EFPIA & EFGCP Multi-Stakeholder Workshop on Paediatric Unmet Medical Needs

REPORT

12 December 2019
HOTEL NH SCHIPHOL AIRPORT
Amsterdam, The Netherlands

www.efgcp.eu
# Agenda at a Glance

## Thursday 12, December 2019

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<thead>
<tr>
<th>Time</th>
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<tr>
<td>9.00</td>
<td>Welcome coffee</td>
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### Opening remarks and objectives of the meeting

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<tr>
<td>9.15</td>
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### Stakeholders’ perception of Paediatric UMN and expectations

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<tr>
<td>9.25</td>
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<td>• Regulators from Europe and US</td>
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<td>• Parents/Patients representatives point of view</td>
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<td>• Industry point of view</td>
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### How to identify paediatric UMN?

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<tr>
<td>11.00</td>
<td>• Setting the scene &amp; proposals</td>
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<td>• Proposed methodology – Panel Session</td>
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<td>• Q&amp;A on methodology &amp; Conclusions of the morning sessions</td>
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<td>• Conclusions from the Morning Sessions</td>
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### Paediatric Unmet Medical Needs in selected therapeutic areas

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<td>• Neuropsychiatry in paediatrics</td>
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<td>- Neonatology</td>
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<td>• Conclusions of the afternoon session &amp; wrap-up</td>
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Programme Committee

- Solange Corriol-Rohou  
  AstraZeneca, France
- Martine Dehlinger-Kremer  
  EFGCP, EUCROF & Synteract, Germany
- Marie-Yvonne Douste-Blazy  
  Servier, France
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  EFPIA, Belgium
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  European Commission, DG Santé, Belgium
- Marie-Yvonne Douste-Blazy  
  Servier, France
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  University of Padova, Italy
- Jonathan Grigg  
  Queen Mary University of London, United Kingdom
- Karl-Heinz Huemer  
  EMA PDCO, Austrian Medicines and Medical Devices Agency, Austria
- Asimo Koukougianni  
  Karkinaki NGO, Greece
- Koenraad Norga  
  EMA PDCO, Universitair Ziekenhuis Antwerpen, Belgium
- Jun Oh  
  University Medical Center Hamburg, Germany
- Chrissi Pallidis  
  EMA, The Netherlands
- Mark Turner  
  University of Liverpool, United Kingdom
- Gilles Vassal  
  Institut Gustave Roussy, France
- Lynne Yao  
  FDA, USA
- Alessandro Zuddas  
  Università degli Studi de Cagliari, Italy
**PAEDIATRIC Unmet Medical Needs**

A report by Peter O’Donnell (amply and generously assisted and guided by workshop participants!)

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**Summary**

The objective behind this one-day workshop was to find a broadly accepted approach to defining unmet medical needs (UMN) among paediatric patients, in order to make better and safer medicines for children, and to make sure they are available and affordable. This is not in itself a novel ambition, but the workshop was novel in its approach, aiming at primary focus on the patients, involving all stakeholders, and mapping out a plan for action.

The patient focus was a deliberate departure from the practice until now, which has been driven less by paediatric patients’ needs. The workshop tackled the multiple factors complicating the issue of an effective response to UMN among children: definitions, development, ranking, timing, access…

The workshop was also novel in its determination to go beyond a mere discussion, by agreeing a pragmatic process for all stakeholders to take effective action. The design and participation at the workshop were geared to the conviction that multi-stakeholder meetings are major tools for influencing that process. And the timing arose from awareness of an opportunity over the next two years as the EU reviews its paediatric and orphan drug incentive schemes.

The outcome was an outline of potential guiding principles for defining UMN in children, and a programme for testing the principles in selected therapeutic areas over the course of 2020. Among the key recommendations were that, since no one-size-fits-all approach can work at present, progress should be made through addressing UMN by speciality, with an accent on treatment categories or gaps, but not on products. The models to be explored in these workshops, under academic leadership, but with full engagement by all stakeholders, should take account of pharma developments in each specialty, but go beyond issues of PIP and PSP, in the EU and US respectively, to a broader review of drug research and diagnosis, and aim to formulate and validate principles for defining UMN in that speciality – high, low or intermediate, and irrespective of feasibility. The results of the workshops would feed into the generation and subsequent agreement on a more widely valid framework by the end of 2021.

