BioChemMed

Technium BioChemMed vol. 7, pp. 13-18 (2023)
ISSN: 2734-7990
www.techniumscience.com

Legislative analysis regarding the need to change the legislative framework of pediatric medicines

Oana-Raluca Niculae[1], Cristina-Luiza Erimia[2*]

[1] Sf. Apostol Andrei County Emergency Clinical Hospital, Constanța, Romania
[2] Ovidius University of Constanta, Faculty of Pharmacy, Constanta, Romania

*Corresponding author: cristinaerimia@gmail.com

Abstract. There is currently a broad consensus that children deserve access to medicines that have been specifically developed and researched for use in young patients. However, until recently, the development and testing of pediatric drugs was far from satisfactory.
Although awareness of the lack of satisfactory treatment for children in the EU began to rise in the 1990s, the pharmaceutical industry showed insufficient interest in investing in the development of pediatric medicines. Economic considerations have also been a contributing factor to why companies have refrained from investing proactively in this sector. The fact that children grow and mature means that they are not a uniform subgroup. Therefore, in 2007, the EU introduced a regulation to stimulate the development of medicines for children.
In this context, this article aims to examine the regulation of pediatric medicines in the European Union, the impact of this legislation, and the need for future changes to the legislative framework in order to achieve the key objectives of the pharmaceutical strategy for Europe.

Keywords. European legislation, pediatric medicines, EU strategy, health systems, pharmaceutical sector

1. Introduction

The patient care landscape in the EU has undergone major changes. However, considerable unmet needs remain. Around 30 million citizens of the European Union are affected by one of the more than 6000 currently recognized rare diseases. The European Union considers diseases to be rare when they affect no more than 5 to 10,000 people in the EU. 80% of these diseases are of genetic origin and are often chronic and life-threatening; almost 90% can start in childhood.

For these patients and more than 100 million European children, treatment was either limited or non-existent before the introduction of EU legislation on rare diseases and medicines for children (in 2000 and 2006 respectively). This situation represented a huge unmet medical need and a significant public health challenge. There were often no drugs available to doctors treating patients with rare diseases.

When these policy challenges were identified, the EU already had a well-established legislative framework for medicines, which had developed considerably since its establishment in 1965. It covered the entire life cycle of medicines, from clinical research to post-market surveillance (pharmacovigilance). Its main purpose was and still is to ensure that

Technium BioChemMed vol. 7, pp. 13-18 (2023)
ISSN: 2734-7990
www.techniumscience.com

all medicines in the Union are authorized by demonstrating safety, quality and effectiveness before they reach patients.

Many of the products used in children were prescribed and administered based on the physicians' own experience rather than the results of clinical research. In addition, the drugs were often not available in a pharmaceutical form suitable for children. Pediatricians had to turn to drugs authorized for adults by adapting the dose and form.

2. Theory

Surveys suggested that in many therapeutic areas, off-label use was widespread, often reaching figures of over 50%. Immunization of children was a notable exception, being one of the success stories of modern medicine.

There are several reasons why the development of pediatric medicine has been largely neglected. Until the 1980s it was often argued that children should be protected from clinical research for ethical reasons. Economic considerations have also been a contributing factor as to why companies have refrained from proactively investing in the sector. The fact that children grow and mature means that they are not a uniform subgroup.

The Pediatric Regulation [1] was enacted to address this issue and legislative intervention was deemed necessary to reverse previous trends.

The regulation is structured around three main objectives:

- ✓ to encourage and enable high-quality research in the development of medicines for children;
- ✓ ensure, over time, that most medicines used by children are specifically authorized for such use in age-appropriate forms and formulations; and
- ✓ increasing the availability of high-quality information about medicines used by children.

To achieve these objectives, the regulation establishes a system of obligations, rewards and incentives and implements measures to ensure that medicines are regularly researched, developed and authorized to meet the therapeutic needs of children. It is based on the simple idea that a company should be required to check every product it develops for potential use in children, thereby progressively increasing the number of products with pediatric indications.

The regulation obliges companies to agree at an early stage in the development of a pediatric research and development program ("pediatric investigation plan") with the EMA. The regulation has a direct impact on companies' R&D spending, as it requires an investment in pediatric research. If a company does not comply with the agreement, its (adult) marketing authorization may be blocked. The regulation therefore goes beyond the mechanisms established by the legislation on rare diseases [2], which only provide incentives for companies.

