An overview of the orphan medicinal products licensed during the first 13 years of EU Orphan Drug Legislation

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Background

Since 2000, when the European Union (EU) Regulation on orphan medicinal products (OMPs) was implemented, development and marketing of drugs for the treatment of rare diseases have been fostered through specific incentives (10 years-marketing exclusivity, fee reduction/exemption, financial incentives, protocol assistance) and a number of previously unmet medical needs have been satisfied. However, in some cases, pharmaceutical companies appeared to exploit the privileged position of orphan medicine to get easier access to the market and maximize revenues. In fact, to take advantage of the EU incentives, pharmaceutical companies may purposely seek for niche indications. Drugs with questionable selectivity may be proposed for a rare condition and, once approved, may broaden their indications toward more frequent diseases (e.s. imatinib). Vice versa, drugs already approved for common disorders may seek for an orphan indication (e.g. ibuprofen). Other ambiguous approaches concern the recycling of old substances already used in therapy that may be reproposed as orphan, sometimes using mostly preexisting data, and sold with many folds increased prices (e.g. amifampridine). For this reason, there is an increasingly common concern regarding the need of refining the special market access status of orphan drugs to avoid possible cases of 'abuse' of the EU Regulation.

Aim

To provide an overview of OMPs approved so far in EU through a classification of the drugs according to a combination of criteria such as nature and origin of the active substances, number of authorized indications and development strategies suggesting possible cases of abuse/occupancy of artificial niche indications.

Methods

All orphan medicines approved between 2000 and 2012 were retrieved from the European Commission website. Multiple sources of information were consulted: the European Medicine Agency website, PubMed, the clinical database Micromedex and the drug reference Martindale. Information collected were used to classify OMPs on the basis of the active ingredient's nature (*synthetic*, *recombinant* or *natural/extractive*), origin (*new molecule*, *new indication of a known medicine* or *substance already used in therapy, now marketed as medicine*) and number of authorized indications, either orphan or non-orphan. Through authors' consensus, we also attempt to classify possible cases of abuse/occupancy of artificial niche indications (*from common to rare*, *from rare toward common* or *straight to rare*). Using marketing authorization (MA) dates, we observed the distribution over time of the different categories identified.

Results

Between 2000 and 2012, 77 OMPs have received MA for a total of 92 therapeutic indications corresponding to 69 main rare disorders. Fifty-six out of 77 orphan medicines (72.7%) contained a synthetic active ingredient while 17 (22.1%) were produced through recombinant technology. Considering the 92 indications at the respective time of approval, 48 (52.2%) concerned a *new molecule*, 35 (38.0%) a *new indication of a known medicine* and 9 (9.8%) a *substance already used in therapy, now marketed as medicine*. Thirty-two percent of OMPs were classified under the category *from common to rare* and 9.1% as *from rare toward common*. The distribution over time of the above mentioned categories showed a trend of increase regarding the approval of *recombinant* drugs, as well as a slight decrease of OMPs that followed potentially questionable development/marketing strategies.

Conclusion

Our results showed that MA have been increasingly granted to 'true' orphan medicine (new molecules specifically developed for an orphan disease), resulting in a more fair application of the EU legislation. The categories identified in this study, together with other indicators of quality and quantity of the evidence newly produced by applicants, may help to better address EU incentives through a merit-based approach and limit cases of 'abuse'.