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**Background**

The workshop was organised as a contribution to the development of criteria for a definition of paediatric UMN, in response to the growing need for such a definition to enable industry, academia and public funders to focus on most relevant areas of indications for their treatment, and to promote the provision of better treatment options during a window of regulatory opportunities.
The history of attempts to define UMN in this area goes back nearly 20 years, to the development of the concepts in the Orphan Drug Regulation and the Paediatric Regulation (PR), which required the Paediatric Committee to establish an inventory of therapeutic needs.

The 10 years report on PR 2017 also spoke of “exploring opportunities to discuss paediatric needs in an open and transparent dialogue involving all relevant stakeholders like academia, health care providers, patients and caregivers, paediatric clinical trial networks, Industry and regulators.”

In 2018 the European Commission and the European Medicines Agency (EMA), in consultation with stakeholders, developed a plan to boost the development of medicines for children in Europe. The aims were to develop an overview of selected therapeutic areas to help identify and raise awareness of paediatric medical needs. The hope was to provide a basis for strategic decision making on paediatric medicine development. Proposals included conducting a public survey on criteria for determining paediatric medical needs and on perceived areas of needs. The concept also extended to selecting therapeutic areas for further analyses by multi-stakeholder focus groups, and conducting multi-stakeholder workshops in selected therapeutic areas. However, the EMA’s relocation from London to Amsterdam delayed implementation of this process.

In June 2019, an EU Commission stakeholder conference on the two regulations discussed (among other topics) “the importance of a common understanding and of quantifying unmet medical need”. This noted the divergent understanding among distinct stakeholder groups of UMN (“If a treatment for a specific condition is not a cure, there is still an unmet medical need,” was one conclusion) and urged greater use of patient input, and “quantifying” of UMN. It saw a role for a broader understanding of UMN in promoting both paediatric and orphan medicines development.

Significant work has already been done in the field of paediatric UMN under the umbrella of non-official groupings such as the Conect4Children (c4c) consortium – an IMI funded project aiming to improve the way clinical studies for children are planned and conducted. c4c has developed expert groups on gastroenterology & hepatology, endocrinology & diabetes, rheumatology & autoimmune diseases, infectious diseases & vaccinology, cardiology, neuroscience & epilepsy, neuromuscular diseases, metabolic diseases, oncology, nephrology, respiratory diseases, intensive care, psychiatric disorders, and neonatology. Initiatives are also underway in other fora to speed development of needed formulations, including the paediatric HIV treatment initiative to develop and deliver specific paediatric formulations, the global paediatric antiretroviral commitment to action, and a number of broad consultations exploring mechanisms to advance paediatric formulation development and introduction.

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**REPACK**
Organisation

The event was organised jointly by the European Forum for Good Clinical Practice (EFGCP), a multi-stakeholder not-for-profit organization, on the basis of a programme developed in its Children’s Medicines Working Party, with input from industry, patient and academia members, and the EFPIA Paediatric Working Group. EFPIA provided an unrestricted grant to cover some of the costs of the workshop. The neutral leadership provided wide scope to shape the initiative and maximise the chances of winning broad support for the results. It gave a crucial role to academia in providing the ideas and concepts. And the multi-stakeholder approach allowed participation by patients, regulatory authorities, and industry representatives in the fact-finding and decision-making process. There was also good and active support from EU and US regulatory authorities. There was, however, an acknowledged limitation, in that no representatives of Health Technology Assessment (HTA) bodies had accepted the invitation to take part; the aim is to fill this gap (referred to below) at the earliest moment in 2020.

The burden

The scope of paediatric UMN – already well documented - was graphically and movingly confirmed by patient representatives at the meeting, underlining the harsh reality at personal level of the familiar statistics that more than 50% of drugs used in children and more than 90% of drugs used in neonates are prescribed off label without adequate data. Innovative drug development in paediatrics remains slow and inefficient, typically taking 15 years to complete a paediatric drug development program, and seven to nine years from adult approval for a paediatric label to be made available.

