). However, filing a patent application can be a good way to test the water as the application will be reviewed and analysed by the relevant patent office which should identify any issues with the patentability of the 'new' indication (e.g. it is not novel or inventive because there are prior published documents which disclose the same idea). If such issues are raised, a strategic decision can be taken at that stage as to whether or not to proceed with the application. The application will be published around 18 months after filing with the European Patents Office and as of that date, the public are on notice that a patent application has been filed and on notice of its contents.

In the case of a patent to a compound itself, the patentee can prevent third parties making, using, selling, importing or keeping the compound covered by the patent (often called 'direct infringement'). In the case of an orphan product where it is the indication which is protected, the analysis is more difficult because there may only be infringement where the compound is sold etc. for the protected indication. The scope of such second medical use patents is currently being tested in the on-going UK case of *Warner Lambert v Actavis* where Warner Lambert has a second-medical use patent to pregabalin for the treatment of neuropathic pain.

A granted patent is a valuable asset. The patent holder can exploit the invention exclusively (subject to other third party IP) or can licence the patent to third parties in return for a licence fee. It is important that the patent holder monitors the market to ensure that third parties are not infringing its rights; otherwise there is little value in holding the patent in the first place.

If it is intended that the orphan drug will have a brand name then trade mark registrations should be filed. Again, this can be done centrally for the EU through EUIPO (the European Union Intellectual Property Office) which results in an EU Trade Mark (EUTM) which offers protection throughout the

EU. As with patents, there is a filing fee and the trademark has to be renewed every ten years for a relatively modest fee.

v. Orphan Drug approval in Europe: step-by-step guide

The regulatory steps to be undertaken during a drug development programme for an orphan drug in Europe are listed in Table 2. Of note is that the regulatory demands of bringing an orphan drug to market is managed by the European Medicine Agency (EMA), as a centralised procedure according to Regulation (EC) No 726/2004 [29], and not by each Member State National Competent Authority.

--- Insert Table 2 here ---

Orphan designation is a free service. The procedure involves submission of an application form and scientific description of the condition, the product, its mode of action and data showing a promise of efficacy using pre-clinical *in vivo* and/or preliminary clinical data, prevalence estimates and, where there are already authorised medicinal products in the condition in Europe, a case for significant benefit. Assessment for orphan designation is made by the Committee on Orphan Medicinal Products (COMP) which meets every month. Orphan designation may also be granted on the basis that the development of a treatment would not otherwise be commercially viable, irrespective of the rarity of the disease.

The cost of regulatory advice represents a potential barrier, so fee reductions or exemption should be considered where possible, as appropriate advice can significantly focus the data requirements thereby reducing costs overall. Once an orphan designation has been granted, the sponsor is eligible for total or partial fee exemptions [1]. This includes free pre-authorisation activities such as protocol assistance (scientific advice), and greatly reduced fees for products using the centralised procedure for market authorisation applications, inspections and post-authorisation activities such as variations, annual fees, etc. To be eligible for fee waiver, the applicant must register as a Small Medium Enterprise (SME) via the SME office at the EMA. Fee waivers for scientific advice requests on medicinal products falling under the scheme for priority medicines ("PRIME") are also available to applicants from the academic sector.

Protocol assistance is a voluntary procedure to obtain scientific advice on the proposed development plan, to gain an understanding about regulatory demands and expectations relating to the non-clinical, clinical and quality data, and the standards required for market authorisation. The procedure requires the sponsor to provide a detailed overview of their development plans for the Scientific Advice Working Party (SAWP), to review and respond to specific questions. The opinion of

the SAWP is not legally binding; however better dialogue with regulators has become a key positive factor in facilitating market authorisation. It is crucial that protocol assistance is sought before the initiation of any pivotal trials, to ensure that the planned work is in line with regulatory requirements.

The proposed legal basis of the market authorisation, determined from Directive 2001/83/EC [13] and Regulation (EC) No 726/2004 [29], should be established during protocol assistance. Articles 10 (Generic, hybrid or similar biological application) and 10a (Well-established use application) are relevant to repurposed drugs. Other regulatory considerations for marketing orphan drugs include Exceptional Circumstances, Conditional Approval (Article 14 (8)), Accelerated Access (recital 33 and Article 14(9)) and Compassionate Use (Article 83) of Regulation (EC) No 726/2004 [29]. Sponsors who repurpose a product for a new indication should consider whether a paediatric investigational plan is appropriate, which can add an additional 2 years extension to a product's 10 years of marketing exclusivity. This operates separately from the Orphan Regulation.

