Orphan drugs: post-marketing surveillance in Italy

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Although premarketing clinical trials are characterized by rigorous methodological approach, their several limitations do not allow to define the real efficacy and safety profiles of drugs. Only the use of drugs in a wide variety of people (i.e. different age groups, genders, races, lifestyles people with comorbidities or on multiple drugs, with varying nutritional status, etc.) will allow to obtain a complete knowledge regarding their safety profile, including information on rare, latent, long-term adverse drug events or changes in drug-effect frequencies, not identified during premarket clinical phases. For specific drug categories, such as orphan drugs, which are intended for the treatment of rare diseases, post-marketing surveillance performs a more important key role. In fact, differently from non-orphan drugs, orphan ones can be tested only in small numbers of patients, given the limited patient population with the rare disease.

According to the European Medicines Agency (EMA), an orphan drug is intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating, whose prevalence must not be more than 5 in 10,000; the medicine must be of significant benefit to those affected by the condition.. Rare disease and orphan drug development represent a relevant health issue worldwide. In the EU countries, almost 30 million people may be affected by one of over 6000 existing rare diseases. The 80% of rare diseases have identified genetic origins and almost 50% of rare diseases affect children. Considering the rarity of these diseases, pharmaceutical companies are reluctant to develop orphan drugs under normal market conditions, since the investments in research and product development is not recovered through sales due to the low demand. For such reasons, both the US and EU regulatory agencies, through specific legislations, are trying to boost and support the development programmes for medicine for rare disease. During 2015, 87 orphan drugs received marketing approval by EMA; among these, 66 were authorized and sold also in Italy. Almost the 40% of these drugs received the approval "under exceptional circumstances, which means that at the time of the evaluation it was deemed that the applicant could not reasonably be expected to provide comprehensive evidence on the safety and efficacy of the medicinal product. Therefore, such procedures allow drug authorization even when complete clinical data on safety and efficacy are not available; clearly, benefits derived from the availability of a drug on the market have to exceed any risks. So, authorization of orphan drugs relies on post-marketing research to cover incomplete information. In this scenario, the surveillance of orphan drugs in Italy turns out to be a topic of great importance and interest, because it represents a necessary strategy in order to guarantee effective and safe therapies for patients affected by rare disease.

In conclusion, nowadays in EU countries, including Italy, although the encouragement of drug development for rare diseases (by reducing pre- marketing times and regulatory processes), there is an urgent need to demonstrate that the orphan drug is safe and efficacious before its marketing approval and subsequent use by patients. This gap can be covered only with an accurate and reliable postmarketing surveillance. The management of post-marketing studies, such ad natural

history studies and observational studies, based on database and registries, will be able to provide us more information on safety profile of orphan drugs.