BIOBUSINESS BRIEFS

REGULATORY WATCH

The orphan drug pipeline in Europe

The European framework for orphan medicinal products offers a range of incentives to encourage the development of medicinal products for the treatment of rare diseases. To qualify for these incentives, sponsors must obtain — at any stage of development — orphan designation status from the European Medicines Agency (EMA) by fulfilling a set of criteria (see Supplementary information S1 (box)). Once designation is granted, sponsors are required to submit annual reports to the EMA summarizing progress in development. However, little is known about the current state of development of the orphan designations (ODs) that have not yet obtained marketing authorization. With this in mind, we analysed the orphan drug pipeline in Europe by reviewing the active ODs granted between 2002 and 2012 for which an annual report was available in 2013 or 2014. For each OD, data related to the latest completed study, target therapeutic area and sponsor type were collected. We also applied standard success rates for each development phase to our dataset to estimate the number of ODs that may receive marketing authorization (see Supplementary information S1 (box) for details of the dataset and analysis).

Between 2002 and 2012, our sample of ODs ($n = 605$) was spread across a portfolio of 21 therapeutic areas (FIG. 1a), suggesting that translation of rare disease research into product development and healthcare innovation is happening across an increasing number of diseases — notably rare genetic diseases. Oncology remained the most common therapeutic area (36% of the total), followed by neurology and haematology. Clusters were observed, with emerging clusters of designations targeting, for instance, Duchenne muscular dystrophy, haemophilia or mucopolysaccharidosis. Novel therapeutic targets included rare endocrine diseases (for example, acromegaly and Cushing syndrome), rare skin diseases (for example, epidermolysis bullosa) and rare systemic or rheumatological diseases (for example, systemic sclerosis). Approximately 10% of ODs were for innovative cell or gene therapies (Supplementary information S1 (box)). Around 39% ($n = 234$) of ODs targeted conditions with prevalence levels below 1 per 10,000 people in the European Union (EU) and another 52% ($n = 313$) were aimed at conditions with a prevalence between 1 and 3 per 10,000. At the time of the designation decision, significant benefit did not need to be demonstrated by sponsors for 275 medicinal products (46% of the sample) as they targeted rare conditions lacking any approved therapies in the EU — a proxy for unmet medical need.

Our analysis showed that of our sample of ODs, development had been discontinued for 17% ($n = 103$). Of the 83% ($n = 502$) that were still in development, 63% ($n = 316$) had reached clinical development, with 35% at Phase I, 48% at Phase II (46% of which targeted rare cancers) and 17% at Phase III (FIG. 1b). Of the ODs in preclinical development ($n = 123$), non-clinical evidence packages (encompassing pharmacology, pharmacokinetics and toxicity data) were reportedly being compiled for 39% ($n = 48$). Importantly, data indicated that half of ODs in ongoing development ($n = 254$) were held by small or medium-sized enterprises (SMEs), who were represented in equal proportion across all development phases (Supplementary information S1 (box)) — highlighting the role of SMEs in orphan drug development.

By applying published non-orphan specific success rates per phase (*Nat. Rev. Drug Discov.* **9**, 203–314; 2010) to our sample of ODs in preclinical or clinical phases, we estimated that ~90 ODs in our sample could reach marketing authorization in the future. Adjusting this calculation to reflect that a proportion of orphan drugs have historically been approved on the basis of Phase II pivotal studies increased this number to ~110 ODs.

Overall, our study findings confirm the success of the European regulatory framework in promoting therapeutic innovation for rare diseases, and in being a catalyst for SME growth. Ongoing rare disease research, recently bolstered by initiatives such as the International Rare Diseases Research Consortium and the EU Horizon 2020 plan, is likely to result in a steady expansion of OD applications to the EMA in the near future.

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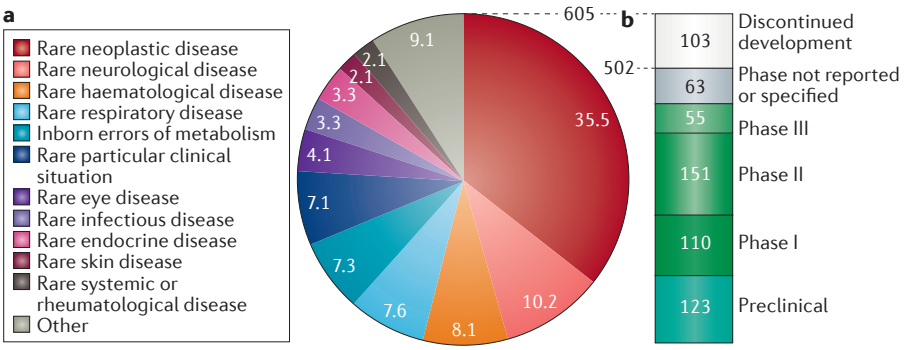

Figure 1 | **Analysis of orphan designations in the European Union.** The data are for orphan designations granted between 2002 and 2012 with annual reports filed to the European Medicines Agency in 2013 or 2014 ($n = 605$). **a** | Orphan designations granted, subdivided by therapeutic area. **b** | Orphan designations granted, subdivided by development stage.

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