Patient representatives offered a salutary reminder to the meeting that there are differences between the perceptions and expectations of UMN held by patients on the one hand, and by social and regulatory systems on the other: “Patients and carers know that 50% of people affected by rare diseases are children, and rare diseases are responsible for 35% of all deaths in the first year of life. 30% of children with rare or genetic diseases will not survive till the fifth year of life.” But still medicines for children lag medicines for adults. Despite the EU and US paediatric legislations, the persistent lag between approval for use in adults and time to paediatric-specific labelling means delays with real consequences, because of the urgency for many children who will suffer or die needlessly without additional treatments. Children are left behind in terms of research and innovation.

Cancer in young people in Europe offers further demonstration: each year sees 35 000 new cases, 15 000 of which occur in people under 15 years of age, and 20 000 among 15-24 year-olds. Only 10% of them have access to innovative treatments. While treatment now allows 80% to be disease-free at 5 years, gaps persist even for them, since of the 300 000 EU survivors of childhood cancer, two-thirds have long-term side-effects. And 6 000 young people die each year, with cancer remaining a leading cause of death from disease beyond
1 year. But still it is the case that many anticancer drugs are developed in adults, with paediatric development based on the adult indication, despite the many differences between paediatric malignancies and adult cancers.

The 10-year report on the EU PR noted that “the possibilities of the Regulation to steer activities towards certain therapeutic areas are limited”, and “the qualitative impact is still dependent on market forces, drivers of growth and strategic considerations of companies”. Where the Regulation has boosted paediatric research, the research “is geared towards product development”, and “for some diseases or therapeutic areas, a good understanding of the underlying disease is still lacking”. In addition, even where there are positive results, they are “not evenly spread among all therapeutic areas, but concentrate in some, often linked to research priorities in adults rather than children.”

The June 2019 EU conference concluded that the general effectiveness of the system to address unmet needs and achieve availability and equal patient access across the EU “can be improved”. And in late 2019 the EU’s Pharmaceutical Committee of senior national experts was asked to turn its attention to the subject, with a paper from the European Commission noting that “Although there has been a gradual increase in medicines for patients with rare diseases and children since the introduction of the Orphan and Paediatric Regulations, there is still a very large unmet need. This can be partly explained by the long development timelines for medicines and hence the delayed onset of the effect of the Regulations. However, as many paediatric developments are linked to an adult medicine, the primary drivers are adults’ needs rather than the specific needs of children.” It added that “the current design (of the incentives for rare diseases) has limitations in terms of redirecting investments in areas of unmet need.”

**Challenges**

In this context, the workshop explored the principal issues that routinely impede smooth access to comprehensive treatment options in areas of paediatric UMN, and discussed possible solutions.

*Definitions:* The lack of a uniform definition hampers progress. Unmet Medical Need covers a wide scope with different types of needs viewed differently by the many stakeholders – and all the more so in paediatrics. Sixteen current definitions were enumerated, citing regulators, academia, HTAs, and payers, in addition to distinct views among patient representatives and manufacturers. Divergent legal definitions, particularly in the Paediatric Regulation and the Orphan Regulation, or in the PRIME scheme, create tensions in defining target disease and population for a same development. By contrast, a widely accepted definition could ease R&D decisions, facilitate regulatory and pricing and reimbursement decisions, assist buy-in from patients, and enhance predictability.

Differing criteria have to be considered, in addition to those already spelled out in the
Paediatric Regulation. Qualitative definitions of UMN include some form of disease severity, limited effective treatments, non-availability of alternative treatments, and long term side effects. They can also reflect factors such as the current standard of care, and whether the disease is life-threatening or severely debilitating, or rare. Additional issues can include whether substantial improvement is expected, or a specific population is involved, and whether it is sufficient to assume an advantage, or the benefit requires demonstration.

Studies of expectations among clinicians indicate that the most common criteria are prevalence of the conditions in the paediatric population, seriousness of the conditions to be treated, and the availability and suitability of alternative treatments for the conditions in the paediatric population. This final consideration takes account of the efficacy and the adverse reaction profile of those treatments, any unique paediatric safety issues, and any data resulting from studies in third countries. Two further, paediatric-specific, criteria are non-availability of appropriate formulation for age-subsets, and impact on child development. The discussions included how to define unmet therapeutic need for PIP purposes. And many patient representatives made clear that the concept of “ensuring patient focus throughout” must be more than a nice slogan, expressing concern that patient focus is not being ensured by the current arrangements.

