Introduction

Historically, there was little commercial interest in the development of drugs for rare diseases (DRDs) due to the limited market from which to assure adequate returns on investment [1]. Orphan drug legislation was introduced in many jurisdictions as a means to encourage investment into the research and development (R&D) of DRDs.

In 1983, the Orphan Drug Act (ODA) was established by the Food and Drug Administration (FDA) in the United States [2]. In December 1993, Regulation (EC) No 141/2000 of the European Parliament and of the Council on Orphan Medicinal Products was established in the European Union [3]. While legislation differs across jurisdictions, most offer similar incentives, including:

- Waived application fees and rapid regulatory review processes
- Market exclusivity (e.g., 10 years in the EU and 7 years in the US), and in some cases extended patent protection
- Financial grants and tax credits [1].

Orphan drug legislation has had an increase in the development of DRDs; however, this has not translated into improved patient access to DRDs.

Objectives

- Quantify the impact of orphan drug legislation on the development and market approval of DRDs in the US and EU.
- Explore the impact of orphan drug legislation on the funding of DRDs in the US and EU.

Methods

A comprehensive search of the published literature was performed using various search engines (e.g., PubMed, Google, and Google Scholar). Reference lists of relevant articles and quantitative studies that address the objectives outlined above were also reviewed.

Key search terms included variations of the following terms: orphan, orphan drug, orphan drug legislation, orphan drug designation and market authorization, access to DRDs, reimbursement, and funding.

Results

Success of Orphan Drug Legislation is Bittersweet

Orphan drug legislation successful in bringing new DRDs to market

- The introduction of orphan drug legislation in the US and EU has been extremely successful in stimulating R&D into DRDs, resulting in a rapid and significant increase in the number of commercially available DRDs (Figure 1).

- In the US, more than 200 orphan drugs and biologics have been approved and marketed since the inception of the ODA [4].

- In the EU, from the inception of Regulation (EC) no. 141/2000 in late 1998 to October 2010, 720 drugs received orphan drug designation from the European Medicines Agency (EMA), of which 65 were granted market authorization [5].

- In Europe, while decisions regarding orphan drug designation and marketing authorization are made at the EU level and encompass all 27 member states, individual member states retain the responsibility for reimbursement decisions.

- In a converging environment of cost containment, the growing number of DRDs reaching the market has led to concern among health care providers and payers regarding the high cost of DRDs, at both the per-patient and population level [6].

- In response to these concerns, some decision-makers are adopting approaches to evaluating DRDs for funding that are similar to those used to assess drugs for more common diseases.

- A gap has began to develop between the approval of DRDs and patient access as market authorization does not translate into market access for DRDs.

- Funding for DRDs will become increasingly more difficult to secure as additional DRDs reach the market and decision-makers become increasingly more prohibitive in their approval of new and expensive drugs.

- As a consequence, a gap has begun to develop between the regulatory approval of DRDs and patient access, as without funding from private and public insurers, DRDs are not affordable for the vast majority of patients [1].

- From 1983 through 2006, a total of 2,112 orphan drug designations were granted by the FDA; of these only 347 (16%) were approved by the FDA.

- Of the 347 orphan drugs, 95 were evaluated for Medicaid (Prescription Plan coverage) and only 44 (44%) had complete coverage [7].

- From 2001 to 2002, 492 orphan drug designations were granted by the EMA; of these only 44 (9%) were granted marketing authorization by the EMA; only 21 (47.7%) of the 44 drugs with marketing authorization were funded in all five of the largest European countries (Germany, France, the UK, and Spain) [8] (Figure 2).

- Even when funding exists, it can vary significantly across jurisdictions, resulting in inequality in patient access [9-11] (Figure 3).

- Across plans that constitute Medicare, there is a large variation in the coverage rate, with coverage varying from no or very low coverage (<5% plan coverage rate) to complete coverage (100% plan coverage) [12].

- In the Netherlands, manufacturers of DRDs are exempt from providing a pharmacoeconomic submission, whereas Scotland undertakes no such examination.

- Of the 38 orphan drug submissions to the Dutch Committee for Pharmaceutical Assistance in the Netherlands were granted a positive recommendation [11] (Figure 3).

- Of 37 orphan drug submissions to the Scottish Medicines Consortium in Scotland were granted positive recommendation, 16 of which were restricted recommendations [11] (Figure 3).

- In the US, orphan drug designations are assigned by the FDA’s Office of Orphan Product Development (OPD), while formulary decisions reside with individual payers.

- These approaches would be most successful if developed in collaboration with payers and manufacturers.

Conclusions

- The introduction of orphan drug legislation has led to unprecedented investment by manufacturers into the R&D of new and innovative DRDs.

- The growing number of ORs reaching the market has caused great concern among health care providers and payers regarding the high per-patient cost of DRDs and the cumulative impact of DRDs on total drug and healthcare budgets.

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