The obligation provided for in the regulation is complemented by other measures, in particular:

- ✓ a system of exemptions for medicines that are unlikely to benefit children and a system of postponements in relation to the calendar of pediatric measures to be carried out;
- ✓ a reward for fulfilling the obligation: a six-month extension of the additional protection certificate [3];
- ✓ a specific reward for orphan drugs: two additional years of market exclusivity added to the existing 10 years granted under the Orphan Regulation;
- ✓ - a new type of marketing authorization, the pediatric marketing authorization (PUMA), to stimulate the development of pediatric indications for off-patent products;

Technium BioChemMed vol. 7, pp. 13-18 (2023)
ISSN: 2734-7990
www.techniumscience.com

- ✓ - an expert committee, the Pediatric Committee (PDCO), within the EMA; and
- ✓ - a system of free scientific advice for industry, provided by EMA.

In addition, the regulation promotes high-quality information and high-quality research through other measures, such as: an EU network of networks of investigators and study centers carrying out pediatric research (Enpr-EMA); an EU inventory of pediatric needs; a public database of pediatric studies.

One of the indisputable achievements of the regulation is that it attracts more attention and financial investment for pediatric development. Companies were virtually forced to establish pediatric infrastructure and develop expertise to ensure adequate pediatric research capabilities to support their product development.

3. Results and discussion

In 2013, the Commission published a first report on the impact of the regulation and concluded that there are some promising signs of progress [4]. In any case, he found that, because of the length of drug development, it would take at least 10 years to get a full understanding of the situation.

Article 50(3) of the Regulation required the Commission to publish a second report in 2017 [5]. The second report was also to consider whether changes to the regulation should be considered. This report is based on a 10-year report prepared by the European Medicines Agency (EMA) and its Pediatric Committee [6], an external study on the impact of the regulation ordered by the Commission [7], a public consultation and discussions with Member States, Parliament [8], patients, companies, stakeholders and external partners about their experiences of the regulation's impact.

The figures show that the regulation has had a substantial impact on the development of pediatric medicines in the EU. Pharmaceutical companies now view pediatric development as an integral part of global drug development, even though some continue to perceive pediatric research as regulatory rather than company-driven.

Between 2007 and 2016, more than 260 new medicines were authorized for use by children (new marketing authorizations and new indications), most of which were related to the requirements of the Regulation. The number of agreed Pediatric Investigation Plans (PIPs) exceeded 1,000 in 2017, of which 131 were completed at the end of 2016.

A comparison of the situation before and after the regulation demonstrates a clear positive effect in terms of new authorized medicines. The same is true for international comparisons between legal systems with and without pediatric legislation: legal systems with legislation in place have a significantly higher number of new pediatric medicines.

At the same time, the issuance of a marketing authorization or the addition of pediatric information to existing marketing authorizations does not automatically translate into the immediate availability of the product for all pediatric patients in the EU. This may be due to pending national reimbursement decisions or prescribing habits where physicians cannot switch directly to newly licensed products.

In this context, it is noted that companies often rely on a staggered launch of new products, resulting in delays until the product is finally available across the EU. This cannot be fully prevented even though the regulation includes several tools to ensure that once a PIP is completed and the pediatric medicine is authorised, the product is placed on the market. For example, the reward for the supplementary protection certificate under Article 36 will only be granted if the product is authorized in all Member States. Article 33 also contains the obligation to place the product on the market within two years of the date on which a new pediatric indication is authorised.

Technium BioChemMed vol. 7, pp. 13-18 (2023)
ISSN: 2734-7990
www.techniumscience.com

Timely availability of pediatric medicines may also be affected by the delayed completion of pediatric studies compared to the completion and authorization of the corresponding adult product. The regulation includes provisions for delaying the initiation or termination of some or all of the measures contained in a PIP (Article 20), so as to ensure that research is only carried out when it is safe and ethical. In addition, it is intended to avoid blocking or delaying the authorization of products for the adult population.

Experience shows that postponement is a widely used tool. Deferral is, in principle, a useful and appropriate tool, and there is no evidence that pediatric requirements have delayed the processing of applications for adult medicines. However, the Pediatric Committee agreed in some cases to very long delays. In addition, if the start of a pediatric study is delayed until after the authorization of adult medicines, experience shows that the recruitment of patients in pediatric studies becomes more difficult.

Given the progress of the science, it can be argued that accepting long delays is tantamount to calling into question the significant therapeutic benefit of product development over existing treatments for pediatric patients. In such cases, the added value of pediatric studies could be marginal. In addition, long deferrals may undermine the enforceability of pediatric requirements and the availability of any reward, particularly if the deferral ends after product protection periods have expired.

Regarding the Pediatric Regulation, the Commission Staff Working Document [9] shows that the main innovation to improve the landscape was the introduction of a legal obligation for all new medicines under development.

Also, the presentation and analysis of clinical data already available before the entry into force of the regulation allowed information on use in children to be added to almost 200 medicines. This means that these medicines can now be used more safely to benefit children too.

