RICERCA E ASSISTENZA NELLA PEDIATRIA CHE CAMBIA: LA PRESCRIZIONE OFF LABEL

TAVOLA ROTONDA: PROPOSTE E POSSIBILI SOLUZIONI SULLA GESTIONE DEI FARMACI OFF LABEL IN PEDIATRIA

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Public consultation on Paediatric Regulation No 1901/2006

Nov 2016: the EU Commission launched a public consultation on the experience acquired on the Paediatric Regulation No 1901/2006

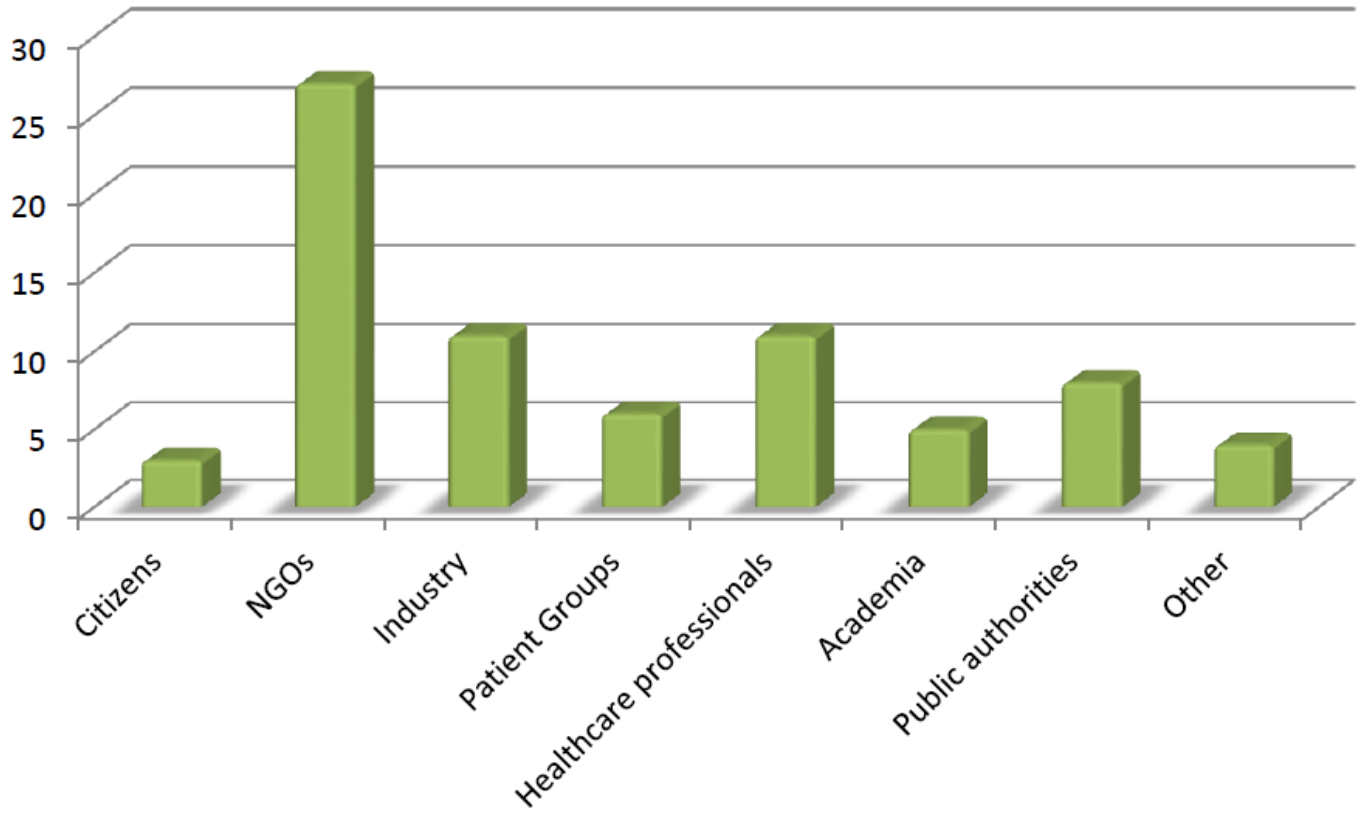
The **Paediatric Regulation** came into force in the European Union (EU) on 26 January 2007. Its objective is to improve the health of children in Europe by facilitating the development and availability of medicines for children aged 0 to 17 years.

