An assessment of orphan drug success rates in US and Europe

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Objective

• It has been 30 years since the introduction of orphan drug legislation in the US, and 13 years in Europe.1
• These legislation explicitly recognised the unmet need for rare disease treatments, and have led to a large number of drugs receiving orphan designation on both sides of the Atlantic.
• However, the number of drugs subsequently receiving marketing authorisation is relatively low. The aim of this study was to explore how the orphan drug success rate (approvals relative to designations) has changed over time in the US and Europe.

Methods

• Indication-level data on designations, approvals and withdrawals were obtained from the FDA and EMA orphan drug databases2,3, from the introduction of legislation (1983 US; 2000 EU) through to the end of 2013.
• The data was de-duplicated, such that only one indication per drug was considered – where multiple indications existed the earliest successful indication was selected.
• Previous studies have defined success rates as the proportion of approvals from the total pool of designations at any point in time. However, this does not provide an accurate understanding of temporal trends in success rates, as it fails to reflect the lag between designation and approval.
• For this study a dynamic, time-dependent analytical model was created to measure the annual success rate for orphan drugs by age (i.e. the number of years since a drug received designation).
• Figure 1 describes the analytical approach. A stock and flow matrix was created capturing new designations, withdrawals and marketing approvals by year. The model recorded the ‘age’ of each drug at each time point.
• The success rate in any year was calculated according to the age of drug at that time point, by dividing the number of approvals by number of designations of the same age. Figure 1b and 1c provides this information for 2013.
• Age-specific success rates were combined across time points and then compared for different time periods. For the US, data was compared by decade for the 30 years since the introduction of orphan legislation.
• Where orphan designation had been withdrawn before approval, these drugs were removed from the analysis.

Results

• 2,979 drug-indications were listed in the FDA database representing 2,200 unique drugs. 365 of these drugs received marketing authorisation between 1983 and 2013. 266 drugs were withdrawn from the list. Nine drugs had an approval date earlier than designation date, and were therefore also excluded.
• Figure 2 depicts the distribution of orphan drugs in US that obtained marketing approval by age (number of years since obtaining orphan designation). 80% of successful orphan drugs in the US obtained marketing approval within 6 years of designation.
• Figure 3 shows the annual success rate for orphan drugs in the US for three separate decades: 1983 – 1992; 1993 – 2002; and 2003 – 2012, and also the success rates in the EU from 2000 - 2013.
• Success rates in the US were seen to decrease consistently across all three decades, independent of drug age. Success rates in Europe were lower than in the US, even when comparing against the most recent decade of US data.
• When European data was analysed by 4 year time periods between 2000 and 2012, a similar pattern of diminishing success rates over time was observed.
• The number of orphan drugs that had not received marketing authorisation after 10 years of designation increased over the three decades (Figure 4). 93% of drugs that get approved do so within 10 years. Increasingly, there is a growing cohort of ‘zombie’ orphan drugs that account for 25% – 30% of current orphan drug designations in the US and which are unlikely to ever be approved.

Conclusion

• Success rates for orphan drugs appear to be falling over time in both the US and EU.
• This analysis looked at success rates by drug age (time since designation) and therefore adjusted for lag-effects which cannot explain the change in success rates over time.
• This trend may reflect the difficulty manufacturers face as they attempt to develop drugs for ever-more difficult to treat rare diseases.
• These results emphasise the need for continued support for research and development for rare diseases.
• The existence of ‘zombie’ orphan drugs that are unlikely to obtain marketing approval means that budget impact projections based upon designation numbers may overestimate the future cost impact of orphan drugs.

References

2. Orphan Drug Act 97-414, Jan 4 1993

Figure 1: Analytical approach

a) Age-specific matrix of designations and approvals by year

b) Distribution of drug ages in 2013 (US)

Figure 3: Success rate by year since designation after introduction of orphan legislation in US (by decade) and EU

Figure 4: Number of ‘zombie’ orphan drugs (US)