One of the evident preconditions for agreeing on a definition of paediatric UMN is to improve the information base, and this presupposes understanding what distinct stakeholders consider important, in terms of the different perspectives they might have in products, categories or gaps, or their lists of priority needs. The workshop explored whether a basis for a common definition can be identified in the face of the divergences between (and among) developers, patients and caregivers, academia, regulators, HTA bodies, payers, health care providers, and even among therapeutic areas and society at large. Discussion turned upon how to effect a genuinely multi-stakeholder discussion on definition alignment, and how far it might be possible to agree on scope or criteria independently of the specifics of therapeutic areas, or, in the interim, on a process for establishing criteria in specific areas. The outstanding question was how far a more generally valid methodology or process could be identified to characterise UMN. In parallel, the discussion covered the question of what form of multi-stakeholder cooperation can be envisaged to capture the wide range of (often divergent) stakeholder views – a gap highlighted by the absence of representatives of HTA bodies.

**Development:** Prominent among the many obstacles confronting the process of developing paediatric therapies is intrinsic UMN that results from the lack of essential elements: the absence of treatment options, or limitations or lack of information on available treatments; the lack of an appropriate molecule, active ingredients, information about the exact indication, suitable dose, efficacy and safety, or the formulation (appropriate, or at least usable). The absence of information and the lack of agreement on the best ways to collect information in specific populations - such as inclusion of adolescents in
adults trials, or the ethical and methodological complexity of dedicated trials in neonates - is another obstacle.

In addition, there is a need for better understanding of diseases, physiopathology and biology, and drug mechanisms of action. “More science is part of addressing paediatric UMN”, one participant observed. Many comments during the discussion reflected the remarks in the 10-year report on the PR: “Additional basic research on the diseases themselves would be beneficial to enable and inform appropriate product development. This cannot be guaranteed through the Regulation but requires additional efforts and funding from public and private sources.”

There are also what might be described as contextual rather than intrinsic challenges in paediatric development: preclinical testing (toxicology etc), development of pharmaceutical formulations, selection of relevant endpoints where they exist (and extrapolation of data from adults, in the face of uncertainty), availability of validated paediatric-specific biomarkers, and segmentation of age-distinct paediatric populations. There are difficulties in harnessing advances in science – particularly in biologics; and there are difficulties in trial recruitment, and in the inevitable paucity of patients in rare diseases. Decisions over development are also subject – particularly for commercial developers – to considerations of scientific opportunity.

Paediatric clinical trials of themselves present difficult methodological issues and problems, complicated by the unique growth and developmental considerations of paediatric patients, with the wide variations in physiology between new-borns and teenagers. The cancer field again provides powerful illustrations of the challenges in drug development. There are more than 60 different malignancies, and even more through molecular classification. In medulloblastoma, there are in fact 7 different diseases, each of which is rare or extremely rare.

The merits of information sharing and collaboration were repeatedly emphasised in the discussions – a theme already articulated at EU and FDA level. The June 2019 EU conference noted: “The importance of global cooperation and data sharing, in order to facilitate the development of medicines addressing unmet medical need - especially in the area of medicines for children – was considered important. However, the different regulatory frameworks in place across the world can hinder this type of cooperation.”

FDA recognizes the global scope of drug development and in its current draft guidance on paediatric studies of molecularly targeted oncology drugs “strongly encourages all stakeholders to support internationally coordinated and collaborative approaches to development of drugs to treat cancers in paediatric patients.” It goes on: “Due to the rarity of paediatric cancers, international collaboration is increasingly important for facilitating the development of new treatments. Furthermore, the number of investigational drugs of potential interest far exceeds the number of paediatric patients available to enrol in clinical trials. Therefore, global coordination is increasingly important for prioritizing drugs of interest in general, and for specific cancers
in paediatric patients, especially for drugs of the same class, for early paediatric evaluation. This will aid in preventing duplication of studies and competition for scarce patients, and limit unnecessary exposure of paediatric patients to investigational drugs."

**Ranking of potential treatments:** The discussions explored the wide range of criteria that govern allocation of attention or resources to particular therapeutic areas of UMN: disease incidence/prevalence, severity, paediatric-specific criteria, the balance of rarity/prevalence, the mechanism of action, safety profiles, acceptability, convenience, or requirement for an appropriate pharmaceutical form. Discussion highlighted the diversity of influential factors from one therapeutic area to another. In haemat-/oncology, top criteria in one survey were whether the condition was life threatening, or there were only limited effective treatments, or those that exist have long-term side effects. In respiratory care, the key issues focused on the availability of appropriate formulations for younger patients. In neuropsychiatry, the top factor was the extent to which the condition had an impact on daily life.