This consultation, reflecting the period between 2007 and 2016, includes:
- an analysis of the economic impact of its rewards and incentives
- its consequences for public health and child health

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp

Respondents to the public consultation

75 responses: from a variety of stakeholders representing pharmaceutical undertakings, patient organisations, NGOs, as well as public institutions including regulatory agencies and national ministries. Healthcare professions, academia, research networks and other associations also contributed



A 10 year-report on Paediatric Regulation

The Paediatric Regulation has had a very positive impact on paediatric drug development. It has led to:

- more medicines for children as well as better and more information for prescribers and patients;

- better paediatric research and development;

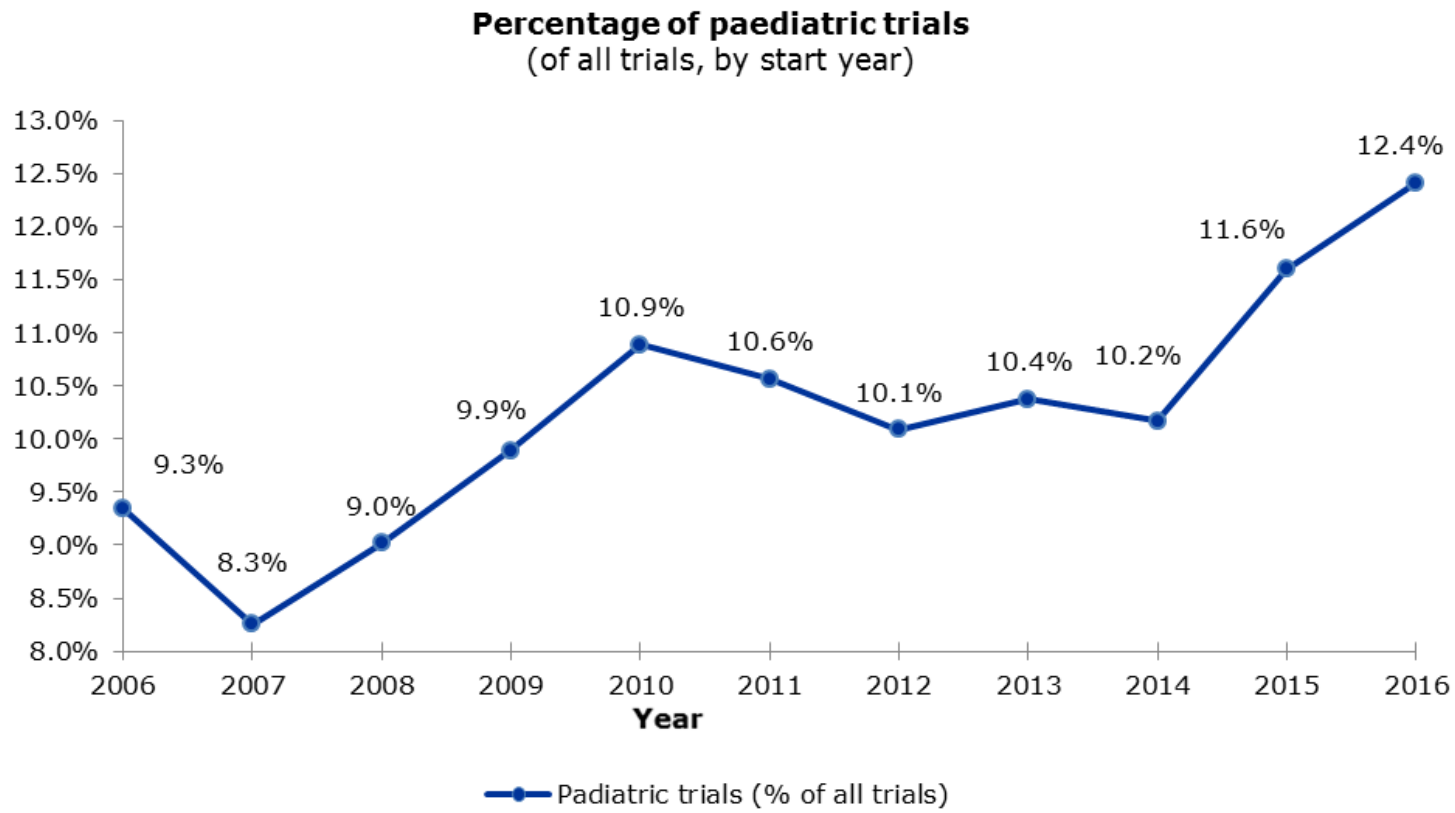
- more regulatory support for paediatric matters and

