Accelerating orphan drug development

Interest in developing drugs for rare diseases has increased substantially in recent years. This article from the US Food and Drug Administration highlights the role of regulators in catalysing further progress in this field.

Timothy R. Cotè, M.D., M.P.H., and Kui Xu, M.D., Ph.D., are at the Office of the Commissioner, Office of Orphan Products Development, and Anne R. Pariser, M.D., is at the Center for Drug Evaluation and Research, Office of New Drugs, US Food and Drug Administration, Silver Spring, Maryland 20993, USA. Correspondence to T.R.C. e-mail: timothy.cote@fda.hhs.gov

In this issue, Tambuyzer provides an industry perspective on the challenges in developing drugs to treat rare diseases, commonly known as orphan drugs (see page 921). Like industry, governments in the United States, Europe, Australia, Singapore and Japan have adopted strategies to accelerate research and development (R&D) in this field, and to address specific issues in orphan drug regulation. Indeed, orphan drugs are developed within a unique regulatory framework: they are first 'designated' in recognition of their promise for treating a rare disease, but like any other drug, they cannot be marketed until data establish their safety and efficacy. Here, using the environment in the United States as a basis, we discuss examples of products that may be designated as orphan drugs under the 1983 Orphan Drug Act (ODA), the need to systematically scrutinize claims of efficacy and safety, and the need to accelerate drug development for the ~7,000 orphan diseases. Finally, we highlight new policy initiatives that aim to boost further progress in this field.

Granting incentives of the ODA

The ODA, which provides a package of fiscal and regulatory incentives for the developers of drugs for rare diseases, is considered one of the most successful pieces of drug development legislation in the United States[1]. So far, it has stimulated more than 2,250 orphan drug designations, 361 of which have culminated in full marketing approval. In 2009, orphan drugs constituted 38% of the 29 new therapies that the US Food and Drug Administration (FDA) approved for marketing. The ODA also established a grant programme for clinical trials, and while the budget in the 2010 fiscal year was only US$14 million, these grants have nevertheless generated data that have brought 45 new rare disease products to market.

A rare disease is defined in the ODA as one that affects fewer than 200,000 patients in the United States. Given that there are ~7,000 such diseases, rare diseases overall are estimated to affect more than ~25 million patients in North America alone[2]. Furthermore, if a drug is useful for only a small subset of a common disease, then it may also qualify for orphan designation. For example, Pfizer recently received orphan designation for its drug crizotinib to treat the anaplastic lymphoma kinase-positive subset of patients with non-small-cell lung cancer (NSCLC). NSCLC is a common disease, but because crizotinib is targeted to a medically plausible subset of patients with NSCLC, it is entitled to the financial benefits of the ODA, as the number of patients who might receive it is very small. In a contrasting example, if a drug were to be proposed for the treatment of refractory renal cell carcinoma (RCC) (which has a US prevalence of <200,000), but the drug would probably be beneficial as a first-line therapy for all patients with RCC (US prevalence >200,000), the refractory RCC subset would not ordinarily qualify as a medically plausible subset. However, if the risk/benefit ratio was such that the drug was considered too toxic for treating the disease except in refractory patients, the refractory subset could qualify as a medically plausible subset[3].

The benefits of the ODA also apply to any product that could provide a new treatment for a rare disease, regardless of the drug's development for use in different common diseases or conditions. For example, botulinum toxin type A (Botox; Allergan) was first approved as an orphan drug for the treatment of cervical dystonia and blepharospasm, and Allergan did not lose market exclusivity for those rare diseases when Botox was later approved for aesthetic uses. Conversely, drugs already approved for treating common diseases can secure the incentives of the ODA if usefully repurposed for a rare disease indication; the Rare Disease Repurposing Database on the FDA website[4] lists hundreds of such opportunities.

Assuring safety and efficacy

To be approved for US marketing, all drugs — orphan and non-orphan — must meet the FDA's evidentiary standards. That is, all drugs must demonstrate substantial evidence of effectiveness in at least one adequate and well-controlled study, whereby the effect of the drug is able to be distinguished from other influences, such as spontaneous change in the course of the disease, placebo effect or biased observation[5]. US law also provides for

some flexibility and room for scientific judgement[6] where appropriate, which is often warranted when evaluating orphan drugs. Orphan drugs present multiple challenges: few patients are available for evaluation in clinical trials, and rare diseases are a vastly heterogeneous group of disorders with little in common other than their rarity. They typically have poorly understood natural histories and often lack targeted outcomes measures of effectiveness (clinical end points or biomarkers). Many of these disorders are serious, chronic and progressive with unmet medical needs; patients have few, if any, options for treatment, which adds to the urgency for developing new treatments.