All quality, non-clinical and clinical work must of course comply with Good Manufacturing Practice, Good Laboratory Practice and Good Clinical Practice standards. This is mandatory for subsequent regulatory audits. Developers may delegate these responsibilities to other organisations. Outsourcing such responsibilities to Clinical Research Organisations and manufacturing facilities is common place even among biotech and small scale pharmaceutical companies.

Regulatory obligations do not end at the time of market authorisation; these continue throughout a drug's lifetime. This is particularly relevant with respect to drug safety, as stipulated in the Pharmacovigilance Regulation (EU No 1235/2010) [30].

When a sponsor applies for market authorisation, they will also need to re-submit the orphan designation for review and maintenance of the designation. This follows the same criteria as at the initial orphan designation; however the sponsor must have some data for their product in the condition to support a claim for Significant Benefit if there are other authorized medicinal products in Europe, and that the incidence and prevalence of the disease has not changed. This is important - as it is at this step that the COMP recommends granting of the market exclusivity.

Once market authorisation has been granted for an orphan drug there will be additional legal requirement to address the pharmacovigilance obligations, and any specific obligations defined by the CHMP. Again, this legal responsibility can be outsourced to another organisation that has the necessary skills and expertise to address these.

Conclusion

Opportunities for orphan drug development resulting in affordable products lie mainly with repurposed drugs. These will invariably be limited to small molecules, and so apply to a sub-set of rare conditions; the scope for repurposing biologics (biosimilars in the context of off-patent products) has yet to be defined. Funding opportunities to support research and development are available from national and international public-sector organisations, via charitable and philanthropic donations, and by means of social impact funds or similar such schemes. Although the regulatory steps required to obtain a market authorisation for an orphan drug are numerous and challenging, these are not insurmountable and can be achieved by not-for-profit organisations socially motivated to reduce the costs of orphan drugs to the payers of healthcare. Market authorisation holders may of course contract much of the work to specialized organisations. This is the preferred approach of many biotech and small scale pharmaceutical companies, and is the most effective option for public sector, not-for-profit and charitable organisations.

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Conflict of interest

The authors declare no conflicts of interest.

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Table 1: Overview of orphan designation and orphan drug sponsor / market authorisation holder according to sector

Sector	Orphan Designation	MA Sponsor
Individuals	31 (2.8%)	0
Hospital / University	26 (2.3%)	0
Charity / Patient Group / Not-for-profit	19 (1.7%)	0
Industry	1,034 (93.1%)	93 (100%)
Total	1,110	93

Data obtained from EuOrphan: a database focused on drugs aimed to diagnose, prevent or treat a rare disease. The EuOrphan project, as described by Stakišaitis et al [10] received an initial financial support by the European Union under IT-Technology project (eTen 510774 2003/C 118/19).

Table 2: The regulatory steps required for orphan drug approval

Procedure	Timeline	Detail and Fees	Optional / Obligatory
Orphan Designation	3-9 months	Sponsor applies for orphan designation based on incidence / prevalence and therapeutic need This procedure is FREE	Optional – but allows access to orphan rewards and benefit
Web link: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp			
Protocol Assistance	2-4 months	An opportunity to ensure that all the planned quality, non-clinical and clinical work is in line with what regulators want. This procedure is FREE.	Optional – but highly recommended
Web link: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9			
Paediatric Investigation Plan (PIP)	2-4 months	Sponsor must apply for a PIP at the end of adult Phase I and include all the details of planned studies to be done in children. This procedure is FREE. Scientific Advice from the CHMP is also free on	Obligatory – but waiver may be applied for

		paediatric specific issues	
Web link: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000023.jsp&mid=WC0b01ac05800240cd			
Clinical Trial Authorisation (CTA)	3-5 months excluding clock stop	Sponsor must apply for a CTA in all the MSs that studies will occur. This needs to include all quality, non-clinical and clinical data to date. **Fee applies**	Obligatory in every MS before trial start
Web link: https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk			
Marketing Authorisation Application (MAA)	15-18 months excluding clock stop	Once all the studies are completed, a MAA is submitted to the EMA for evaluation. This must be submitted according to the electronic Common Technical Document eCTD template requirements. Reduced fees apply for orphan designation applications with SME status	Obligatory for MA
Web link: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000197.jsp&mid=WC0b01ac058002251c			