- paediatrics now being an integral part of medicine development.

Since the implementation of the Regulation, from 2007 until 2016, **267 new medicines for use in children and 43 new pharmaceutical forms** appropriate for children were authorized in the EU.

Percentage of Paediatric Clinical trials

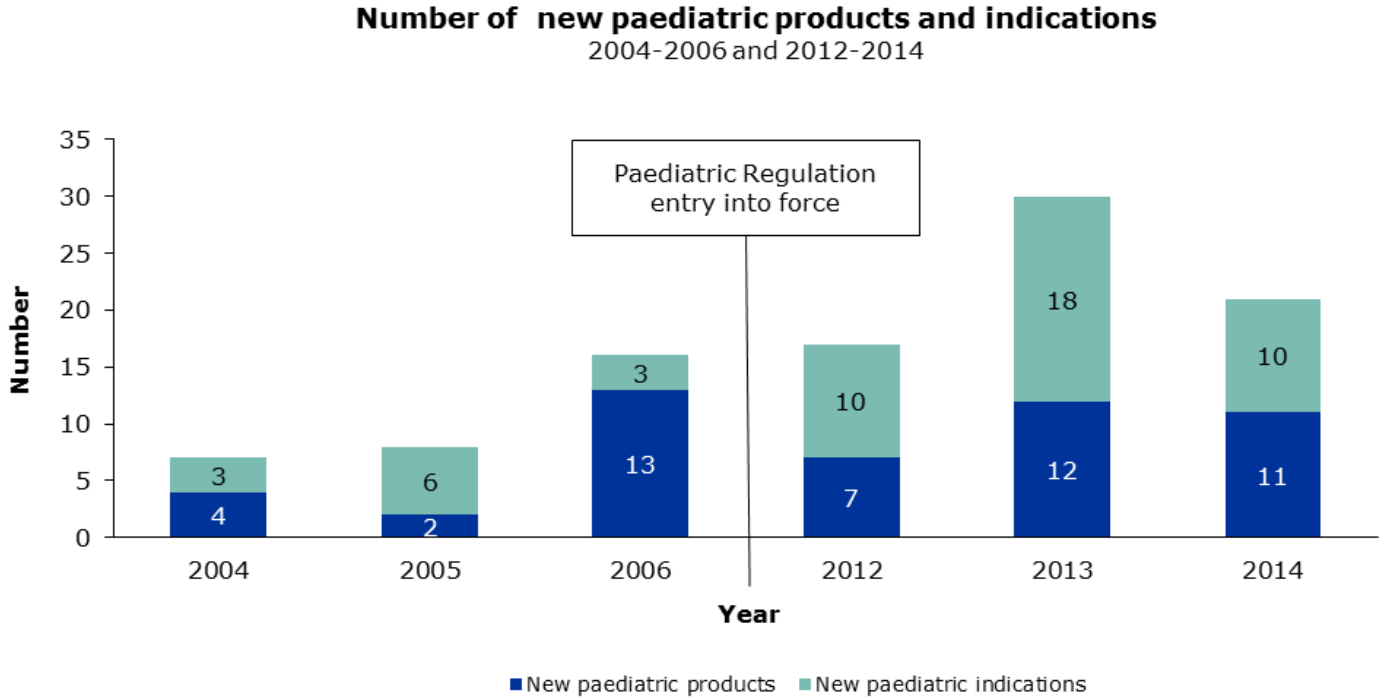
The proportion of clinical trials in the European clinical trial database EudraCT that include children has increased by 50 % in 2007-2016 from 8.25 % to 12.4 %.



