Questions and Answers on 10 years of the EU Paediatric Regulation

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Why does the EU need special legislation for children's medicines?

Before the Paediatric Regulation came into force there was a very serious gap in the development and testing of medicines for children. Many products used in children were prescribed and administered based on physicians' own experience rather than on the results of clinical research. Medicines were often not available in a form suitable to children. Doctors had to do their best to adapt adult medicines and get the dosage right for children, e.g. by crushing adult tablets and using only a portion depending on a child's weight. This off-label use of adult medicines was widespread – estimated at more than 50%. Such practice comes with the risk of inefficacy as well as serious side effects.

What are the main aims of the Paediatric Regulation?

The Regulation is structured around three main objectives:

- More medicines for children
- Better product information
- More paediatric research

How does the Regulation set out to meet these objectives?

The Regulationsets up a system of obligations, rewards and incentives to encourage manufacturers to research and develop medicines for children's specific therapeutic needs. It obliges companies to screen every new product they develop for its potential use in children, to progressively increase the number of products with paediatric indications. This is done at the earliest stage of development through the 'Paediatric Investigation Plan' (PIP) which is an obligatory part of overall product development.

In addition, the Regulation promotes high-quality information and high-quality research into medicines for children through measures, such as:

- an EU network of networks of investigators and trial centres carrying out paediatric research;
- an EU inventory of paediatric needs;
- a public database of paediatric studies; and
- a requirement for companies to submit any existing paediatric studies on authorised medicinal products for scrutiny by regulatory authorities.

Is progress in children's medicines really thanks to EU legislation?

A comparison of the situation before and after the Regulation demonstrates a clear positive effect in terms of new authorised medicines. During the period the Regulation has been in force (2007-2016) over 260 new medicines (new marketing authorisations and new indications) for use by children were authorised, most linked to the Regulation's requirements. The number of agreed paediatric investigation plans (PIPs) surpassed 1 000 in 2017, of which 131 were completed at the end of 2016. There is a clear upward trend in the number of completed PIPs, with over 60 % finalised in the last three years. This quantitative analysis shows clear progress. The figures are also in line with expectations taking into account the time it takes to bring a new medicine to the market - up to 10 years.

Are these new medicines actually reaching children?

Issuing a marketing authorisation or adding paediatric information to existing ones does not necessarily mean that children will immediately benefit from these products. Reimbursement considerations at national level may slow down the roll-out, and Paediatricians may not immediately switch to newly authorised products. In a survey that provided input to this report[1], respondents estimated that the increase in available medicines is in the range of 5-10%. On prescribing habits, 58 % of respondents agreed that doctors increasingly prescribe approved medicines according to their

licensed indication for children, as a result of the Regulation. This demonstrates a positive trend, but also underlines certain inertia. Reducing off-label use in children depends not only on the number of authorised paediatric medicines, but on real availability and use at bed-side.

What are the costs vs benefits of the Regulation?

On the one hand the legislation obliges pharmaceutical companies to carry out paediatric research, requiring additional investment. On the other hand this obligation is linked with a reward system that allows companies to recuperate the additional upfront costs. The report concludes that in economic terms, the Regulation provides overall positive results from a socioeconomic perspective demonstrating the appropriateness of this direct investment in improving the availability of paediatric medicines. The combination of obligations and rewards seems effective to shift focus to paediatric product development. Still a considerable number of completed PIPs (45%) failed to obtain a reward and there are instances of over- or under compensation pointing to certain limitations of the current system.

Where are the biggest advances seen, and why?

In the last 10 years we have seen an increase in medicines for children in many therapeutic areas, the most notable being Rheumatology and infectious diseases. Indeed, the significant surge of new treatments for children with rheumatologic diseases following the completion of PIPs has transformed a sector which was previously neglected.

The areas with the biggest advances are those where the greatest strides are being made in the adult market. As the starting point for most PIPs is a research and development programme for adults, progress in children's medicines depends on companies' adult product pipeline and is influenced by specific market segments that make the biggest profits. Where the adult needs or market expectations overlap with paediatric needs, children will benefit directly.

In which areas is progress considered insufficient?

The least progress is being made in diseases that are biologically different in adults and children, where the disease burden differs, or when it only affects children. This is often the case with rare diseases, including childhood cancers. Considering the progress made in treating cancer in adults in the last decade, this is a very serious shortcoming. Although cancer in children is rare, it is still the leading cause of death in children past the age of infancy.

How can we make progress in rare diseases in children?

The Commission, needs to scrutinise with regulatory authorities and stakeholders, how to combine the effects of the Paediatric Regulation and the Orphans Regulation[2] to increase the number and quality of medicines that treat rare diseases – including rare cancers, in children. On the one hand, the Paediatric Regulation provides the rewards, incentives and obligations described above. In parallel, the Orphans legislation – which aims to increase the treatment options available for rare diseases patients, sets out other incentives such as a 10 year market exclusivity or fee waivers for the regulatory procedure. The Commission needs to – and will by 2019 – conclude a joint evaluation of the Paediatric and Orphan Medicines legislation to allow the next Commission to take an informed decision about possible policy options.

What can be done in the shorter term?

In the meantime, the Commission will, together with the European Medicines Agency, take positive actions to streamline the current application and implementation of the Regulation wherever needed. This includes, for example, looking at ways to ensure speedier completion of PIPs, considering whether the Commission's guidelines for handling PIP applications should be adapted, discussing paediatric needs in an open and transparent dialogue involving all relevant stakeholders, and fostering international cooperation and harmonisation.

Additionally, the European Reference Networks for rare and complex diseases, which started their work in March 2017, have the potential of significantly improving diagnosis and treatment and of influencing prescribing practices. The Commission will help ensure that these Networks have access to sustainable funding and the necessary IT tools so that they reach their full capacity.

For more information

Children's medicines report

Press release

European Commission:https://ec.europa.eu/health/human-use/paediatric-medicines_en

European Medicines Agency

[1] Technopolis study, chapter 5.

[2] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December

1999 on orphan medicinal products, OJ L 18, 22.1.2000, p. 1.

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Press contacts:

Anca PADURARU (+ 32 2 299 12 69)
Aikaterini APOSTOLA (+32 2 298 76 24)

General public inquiries: Europe Direct by phone 00 800 67 89 10 11 or by email