In contrast to these positive results, the evaluation also found that new pediatric products, such as orphan drugs, are not being developed in therapeutic areas where the needs are greatest. The Regulation does not have an effective tool to channel research and development into specific therapeutic areas. Thus, the regulation appears to work best in areas where the needs of adult and pediatric patients overlap. However, major therapeutic advances have mostly not materialized for diseases that are rare and/or unique to children and that often receive equal amounts of support under orphan legislation.

The existing design of rewards may not support the prioritization of product development in areas requiring pediatric specificity. This also applies to the main reward that the Regulation offers: the possibility to obtain a six-month extension of the supplementary protection certificate (SPC) to offset the cost of carrying out mandatory clinical trials in children. This reward has not proven effective in encouraging industry to develop medicines in accordance with the most pressing needs of children, where these differ from the needs of adults.

The other major rewards provided by the regulation, the additional two years of market exclusivity ("orphan reward") and the pediatric marketing authorization, PUMA, were rarely used. The orphan reward, which cannot be awarded in addition to the six-month SPC extension, is considered by developers to be less valuable than the SPC extension. Consequently, developers prefer to look for an SPC extension whenever possible.

4. Conclusions

The pediatric regulation has had a considerable impact on the development of pediatric medicines in the EU. He ensured that the development of pediatric medicine became an

integral part of global drug development. This result would not have been achieved without specific legislation and underlines its continued relevance. In addition, measures taken to improve its implementation have strengthened its effectiveness over time.

The regulation works best in areas where the needs of adult and pediatric patients overlap. In particular, in diseases that are rare and/or unique to children and that in many cases are equally supported by orphan legislation, major therapeutic advances have yet to materialize.

The PUMA scheme, designed to channel EU research funds to boost the development of new pediatric indications in off-patent medicines, has so far produced disappointing results. However, approximately 20 PUMA-related PIPs are ongoing, so results may improve over the next few years.

The regulation includes some tools to ensure that a pediatric medicine is placed on all EU markets once its PIP is completed and it has been authorised. However, the accessibility of pediatric medicines on EU markets can still be problematic, as their launch in the various EU markets is closely linked to the launch of the adult equivalent.

The legislation itself is perceived as burdensome by industry as it requires companies to establish a pediatric research plan (including pediatric study design) with the EMA at an early stage of development. However, in those early stages, the overall product development may be subject to considerable change, requiring changes to the PIP. This means that the companies concerned must submit requests for changes to the Agency. This is particularly problematic in the case of an innovative study design, where development plans are often shaped by results obtained in earlier phases of clinical development. Developers also see national authorization of pediatric studies as potentially burdensome, as in some cases it may contradict what has already been agreed in a PIP.

The effects of the Pediatric Regulation cannot be viewed in isolation. Although it is an enabler, its objectives must be aligned with other policies to create a seamless ecosystem from research and development to marketing. Any future adaptations should take into account all stages of public intervention.

References

[1] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, published in the Official Journal of the European Union L 378 of 27.12.2006.

[2] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, published in the Official Journal of the European Union L 18 of 22.1.2000.

[3] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products, published in the Official Journal of the European Union L 152 of 16.6.2009.

[4] EU Monitor- *Report. Better Medicines for Children - from concept to reality: report on experiences acquired from applying Regulation (EC) 1901/2006 on medicinal products for paediatric use*, COM(2013)443 available at: https://www.eumonitor.eu/9353000/1/j9vvik7m1c3gyxp/vjaskhqodszy

[5] European Commission, Report from the Commission to the European Parliament and the Council, *State of Paediatric Medicines in the EU. 10 years of the EU Paediatric Regulation*, COM (2017) 626, available at:

Technium BioChemMed vol. 7, pp. 13-18 (2023)
ISSN: 2734-7990
www.techniumscience.com

https://ec.europa.eu/health/system/files/2017-11/2017_childrensmedicines_report_en_0.pdf.

[6] European Commission, *10-year report to the European Commission – General report on the experience acquired as a result of the application of the Paediatric Regulation*

[7] Technopolis Group, *Study on the economic impact of the Paediatric Regulation, including its rewards and incentives*, Final Report, December 2016 (SANTE/2015/D5/023, Section 2.3.1).

[8] European Parliament resolution of 15 December 2016 on the regulation on paediatric medicines, (2016/2902(RSP), available at: http://www.europarl.europa.eu/doceo/document/TA-8-2016-12-15_EN.html#sdocta7.

[9] European Commission, Commission staff working document evaluation, *Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products*, Brussels, 11.8.2020 SWD(2020) 163 final, PART 1/6