More Medicines and Better Information

The increasing of medicines becoming available to children are illustrated by an analysis of the medicines authorised via the centralised procedure (CAPs) for the 3 years immediately before the Paediatric Regulation entered into force compared with the 3 most recent years at the time of the analysis.

The number of new medicines/indications receiving authorisation for use in children more than doubled over the second reference period: 68 compared with 31 (Figure 1.)



In addition to supporting new indications and products, data on the use of medicines in children (e.g. safety information, warnings, contraindications) is also valuable as it improves the product information.

A 10 year-report on Paediatric Regulation

Significant problem:

Lack of authorised medicines and consequent **off-label use** due to:

•the difficulty in conducting clinical trials,
•the relatively low patient numbers
•the generally smaller size of the market.

In neonates, the situation is particularly challenging due to the vulnerability of newborns and even lower patient numbers.

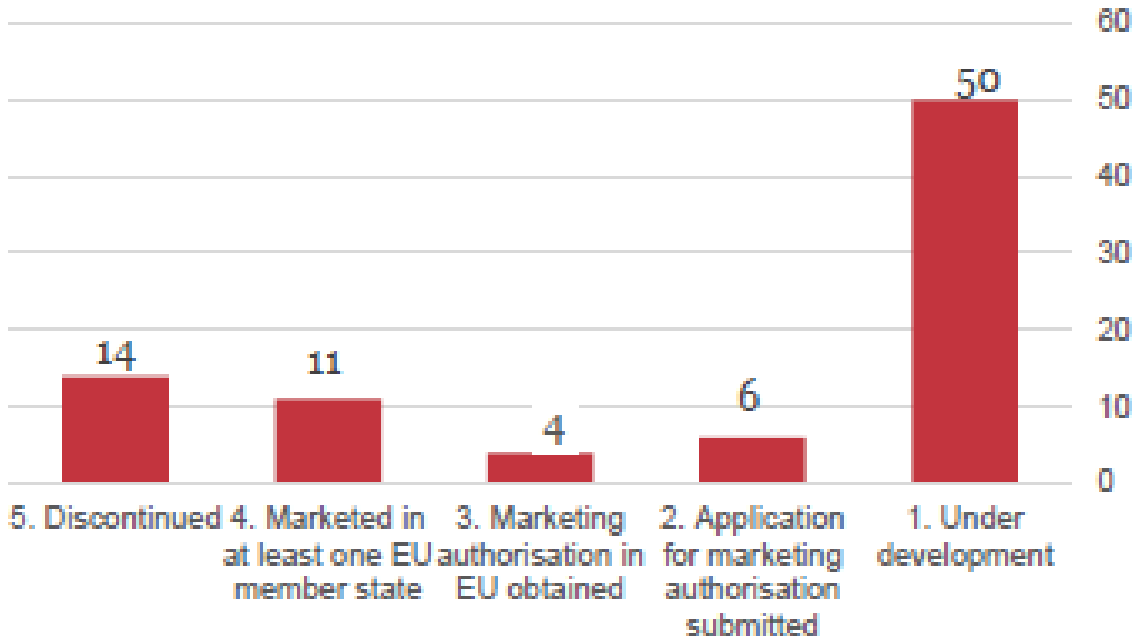
Paediatric Use Marketing Authorisation (PUMA)

The Paediatric Regulation introduced a new type of marketing authorisation, the **Paediatric Use Marketing Authorisation (PUMA)**.

As an incentive to carry out research in the potential paediatric use of off-patent medicinal products that have been authorised for adults, this marketing authorisation offers 10 years of data and market exclusivity to any new off-patent product that has been developed exclusively for use in the paediatric population. Thus, the main goal of the PUMA concept is to stimulate research in existing products. This scheme has been supported in the past by EU funding through the EU Framework Programmes for Research and Technological Development.