Various mechanisms or factors for quantifying UMN were reviewed, including the extent of need (the number of people, the burden per person, and disability adjusted life years...), the lack of alternative treatments, the feasibility of a solution, relevance to health care systems, the relevance (or distraction) of lists... . Discussion extended to quantification of the compound(s) with most chances of success within a TA, the creation of an algorithm applicable across TAs that could integrate agreed paediatric criteria, or high/medium/low unmet need... Quantification was perceived as a complement to prioritization – something to rank need within a speciality, but not to rank specialties.

Prioritisation was perceived as an exercise based on a clear clinical problem, covering the nature of the problem and a well-defined population, and linked to an understanding of which step is needed next, including underpinning research and research that directly addresses the need, the feasibility of marketing authorisation, and resources. It was felt that reimbursement and HTA require separate consideration and should not be part of this discussion.

Results were presented of a survey performed among academics, designed to identify indications with UMN that could serve as case studies for assessing and eventually validating any methodology arising from the workshop. It highlighted three TAs with cumulative high scores in factors contributing to unmet need: haemat-/oncology, respiratory and neuropsychiatry. Other broadly recognised areas of indications with important unmet medical need, according to the internal survey, are neurology, infectious diseases, gastro-enterology, rheumatology/immunology, neonatology, nephrology and metabolism/endocrinology. While the survey was designed to provide only a snapshot for internal use, and was not intended to prioritize and rank specialties, nor to provide guidance to pharma, the responses to it did demonstrate that experts across specialties are eager to work on the topic.
The workshop explored whether a general scheme of criteria was feasible, and how patient benefit, cost, clinical relevance or other criteria would figure. Questions discussed ranged across whether there can be solutions for all cases, or solutions must by nature often be ad hoc, so that the best option is to agree instead on principles to guide the adoption of criteria. The feasibility of developing algorithms to better assess UMN was discussed at length. But it was suggested that any recommendations on general criteria that might emerge from this process would also need to be capable of robust justification and defence beyond the worlds of medicine and health, so as to secure broad societal support in what may be an indifferent or even sceptical political context.

**Regulatory:** Regulatory requirements can present obstacles when the rigidity of legislative frameworks or the need for available safety information impedes or conflicts with a focus on paediatric population needs. Tensions can emerge between methodological requirements of regulators to justify their marketing authorisation, and ethical constraints of developers and clinicians. Flexibility can be constrained by legislation’s needs to ensure transparency of decisions and criteria. Constraints can also emerge at regulatory level simply in terms of resources. And there is a high erosion from Paediatric Investigation Plans (PIPs) to market like in hepatitis C and in asthma. There are real questions over whether the PIPs agreed can be executed and inform paediatric treatment, e.g. a new paediatric indication.

The workshop considered the scope for mechanisms that could reconcile divergent objectives. One option might be to make better use of existing regulatory pathways, e.g. PRIME, adaptive pathways, scientific advice (which is free of charge for paediatric matters). But the question remained as to whether different regulatory, HTA, and reimbursement pathways will persist, or whether it is possible to envisage an aligned blueprint between stakeholders, to provide a holistic approach.

There was intense discussion on whether the focus of the regulatory system might be usefully modified. Even the Commission has pointed out to its own expert groups that the current criteria to classify a medicinal product as a treatment for a rare disease (such as prevalence) may fail to accurately capture rare diseases. Moreover, in the case of paediatric medicines, it may lead to certain adult products that could work in children (due to their mechanism of action) being excluded from the scope of the actual obligation.

The underlying scientific reality is for example that malignancies or other pathologies occurring in children or adolescents harbour the same molecular abnormalities as those found in adults, and therefore many new targeted drugs like in oncology may prove effective in the treatment of paediatric forms of cancer, even if the adult cancer indication does not occur in the paediatric population.

