3.1 Results of the Delphi Survey

Table A.21: Development of clinical trials within the paediatric population

For this first question, the survey revealed a broadly positive view overall of the EU Paediatric Regulation’s effect on medicines development. A majority of survey respondents stated that the Paediatric Regulation had led to a situation where all European medicines in development consider clinical trials within the paediatric population. 54% of respondents judged the EU Paediatric Regulation to have had a positive or highly positive effect on companies’ behaviour already (2015) in respect to their consideration of clinical trials within paediatric populations for all medicines development in Europe. Around 15% of respondents recorded a negative view about this statement, suggesting the regulation has yet to create a situation where all medicines in development will consider paediatric clinical trials.

The survey found that a larger majority expect the regulation will have had an important and positive effect on European medicines development by 2020. Over 70% of respondents signalled a positive view of the likely situation at the end of 2020. Positive developments referred to include the initiation of early consultation of clinicians by sponsors to better consider patients’ needs and improvements in the data on dosing, safety, and efficacy in children. The swing in positive votes between 2015 and 2020 is largely driven by the switching of votes from neutrals to positives.

The proportion of sceptics was largely unchanged: around 14% of survey respondents view the likely situation at the end of 2020 negatively as compared with around 15% for 2015. Respondents provided additional comments in which they expressed reservations about progress and notable concerns included the following:

Source: Technopolis survey. The number of respondents for each sub-question are: 108, 110 and 112
• Relatively small number of marketing authorisations of paediatric medicines, to date
• Slow progress in certain therapeutic areas e.g. oncology, psychiatry as well as in neonatology
• Concerns over the PIP waivers granted
• Scarce (EU) funding provision to sustain future paediatric medicine developments
• Continued use of off-label medicines for children
• Concerns over long delays in the process and deferrals

Table A.22: Increase in research, awareness and information

Survey respondents were asked to what extent they agree with four statements. 69% of the respondents agree or strongly agree that the number of paediatric research projects is increased. 16% of the respondents disagree or strongly disagree with this statement, one of whom went on to write that there has not been enough progress, and to list several studies in support of that position. One of the references included a study by Van Riet et al. (2016)152 that analysed the availability of licenced paediatric drugs and the development of new indications or new routes of administration for the paediatric population. This study concludes that “further research in some areas of paediatric drug development is required in order to ensure that paediatric drugs are age-appropriate and of the required standards, e.g. safety of excipients, acceptability testing”. 65% of the respondents agree or strongly agree with the statement that more quality information is available on approved medicines for their
use in paediatric population (i.e. product label and summary of product characteristics). 15% of the survey respondents disagree with this statement. 87% agree that the awareness of health professionals has increased as regards the need to better evaluate medicines in the paediatric population. A small minority, 7% of the respondents, disagrees with this statement.

A wider range of international paediatric networks (e.g. TEDDY, PENTA, PRINTO) and research consortia have been established in Europe, some with the support from the European Commission (EC) and following the introduction of the Paediatric Regulation. GRiP (Global Research in Paediatrics) and SMART (Small Medicines Advanced Research and Training) are developing training programmes to increase the quality and the methodological level of paediatric clinical research. As a result, public-private partnerships have been able to mobilise the scientific and clinical community to devise clinical development plans that are acceptable to regulators and conduct clinical studies.

There is no consensus as to whether the awareness of the general population has increased as regards the need to perform more paediatric clinical research or the related need for increased participation in paediatric clinical trials. 47% of respondents judged that the awareness of the general population has increased, following the introduction of the regulation. For example, one respondent noted that the regulation had made it easier to explain the importance of allowing children to participate in clinical trials. A significant minority (27%) of respondents disagreed. Several respondents went on to write that awareness of these issues outside of the pharmaceutical industry remains poor. One contributor wrote that more time is needed to see any substantive effect of the regulation on the increased awareness among the general population, simply as a result of the long development phase, deferrals, modifications to PIPs etc., (only a small proportion of paediatric products have labelling changes as a result of the regulation).

Several other respondents argued that the impact on awareness would have been greater if more (EC) support had been devoted to communications campaigns. Respondents referenced several papers that explain the importance of communication, including an earlier study by the RCPCH (2012) highlighting the practical challenge faced by those wishing to increase volumes of paediatric research due to the general difficulties of engaging patients and other members of the public in trials in part because of a limited appreciation of the importance of such work.¹

Table A.23: Changes in the evaluation, testing and approval of paediatric medicine

Question 3 invited respondents to estimate the effect of the regulation on the number of medicines being tested through clinical trials in the paediatric population, and to indicate extent of any such change. The overall results are encouraging, with 84% of respondents indicating that there had been a measurable increase in the numbers of medicines tested within paediatric populations in the period since the implementation of the regulation, with more than a third suggesting the regulation had led to an increase of 20% or more. Respondents felt that without the regulation, the paediatric studies, agreed as part of a PIP, would not have taken place. 16% of respondents reported no observable change. One respondent noted that a number of waivers had been granted. Another respondent argued that while the European Clinical Trials Database (EudraCT) shows there has been an increase in paediatric clinical trials, it may not in whole be the result of the Paediatric Regulation as the increase mirrors a wider trend of increasing numbers of adult and mixed clinical trials.

Table A.24: Number of tested medicine available for approved use in children
The survey asked people to indicate if, as a result of the introduction of the Paediatric Regulation, the number of tested medicines available for approved use in children had increased. The majority of survey respondents indicated that there was an increase (67%) and 43% of respondents estimated that the increase was in the range 5-10%. In addition, respondents flagged the fact that many PIPs are still ongoing, and some have been deferred, and that more medicines would be approved in the near future. For example, in oncology or psychopharmacology, a substantial proportion of the drugs that are used to treat children are still used off-label and, in particular in this therapeutic area, there may not be sufficient research/support for research.