Regulatory impact of the Paediatric regulation

Figure 2 Distribution of PIPs with regulatory data collected, by paediatric product stage



Data collected on 36 waiver applications from 11 organisations (not all organisations submitted a waiver application) and on 85 PIPs from 24 organisations (two organisations only submitted waiver applications).

Regulatory and impact costs analysis

The total cost of the Paediatric Regulation incurred to industry is estimated to be €2,106m/year or €16,848m for the years 2008-2015.

The annual cost estimate includes €2,103m PIP-related compliance costs and €3.6m costs for waiver applications.

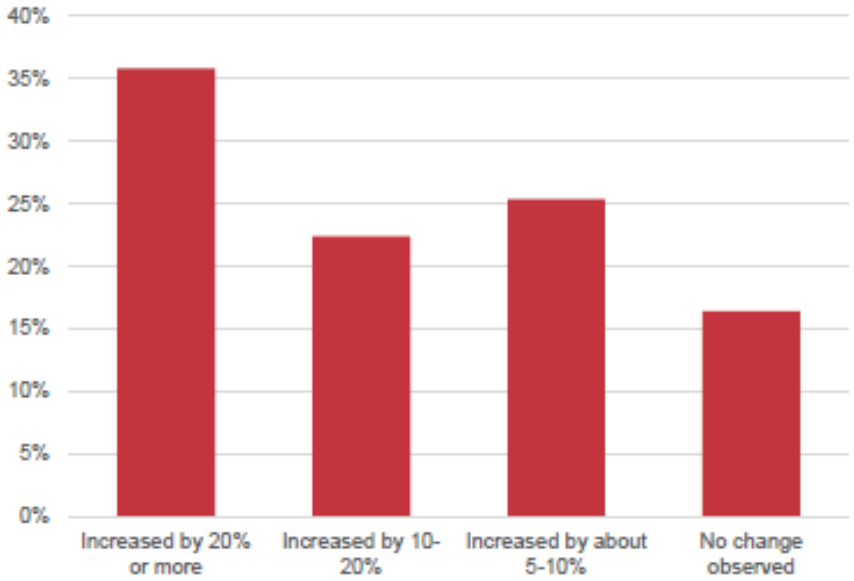
On average, relatively lower than the costs of other R&D costs (considering Clinical Development Plan, in-vitro, etc.).

Table 1 Overview of total costs of developing and executing PIPs

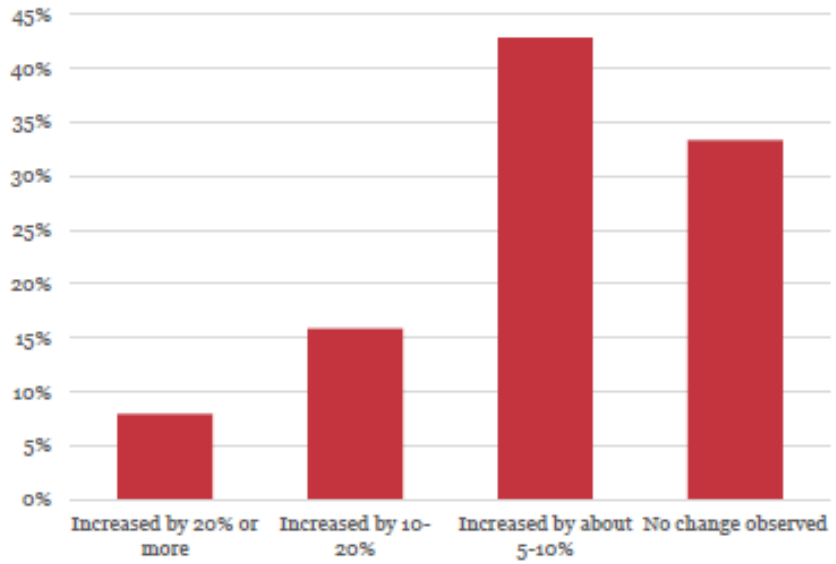
	Estimated annual costs
Total administrative and R&D costs of PIPs for the industry per year (2008-2015)	€2,103m
Average cost per PIP	€19,608k
Average administrative cost per PIP	€728k
Average R&D cost per PIP	€18,879k

Aggregation is based on an average of 107.3 first PIP decisions in 2008-2015 (858 first PIP decisions in 2008-2015 in total).