Regulatory attention might helpfully shift from concern over clinical indication to molecular mechanism of action (MoA). The extension of the advance provided by molecularly targeted drugs has been delayed and limited in paediatric cancer in part because of the requirements for
paediatric assessment of new cancer drugs to be based on indication. The US RACE Act coming into force in Aug. 2020 will certainly be useful to promote the paediatric development of new anticancer drugs through their MoA with respect to the biology of paediatric malignancies instead of their adult indication.

**Access: the elephant in the room:** Even when new treatments emerge and are available in principle, access remains a challenge because of geography (distinct national or regional systems, with known differences between low and middle income countries, and Eastern and Western EU countries) and the healthcare setting.

This highly sensitive area – relating in large measure to issues of strictly national policy and wealth – cannot be ignored but does not fit neatly into the discussion of unmet medical need because it is driven by factors from other horizons and perspectives. The immoveable principle that new treatments should be affordable to the patient meets the irresistible force of national economics, and the consequent national approaches to HTA, reimbursement and pricing decisions. In addition, HTA bodies do not recognise paediatrics as a ‘special’ population.

Access issues also play into the challenges of development, since commercial developers make their operational decisions not only on the basis of unmet need, but also in the light of the expected value of a new medicine. The workshop recognised the importance of this aspect of the challenges, but the discussion was not pursued fully because of the absence of representatives of payer/HTA bodies.
RECOMMENDATIONS

A working consensus on the following points emerged from the workshop but will need to be further defined concerning responsibility for topic leadership and funding.

It appears not feasible to create a one-size-fits-all approach. Unmet needs should be addressed by speciality, maximising the opportunity to get all specialties communities committed and defining their strategy. The process of defining UMN by disease should be led by academia, with patients and parents providing their insight on their needs within the specialty, in partnership with pharma, regulators and HTAs/payers.

Defining unmet medical needs in a given disease/speciality requires defining a research and innovation strategy as well as actions to improve the use of current therapy and their affordability. The aim over 2020 should be some pragmatic demonstration of the relevance/validity/sustainability of some posited guiding principles, tested against specific exploration within a number of TAs. A further EFGCP-EFPIA initiated conference at the end of 2020 will discuss the results and overall conclusions. Those results would feed into the generation and subsequent agreement on a widely valid framework by the end of 2021.

In practical terms, this means conducting at least 4 disease-focused workshops during 2020 to report by year end with a clear endpoint on “in this disease, here are the needs” (in terms of categories, or gaps, but not of products), to assess the feasibility of extending TA-specific criteria/guidelines to a more general level. There is already an ACCELERATE-like workshop planned in April 2020 to assess neuropsychiatry in children, as part of the IMI c4c project.

Addressing the needs in a specialty/disease should be contextualized by what is happening in terms of pharma developments in the same specialty. In neonatology, for instance, where needs are well defined since 2013, very few pharma companies have assets for this population or have interest/incentive to address this population. In childhood psychiatry, the many drugs in adults are not adequately evaluated in children and adolescents, even though many PIPs are approved for those indications not all of them primarily focus on the real needs. In oncology, the urgent need is to prioritise paediatric drug candidates among the many anticancer drugs in development for adults; this should be based on science and unmet needs. Specific development of drugs against paediatric malignancies is a particularly complex topic and should be adequately incentivized. And in respiratory diseases there is a disconnection between academic research (as presented at the workshop) and what pharma companies are asked to do within agreed PIP programmes (in asthma, for example).

Discussions of unmet need must go beyond PIPs and Pediatric Study Plans (PSPs). Addressing unmet medical needs is broader than pharma companies applying the paediatric regulation. It includes basic research to better understand the disease, academic clinical research to address therapeutic or diagnostic questions that will not be addressed by pharma, use of registries and real-world data.
In parallel to this process of a limited number of TA case studies, a forum – still to be defined, but possible models are ACCELERATE Paediatric Strategy Forums in partnership with EMA and FDA - should pursue discussion of a framework of factors relating to a spectrum of all unmet need: high or low or intermediate, and irrespective of feasibility, with a view to formulating principles that are generally valid.

Above all, it is vital to avoid merely agreeing on a set of fine intentions that prove in the end to be no more than meaningless slogans with little impact on the real goal of paediatric care. This consideration also precludes taking months to agree first on a methodology then to address all specialities, only to come up with a catalogue of fine intentions. This two-decades-long process of generating better options for paediatric treatment deserves better: as one put it: “Children are growing up – let’s get a result before they are adults – or worse”.

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