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Big Pharma's new model in orphan drugs and rare diseases

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EXPERT OPINION

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Big Pharma's new model in orphan drugs and rare diseases

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For many years the highly profitable pharmaceutical companies had no interest in the rare disease community or its need for orphan product development. The collective rare disease market by definition was small. It did not offer the profits of drugs like antihypertensives with a market of more than 25 million patients. However, nothing stays the same. The blockbuster model that traditionally drove the pharmaceutical industry seems to have lost its relevance. "Big Pharma" has reached out for a new model and found that orphan drugs may be the answer.

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1. The blockbuster model

The number of drugs in the pipeline from big companies has diminished since FDA market approvals peaked at 145 in the 1994 – 1988 period, and declined to 69 between 2004 and 2008 [1]. In 2012, the drugs in the non-orphan pipeline started to fall off the "patent cliff". Patents were expiring faster than they were being replaced. Competition was rising from manufacturers of generic drugs, biosimilars and follow-on biologics. When the Orphan Drug Act (ODA) was signed by President Reagan in 1983 there was only one orphan drug approval. Since then the number of market-approved orphan drugs has increased to about 400, while the number of approved non-orphan drugs has peaked. In 1996, there were 57 new drugs approved by the FDA, but by 2010, there were only 19 new ones, with fewer of these blockbuster drugs. In 2008, orphan drugs were 35% of all the new drug approvals in the US. Orphan drugs were mostly in the provenance of small biotech companies [1].

2. The new model

Clearly, a new model was emerging [2]. Orphan drugs were becoming an answer to the decline in drug approvals. Thanks to the ODA, therapies for rare diseases have several governmental development drivers – tax credits, a waiver of FDA fees, funding grants for clinical trials and a 7-year exclusivity for the marketable product. The industry has discovered that clinical trials are smaller and some can be fast tracked, although the FDA standards for market approval of a new drug are still the same for non-orphan and orphan drugs [3,4]. Reviews of the impact of the ODA from 2000 to 2009 showed 1138 orphan drug designations and 148 market approvals with an increasing proportion (31%) significantly benefiting children with rare diseases [5,6].

The incentives on the business side have included premium prices, reduced marketing costs, increased reimbursement possibilities for chronic unmet medical need and a longer exclusivity. Meekings *et al.* [4] estimate that Phase II to launch for orphan drugs was 3.9 years compared with 5.42 years for non-orphan drugs. Furthermore, they estimate that orphan drugs have a higher probability (93%) of regulatory success compared with 88% for non-orphan drugs, a significant difference ($p < 0.05$).

An orphan designation is like the FDA seal of approval for a potentially viable new drug. It gives a company a product to raise capital for development, and the

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exclusivity of the marketed therapeutic gives them time to build networks of patients, caregivers, patient advocates and healthcare providers in the specific rare disease community. Orphan drugs have great commercial potential despite small markets because they can dictate high prices where they are the only drug therapy available. Of the top 10 orphan drugs, 60% were indicated for more than one rare disease, leading to a four-fold increase in the peak value of sales potential ($34 billion versus $8 billion) [5]. Against that, one has to recognise the high financial risk and the 10 – 15 years it takes to develop a new drug. Many orphan drugs are developed for specific ultra-rare diseases with only one indication.

Rare diseases are defined as those affecting fewer than 200,000 people in the US, or affecting more than 200,000 people in the US, but for which there is no reasonable expectation that sales of the drug treatment will recover the costs. There are about 7,000 rare diseases affecting 25 – 30 million people in the US or approximately 1 in 10 Americans. The ODA was passed to provide economic incentives to promote orphan drug research and development. From 1983 to 2010, a total of 3,393 applications for orphan drug designation were submitted, with 2,308 applications receiving designated orphan drug status. Of these, 334 became approved drugs for marketing. Some of these have made companies (e.g., Amgen was built on erythropoietin [EPO], which received market approval as an orphan drug).

The number of orphan drug designations by the FDA has increased, but the number of approvals remains small in comparison. Whether consistently high numbers of designations will lead to higher numbers of approvals is not known. Historical data from the FDA Office of Orphan Product Development (OOPD) does reveal a pattern, which indicates there are many difficulties and reasons for not reaching approval. The small number of qualified patients who can participate is a major factor. It may take years to reach the appropriate sample size for statistical power requirements. A comparison of orphan drug approvals versus non-orphan drug approvals does show that orphan drugs were tested in significantly fewer clinical trial participants. The number of participants in the largest trials were significantly less for orphan drugs with a 6.6-fold difference [3].

3. Can orphan drugs be profitable?

Once approved and marketed, several companies have shown that profits can be made on orphan drugs and patients can be served, despite small numbers of potentially treatable patients. Gross profit margins of over 80% are reported in the rare disease industry, whereas the pharmaceutical industry average is 16%. The compound annual growth rate of the rare orphan drug market is 5.7% and currently estimated to be close to $100 billion. 43 brand name drugs have global annual sales of greater than US $1 billion (for example Gleevec, Epogen, Herceptin, Neupogen and Cerezyme). Of these blockbusters, 18 were approved solely as orphan drugs in the US [4]. Within these 18 orphan blockbuster drugs, 11 reached blockbuster status within the 7-year orphan drug market exclusivity period [4].