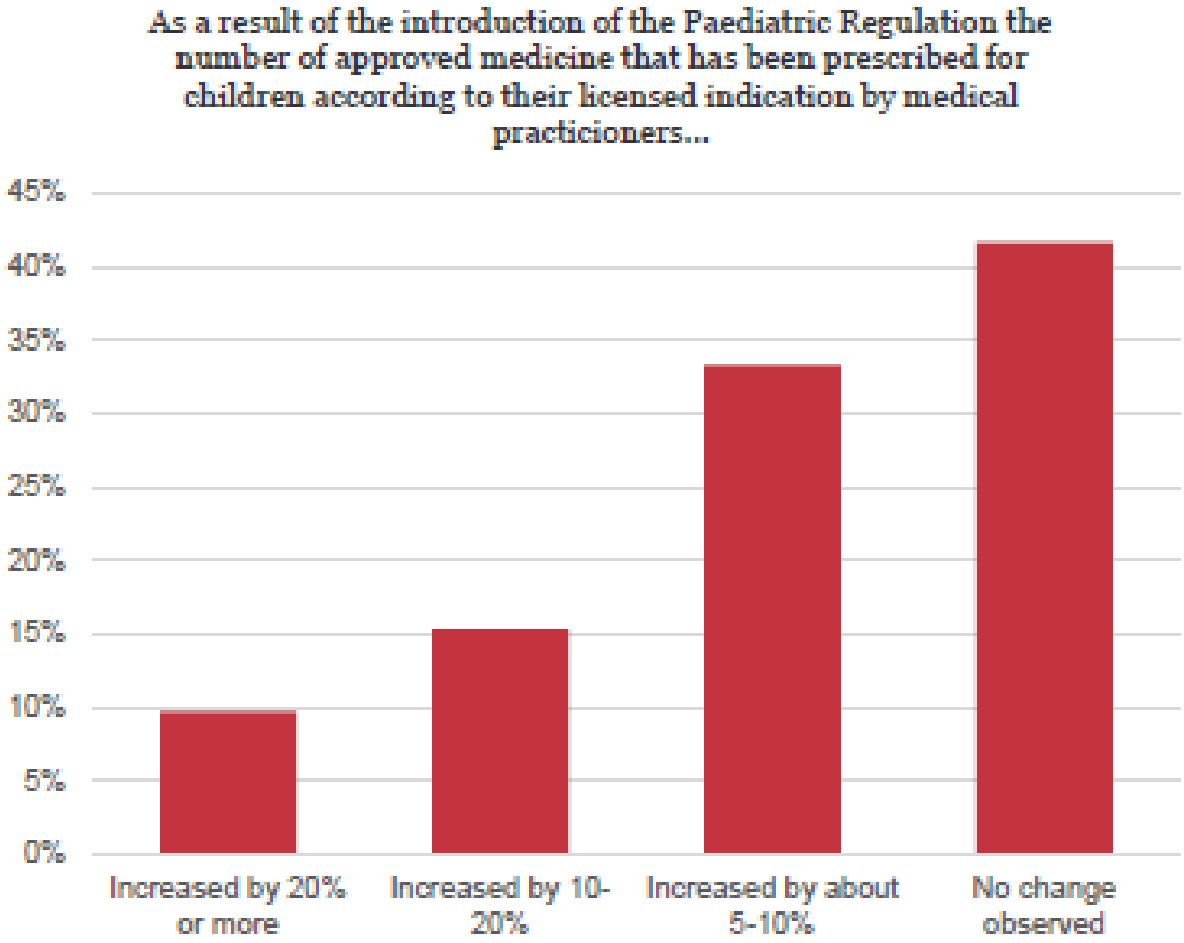
As a result of the introduction of the Paediatric Regulation the number of medicine evaluated and tested in the paediatric population within clinical trials...