A study by David C. Radley et al. (2006) found that 73% of off-label use had little or no scientific support. A 2009 study by Alicia Bazzano et al. found that 62% of U.S. paediatric visits from 2001-2004 included off-label prescribing, with younger children at higher risk of receiving off-label prescriptions.

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3 Alicia Bazzano MD MPH; Rita Mangione-Smith MD; Matthias Schonlau PhD; Marika Suttorp MS; Robert Brook MD ScD (2009). Off-label prescribing to children in the United States outpatient setting. Ambulatory Pediatrics 9.
On the question of prescription, a small majority of respondents, 58%, indicated that medical practitioners are increasingly prescribing approved medicines according to their licensed indication for children, as a result of the Paediatric Regulation. The majority of respondents that reported an increase in prescriptions, estimated the scale of that increase was in the range of 5-10%. Several contributors went on to provide written comments noting the large volume of PIPs that are yet to achieve marketing authorisation and the natural time lag that this creates, with only limited numbers of new or newly indicated medicines available to be prescribed. Survey respondents also noted that paediatric drug development had been swifter in some therapeutic areas, e.g. antibiotics, and less swift in others, e.g. oncology and tuberculosis. Respondents also noted that paediatric drug development for infants and neonates is particularly slow (lagging); and that many medicines have not yet been tested and are currently often used off-label.

Table A.25: Number of approved medicine prescribed for children

<table>
<thead>
<tr>
<th>Percentage Increase</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased by 20% or more</td>
<td>0%</td>
</tr>
<tr>
<td>Increased by 10-20%</td>
<td>5%</td>
</tr>
<tr>
<td>Increased by about 5-10%</td>
<td>35%</td>
</tr>
<tr>
<td>No change observed</td>
<td>45%</td>
</tr>
</tbody>
</table>

Source: Technopolis survey. The number of respondents is 72.

Table A.26: Changes in research capacity, funding and collaboration
Respondents were asked to indicate the extent to which they agreed with each of three statements about paediatric research: Increased paediatric research capacity is available in the public and/or private sectors; Increased public and/or private research funding is available for paediatric research; and More extensive and sustainable research collaboration is available across private and public sector (i.e. leading to knowledge sharing, co-investment, or product development partnerships).

The survey revealed a broadly positive view about improving research capacity (60% in agreement) and research collaboration (65%), with a somewhat more neutral view expressed about any improving trend in paediatric research funding in the period since the introduction of the regulation. A substantial proportion of the respondents are neutral (neither agree not disagree) and a slightly smaller proportion disagree/strongly disagree (18%, 28% and 18%) with these statements. Survey respondents provided several arguments that explain the lack of consensus around the statements:

- Capacity building: several respondents argued that developments had been very positive and that, as a result of the regulation, institutions had been able to build bigger teams working with clinical trials in children. However, other respondents wrote that the expansion in research capacity had been patchy and looked very different across therapeutic areas and institutions. It was argued that (in some cases) capacity building was considered only after the regulation came into force and that as
no specific funding was available for infrastructure development, one inevitably saw rather uneven progress.

- Research funding: one contributor argued that when the paediatric legislation came into force, there was an increase in funding and paediatric research collaboration but that this increase in funding had been interrupted and industry continues to focus on adult drug development and less on paediatric drug development, where financial returns are less interesting. Other contributors noted that there is substantial variation in the support for paediatric drug development across national governments. Several others remarked on the shortcomings of the Commission’s main research instruments, FP7 and Horizon 2020, stating that the funding instruments were poorly adapted to the needs of clinical trials in children.

- Collaboration: In some therapeutic areas the regulation is thought to have increased multi-stakeholder dialogue and cooperation, e.g. on childhood cancer drug development but in other therapeutic areas collaboration was reported to be poor still with no new networks for collaboration having been established. Also, it was suggested that the regulation had led to more industry-led research, while having had little or no effect on the volume of collaborative research (public private) or investigator-led research (public, academic).

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The RCPCH (2012) Turning the Tide report finds that only 5% of research funding is spent on child health research.
Survey respondents were asked to reflect on whether the 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. Regarding the replacing of existing treatments for a paediatric condition (either by treatment with less toxicity or enhanced efficacy), close to half of the respondents stated that the regulation had led to an increase (47%, 51%). While 68% stated that there had been an increase in the number of children treated with the right medicine at the right time with the right dose.

In all three cases, most respondents opted for an increase of around 5%-10% in the numbers of ‘correct’ treatments. Several respondents wrote stating they had difficulty in attributing changes in treatment to the Paediatric Regulation alone, while others acknowledged that there had been some limited progress, involving quite small steps so far as regards to efficacy and toxicity in general but more progress around specific treatments such as anti-rheumatic, immunosuppressive drugs and anti HIV drugs.

Others noted that the regulation has begun to make a difference, however, the rather complex and involved development process inevitably slows the rate of progress and arguably reduces the absolute potential for change:
The need for certain drugs and for age-appropriateness of drug forms and formulations still exist. To date, only a small percentage (24 out of 135, about 18% of the total for 2007-2013 according to one survey respondent) of active substances included in the Priority Lists of off-patent drugs issued are subject of an agreed paediatric development in a PIP. A very low number of PUMAs are granted, i.e. only 2. Paediatric off-label use has not been reduced.