Drug repositioning: when compounding is worth for children treating

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DRUG REPOSITIONING

Pharmacological treatments of several pediatric diseases are limited by the lack of medicinal products properly indicated for the pediatric population. Pediatric-centric strengths of medicinal products are not always available, pushing healthcare operators and caregivers to manipulate existing adults' strengths to meet the therapeutic needs of children. Moreover, children are hardly enrolled in clinical trials performed in the pre-authorization stage of medicinal products, e.g., due to ethical issues, or the higher costs of enrollment. Such difficulties in conducting clinical trials have negatively influenced the authorization of innovative pharmacological treatments for pediatric and rare diseases. A possible solution for overcoming such issues may be found in drug repositioning. It is frequently associated with the serendipitous discovery of a novel therapeutic indication of an old active molecule for which the safety and efficacy profiles are well known to regulatory agencies and the scientific community [1]. Repositioned drugs can reach the market in 3-12 years, with an average cost of $300 million; the estimated success rate is five times higher (+ 30-75%) than for new compounds [2]. Despite these undisputed advantages, the cost-effectiveness of repositioned products is not easy to be estimated, especially when robust patent protection cannot be gained due to the available scientific knowledge and current clinical practice. For several rare diseases or for pediatric indications, many repositioned drugs are commonly compounded in hospital pharmacies regardless of the availability of industrial products (e.g., amifampridine for treating Lambert-Eaton myasthenic syndrome, ibuprofen for neonatal patent ductus arteriosus).

ANALYSIS ON REGULATORY HISTORY OF REPOSITIONED DRUG PRODUCTS

The study aims to analyze the clinical and regulatory history of some repositioned medicines intended to be used in rare diseases affecting childhood. Clinical and regulatory data were collected from the documents available on the EMA portal (e.g., EPAR, SPC). The treatment costs of industrial products and compounded preparations, equivalent in drug strengths, were extrapolated from the AIFA resolutions published on *Gazzetta Ufficiale* (i.e., Italy Official Journal) and calculated based on the *Tariffa Nazionale per la vendita al pubblico dei medicinali* (i.e., National rate list of medicines). Examples of medicinal products included in the study cholic acid for inborn errors in primary bile acid synthesis, glycopyrronium for sialorrhea, and propranolol for infantile hemangiomas. All analyzed medicines were authorized by EMA following a centralized procedure, in consideration of their status of orphan drugs as stated by EC regulation No. 726/2004. However, clinical data included in the authorization dossier is very heterogenous, ranging from literature data to clinical evidence. Since most of the investigated drug products had been compounded in hospital pharmacies before the MA application, a comparison of treatment costs between industrial product and compounded preparation (equal strengths or doses) was performed. The treatment costs of former ones resulted significantly higher than those of equivalent compounded preparations. For example, an equivalent dose (1.5g) of cholic acid (1.5 g) costs € 2,692.52 for the industrial product versus € 6.78 for the compounded preparation. This finding agrees with literature from other European countries [3]. Similar results were obtained for glycopyrronium and propranolol: in both case the treatment costs of industrial product is around 10-time higher than the compounded preparations.

CONCLUSION

The results highlight a clear need in reconsidering how to assess properly the cost-effectiveness of repositioned products, also considering the MAH frequently receive significant financial/scientific support from public or no-profit organizations, to find a balance between the MAH's economic sustainability and the patients' access to therapies.

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