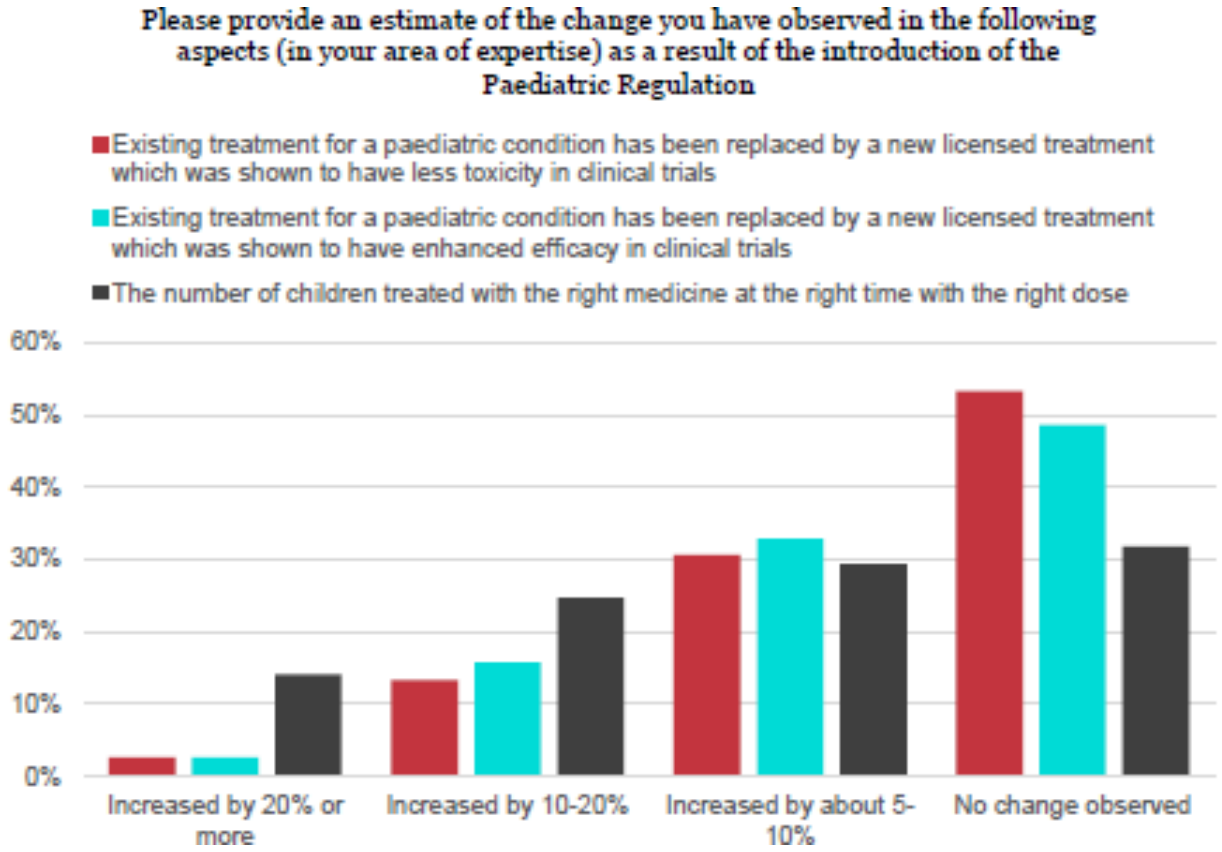
As a result of the introduction of the Paediatric Regulation the number of tested medicine available for approved use in children (ie. marketing authorisation obtained for paediatric use)...



