*Commentary*

# What Can Big Data Offer the Pharmacovigilance of Orphan Drugs?

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**ABSTRACT**

The pharmacovigilance of drugs for orphan diseases presents problems related to the small patient population. Obtaining high-quality information on individual reports of suspected adverse reactions is of particular importance for the pharmacovigilance of orphan drugs. The possibility of mining "big data" to detect suspected adverse reactions is being explored in pharmacovigilance generally but may have limited application to orphan drugs. Sources of big data such as social media may be infrequently used as communication channels by patients with rare disease or their caregivers or by health care providers; any adverse reactions identified are likely to reflect what is already known about the safety of the drug from the network of support that grows up around these patients. Opportunities related to potential future big data sources are discussed. (*Clin Ther.* 2016;38:2533–2545) 

**Key words:** big data, drug safety, orphan drug, pharmacovigilance, rare disease, social media.

## THE ORPHAN DRUG LANDSCAPE

Under the US Orphan Drug Act of 1983, a rare disease is one that affects <200,000 individuals (prevalence <650/million population);[1] ultra-rare diseases affect <20/million. In the European Union, Regulation EC 141/2000 defines orphan drugs as being for the treatment, prevention, or diagnosis of life-threatening or chronically debilitating disease affecting <5/10,000 (500/million).[2] Over a medical career, general practice physicians are unlikely to encounter an orphan disease, leading to a risk of missed cases even when an approved, effective therapy is available. It can take up to 20 years (average of 5.6 years in the United Kingdom and 7.6 years in the United States) to obtain a diagnosis for a rare disease, and patients with an orphan disease may visit a mean of 7.3 physicians before receiving an accurate diagnosis.[3] Many rare diseases are life-threatening or debilitating for the patient, emotionally and physically demanding for the caregiver, and financially burdensome to the health care system and society. Nevertheless, these so-called "orphan diseases" were historically an infrequent target for pharmaceutical companies because of limited opportunity for return on investment of expensive development costs, a lack of understanding of disease etiology, and the limited power of traditional drug discovery tools to target and modulate specific molecular targets. This situation has changed significantly in the last 10 to 20 years.

In the United States, the Orphan Drug Act of 1983[1] set up a dedicated office (ie, the Office of Orphan Products Development) and made provision for incentives for the development of drug treatments such as a period of market exclusivity and favorable tax treatment. The Rare Diseases Act of 2002[4] added the Office of Rare Diseases at the National Institutes of Health and increased funding, and draft guidance (*Rare*

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*Diseases: Common Issues in Drug Development*) was published by the US Food and Drug Administration (FDA) in 2015. Parallel initiatives, including the Precision Medicine Initiative[5] and the 2016 Orphan Products Natural History Grants Program,[6] encourage research into rare diseases and their treatment.

The EU Regulation EC 141/2000 established a centralized procedure for designating products as "orphan" and introduced incentives for the development of orphan products, including waived fees and market exclusivity for 10 years after authorization. The European Medicines Agency's Committee on Orphan Medicinal Products has reviewed applications for designation of a product as an orphan drug since its inception in 2000. Over the same time period, major scientific advances such as the Human Genome project and the eventual realization of the therapeutic promise of biotechnology, including monoclonal antibodies, antisense oligonucleotides, fusion proteins and many more approaches, have enabled pharmaceutical companies to bring forward potential drug treatments to address unmet medical needs for an increasing number of orphan diseases.

The result of these trends has been a large increase in orphan drugs under development and reaching marketing authorization in the United States and the European Union. There were 3735 products with orphan designation by May 2016, with 531 approvals since 1983[7] (Figure 1). There were 472 applications to the FDA for Orphan Drug Designation in 2015 alone, and the FDA's Director of the Office of Orphan Products Development, Gayatri R. Rao, MD, JD, predicted a 30% increase in 2016.[8] Of the 45 new molecular entities approved in 2015, a total of 21 (47%) were orphan drugs.

The European Medicines Agency website[9] listed 1314 products with active orphan drug designation by mid-2016 and an additional 373 products with a designation that had expired or been withdrawn; the number of orphan designation approvals by the Committee for Orphan Medicinal Products showed a steady increase from 2000 to 2015 (Figure 2). In the first 10 years after EC 141/2000, 58.3% of the marketing authorization applications for orphan drugs were approved,[10] and the number of marketing authorizations for orphan drugs increased 4-fold from ~3 per year to 12 per year over 15 years from 2001 to 2015.[11]

A comparison between the drugs approved in the first 7 years after the Orphan Drug Act and the drugs approved in the most recent full year (2015) listed at the FDA website reflects the evolution in science and increasing understanding of the molecular basis of

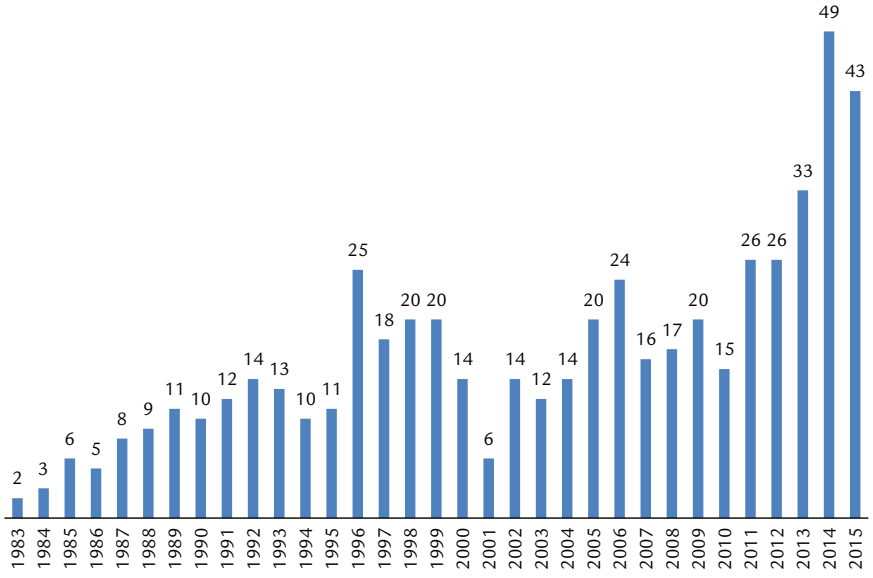


Figure 1. Approvals of drugs with an orphan designation by the US Food and Drug Administration, 1983 to 2015.