Approximately 90% of approved and investigational orphan drugs are reviewed and regulated by the FDA's Center for Drug Evaluation and Research (CDER); the remaining 10% are regulated by the Center for Biologics Evaluation and Research, which include predominantly blood-derived products such as coagulation factors. Orphan designations, orphan drugs in clinical trials and those receiving marketing approvals are all increasing. This is particularly true for newer targeted products intended for the treatment of rare cancers and genetic disorders, for which advances in molecular biology have brought innovative strategies for intervention.

Accelerating orphan drug development

To meet the increasing challenges associated with rising numbers of investigational orphan drug applications, and the scientific complexity that these applications present, the CDER has recently founded a Rare Diseases Program within the Office of New Drugs. The CDER recognizes the need to take a comprehensive approach to rare disease drug development and regulation, and has identified several key areas to focus on, the most important of which are regulatory and biomedical scientific development.

Regulatory science is the "development and use of the scientific knowledge, tools, standards, and approaches necessary for the assessment of medical product safety, (and) efficacy", and is "the critical bridge between biomedical research and new medical products"[7]. This need for scientific development obligates the FDA, the US National Institutes of Health and other stakeholders to collectively define and implement strategies and information needed for the seamless progression of investigational drugs from basic science to translational science through to clinical evaluation. A description of the disease's natural history is the indispensable first element to be defined in any clinical development programme. This leads to the identification of disease-specific targets for intervention, and the development of innovative trial designs and analytical methods that may be useful and reliable in small patient populations. Enhanced sharing and dissemination of this essential knowledge, pre-competitively wherever possible, is also particularly important for rare diseases research.

Policy initiatives and future directions

Several recent events and policy initiatives are poised to increase the momentum of rare disease R&D, including a report by the Institute of Medicine (IOM) on accelerating rare disease drug development[8] and the FDA's internal Rare Disease Review Committee mandated by the Section 740 Amendment[9].

The overall message of the IOM's report was the implementation of a national strategy to promote rare disease research and product development; that is, the need for all participants to improve their individual efforts and relationships in order to play essential roles in the process. Other key recommendations include the timely application of advances in science, and for all rare disease stakeholders to devise partnerships to share resources. The CDER was specifically called upon to develop a better overall understanding of the adequacy of the evidence needed to support approvals and to identify problem areas in drug development that may be ameliorated by further study. We are in agreement that further development in these areas would be valuable.

In response to the mandate of Section 740, an FDA committee composed of multidisciplinary, multi-centre rare disease experts is currently performing a comprehensive analysis of current and projected practices for rare disease review and regulation at the FDA. The report describing the findings and recommendations of the review group is due to be presented to the US Congress in March 2011.

Given the limited resources available for rare disease R&D, it is imperative that all knowledge gained is used to maximum benefit at each phase. The record of the CDER's 27-year history of orphan drug approvals contains examples of achieving evidentiary sufficiency through many scientific means. The FDA is committed to accelerating orphan drug development through a regulatory system built on integrity, consistency and transparency; a system that has delivered benefits to people who desperately need them and promises to deliver much more.

Timothy R. Coté, Kui Xu and Anne R. Pariser

1. Braun, M. M. *et al.* Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. *Nature Rev. Drug Discov.* **9**, 519–522 (2010).
2. National Organization for Rare Disorders (NORD). About NORD. *NORD website* [online], http://www.rarediseases.org/info/about.html (2010).
3. Department of Health and Human Services. Food and Drug Administration. 21 CFR Part 316. Orphan Drug Regulations: Proposed Rule. *Federal Register* **56**, 3338–3351 (1991).
4. US FDA. New resource for drug developers: the rare disease repurposing database (RDRD). *US FDA website* [online], http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm216147.htm (2010).
5. US FDA. *Code of Federal Regulations Title 21: Adequate and Well-Controlled Studies Pt. 314.126* (US Government Printing Office, Washington, DC, 2009).
6. US FDA. *Code of Federal Regulations Title 21: Approval of an Application and an Abbreviated Application Pt. 314.105* (US Government Printing Office, Washington, DC, 2009).
7. Hamburg, M. A. Announcement of FDA/NIH collaboration on advancing regulatory science. *FDA Website* [online], http://www.fda.gov/NewsEvents/Speeches/ucm201687.htm (2010).
8. Institute of Medicine of the National Academies. *Rare Diseases and Orphan Products: Accelerating Research and Development* (eds Field, M. J. and Boat, T. F.) (The National Academies Press, Washington, DC, 2010).
9. Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 2010, Pub. L. No. 111–180, §740 (2010).

Competing interests statement
The authors declare no competing financial interests.