Question on Prescription



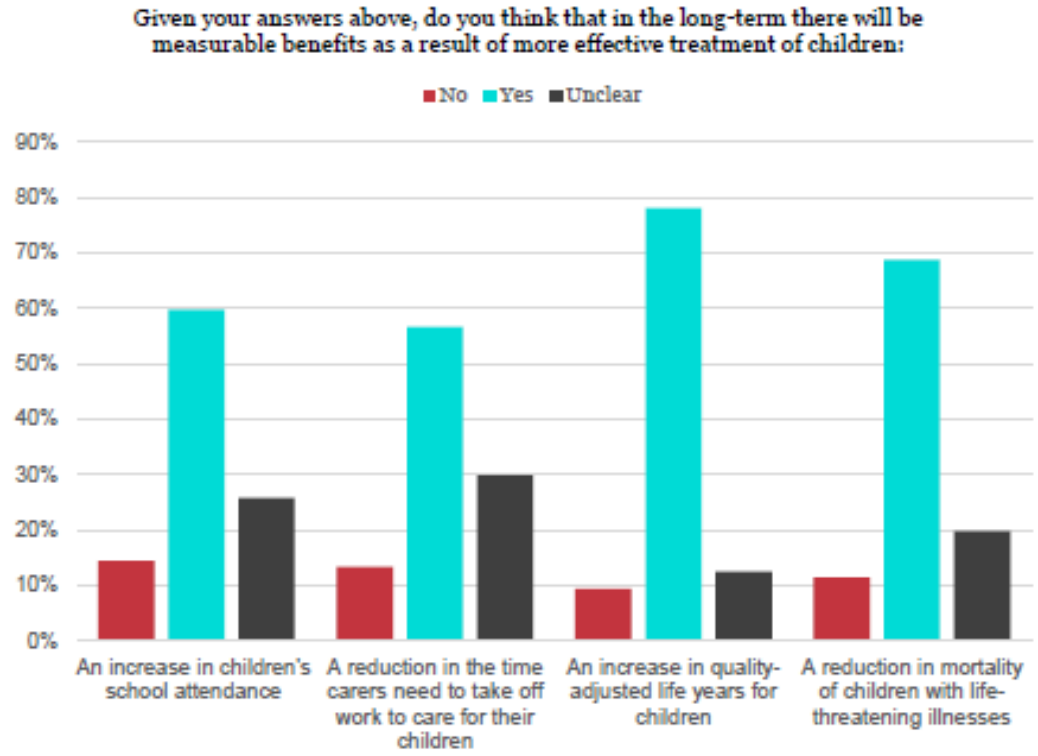
Introduction of the Paediatric Regulation had led to an improvement in the treatment of the paediatric population on one or more of three dimensions: i.e. less toxic medicines; more efficacious medicines; increases in the numbers of children and young people treated with the right medicines at the right time and with the right dosages



Question 7 invited respondents to go one step further in considering wider socio-economic impacts

Respondents were asked to indicate if, in the long-term, the regulation would have a measurable benefit on:
- Children's school attendance
- Time cares need to take off work to care for children
- Quality-adjusted life years for children
- Mortality rates of children with life-threatening illnesses

The majority of respondents, i.e. 60%, 57%, 78%, and 69% respectively, expect there will be measureable benefits. The remainder of respondents are either unclear about the impact or judge there will be no measurable benefits (9%-14%).



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RA Paediatric Cluster and Harmonization

In 2007, EMA and FDA established the Paediatric Cluster to discuss (through monthly teleconference) product-specific paediatric development issues under a confidentiality agreement (now also joined by Japan, Canada and Australia). The objective of these exchanges is to enhance the science of paediatric trials (discussions on end points, safety and feasibility issues) and to avoid exposing children to unnecessary trials. Since 2007, the FDA and EMA have exchanged information on a total of 413 products and held 132 discussions on general topics. A Common Commentary has been developed as a tool to inform paediatric trial sponsors about non-binding discussions at the Paediatric Cluster of products that have been submitted to both FDA and EMA.

Despite some of the difficulties in harmonising the submissions to EMA with those to the FDA, there are substantial opportunities for data sharing. This joint approach has the potential to contribute to lower regulatory costs to companies overall and thus enhanced efficiency.

Take Home Messages

The Paediatric Regulation had a considerable impact on the development of paediatric medicines in the EU.
This result would have not been achieved without specific legislation and underlines its continued relevance.
Moreover, measures taken to improve its implementation have over time strengthened its effectiveness.

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.

However, the PUMA concept with its specific reward has failed to deliver.