The pricing of orphan drugs was critical. Genzyme was the leader in the fiscal model for high profits. They were the first to develop a drug for the ultra-rare market ($\leq$ 10,000 patients) and the first to charge a profitable price. They developed Cerezyme, an infusible enzyme replacement therapy for Gaucher's disease, at a cost of approximately $300,000 per patient per year. Other ultra-orphan drugs have followed providing a unique therapy previously unavailable at a high price. Today, Alexion Pharmaceuticals charges the highest drug price [7]. Their product Soliris is a first-in-class drug for life threatening paroxysmal nocturnal hemoglobinuria with a cost of $440,000 per patient per year [7]. The result is that Alexion share prices in the past 2.5 years have outstripped even the price of Apple shares [7]. Other companies like Sigma Tau and BioMarin have been successful at more modest prices. Shire, formerly a speciality company, has expanded since 2005 into orphan drugs with its Human Genetic Therapies division. Its drug Elaprase for Hunter's Syndrome, a disfiguring disease in 2000 patients worldwide, costs $375,000 per patient per year. How do patients pay for these therapies? So far insurance companies, Medicaid and nonprofit patient assistance organizations have helped and some companies also provide their drug free of charge through a patient assistance program.

Big companies such as Johnson & Johnson, Merck, Novartis and Bristol-Myers Squibb have established products in the rare disease market, while GlaxoSmithKline and Pfizer have created units to increase partnerships with biotech companies already in the rare disease space as well as their own research and development of drugs for rare diseases. Pfizer argues that it has already developed many products for rare diseases. These were in the field of oncology, but they were just not thought of as orphan or rare disease drugs.

Profits increase as the market widens and many rare disease drugs have found a second or even additional market for their product. Novartis demonstrated how its orphan drug Gleevec, which was meant to target the 9,000 patients in the US per year diagnosed with chronic myelogenous leukemia has been profitable because the drug has saved 9,000 lives per year since 2001, and the population of patients needing the drug to stay alive has grown proportionally. Gleevec was later found to be equally efficacious as a therapy for gastrointestinal stromal tumors, expanding the total patient population number using the drug to 120,000. In the 12 years since it was introduced, Gleevec has become a block-buster orphan drug.

4. Future prospects

Despite the seemingly obvious advantages for Big Pharma to increase its penetration into the orphan space, there are caution sign posts. There has been a debate about large pharmaceuticals entering the orphan drug market versus the smaller biotechs.

The concern is that Big Pharma companies may be bullish on rare diseases and enter like a bull in a china shop. The rare disease community has been built on the sensitivities of mothers, fathers and families with their sick loved ones so often going through a difficult and prolonged diagnostic odyssey. The community is largely made up of patient advocate groups and their specific clinicians, and often academic researchers, as the stakeholders. Biotech companies specializing in orphan drugs have built up credibility, compassion and sensitivity to the rare disease community. The community is an asset to work with. Patient advocates for orphan drug development, be it an initial or next-generation therapy, can be the key to increasing awareness and recruiting patients for clinical trials. Like investors, they also significantly control the perception of a company, its intentions and the success of its orphan product. Through their own links, particularly social media, the interconnected rare disease communities have made the old way of marketing a drug by a salesperson's relationship with physicians almost obsolete in the rare disease space. Marketing to a circumscribed community does not need expensive advertising.

Another caution is competition. Premium prices could be set by companies because there was no competition and the drug was first in class, such as Genzyme's Cerezyme. Now there are competing drugs. Pfizer's Elelyso is a new enzyme replacement treatment for Gaucher's disease, being sold at a lower price. Novartis first introduced Gleevec in 2001 for chronic myelogenous leukemia, and now other companies have introduced two other products Spycel (2006) and Tasigna (2007). Several other ultra-orphan drugs are now competing for the very small market.

Big Pharma have to build up trust and understanding in the rare disease space. It is in a strong position to introduce new therapies where they do not exist, and develop the scientific basis of new therapies. With the loss of major pipeline drugs large pharmaceutical companies now have spare facilities to produce large quantities of high quality orphan drugs. The new model may be a synergy of Big Pharma partnering with smaller companies where Big Pharma provides manufacturing and other infrastructure functions, and the smaller companies offer research and development of new orphan drugs as well as community relationships.

The rapid changes in the pharma model have created a complexity of information with new ideas for orphan drugs, and new therapies based on biological, stem cell and gene therapies. *Expert Opinion on Orphan Drugs* has been founded as a new online journal in response to this change. As Editor-in-Chief, we look forward to providing expert opinion at the forefront on many of the issues and bring the reader high quality information. We welcome your submissions on all issues concerning orphan drugs: current innovations and solutions, new regulations, changes in how clinical trials on small patient populations will meet FDA and EMA standards, problems of pricing orphan drugs and news about second generation therapies.

Declaration of interest

The author states no conflict of interest and has received no payment in preparation of this manuscript.

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