Confederation of European Specialists in Paediatrics
IMPROVEMENT OF CHILDREN'S HEALTH IN THE EU
Workshop preceding the CESP annual meeting
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Notes from Louis-Nicolas Fortin, EFPIA

Peter Hoyer, President of CESP
Introduction

Professor Hoyer introduced the conference, the focus of which is the Community proposal for a Regulation on Medicinal Products for Paediatric Use.

He underlined the fact that twenty years ago, it was unethical to conduct tests in children. Today, it is acceptable to involve children in clinical trials under certain conditions, to allow assessing medicines specifically designed for their use. However, we are faced with difficulties in paediatric pharmaceutical development including bureaucratic burdens, costs to be bore, and market considerations.

In the light of a European Union children population of over a hundred million, CESP supports the adoption of a Community proposal to foster availability of medicines for paediatric use. CESP represents 40,000 paediatricians.

José Ramet, Secretary General of CESP
Achievements and outstanding challenges in medicines for children

Professor Ramet outlined the limitations and barriers in developing medicines specifically designed for children. Over 50% of medicines are not tested in children. The paediatric population includes sub-groups with different characteristics and needs. As such, studies in adults are not designed for assessing medicine use in children as the latter are characterised by:

- specific diseases
- specific kinetics
- specific effects on growth
- specific adverse drug reactions

Barriers to paediatric research include:

- Ethical issues:
It is unethical to expose children to premature testing, or unnecessary hazards. When children are taking part in clinical trails they may potentially be administered medicines that are not as beneficial as existing medications. There is a risk of use of sub-therapeutic doses during pharmacokinetic studies. The issue of use of placebo-controlled studies is even more sensitive.

- Off-label prescribing practice:
It is a major issue as it will make recruitment of children for clinical trials difficult. Since medicines are already being used to treat children - even though outside the conditions of the marketing authorisation – parents will be reluctant to agree to the involvement of their children in trials on medicinal products ("why risk involving my child in testing if more or less adapted medicines are already used frequently?").

- Market size:
Children represent a smaller population than the adult population, more so considering the various paediatric sub-populations with widely varying characteristics. This requires, e.g., broadening the geographical scope of trials to recruit sufficient number of paediatric patients.

- Do-ability of paediatric studies:
For studies to be statistically significant, a minimum cohort of patients is required – this poses challenges in paediatrics. Study procedures must be minimal not to be to invasive on children. Clinical trials in children are difficult for various other reasons.
There has generally been low industry investment in paediatric R&D for lack of a legislative framework, lack of financial incentives, fear of harming children.

To achieve the desired goals, it takes at least 6 partners: Children/parents; Paediatricians and allied physicians (including CESP as representative body of specialists in paediatrics at Community level); Academia; Industry; Regulatory agencies; Industry.

For CESP the first priority is to see the Commission's proposal adopted quickly. Another priority is to foster paediatric research and enhance medicines available for children. There is a need to rebalance the equation to attract paediatric R&D in the EU. This requires balance between incentive and requirement measures, and support for paediatric testing in Europe. For this purpose, an adequate solution could be to award an IP-extension incentive of more than 6 months for new medicines in Europe, to offset the differences between Europe and the United States.

Hansjörg Seyberth
Specific Pharmacology in Children

Dr Seybeth made a learned presentation on pharmacology specific to each paediatric population, involving at least five child development stages/age groups. He stressed that drugs should be developed only for those groups for which they are relevant. There are differences in pharmacokinetics in those children sub-populations. The metabolic capacity varies widely: for neonates, for example, there is a low metabolic capacity which therefore warrants low maintenance doses, whilst for toddlers, it is the opposite.

Dianne Murphy – US FDA
US Experience with regard to Paediatric Legislation

Dr Murphy joined by telephone and presented the legislative measures introduced in the US – which were prompted by the fact that between a third and three-quarters of medicines were not developed specifically for children use. She also reported on the impact of the legislation and changes introduced over time.

The reasons for the lack of medicines specifically tested in children range from the smaller children sub-populations; greater technical challenges; problems with surrogate markers that change with age; diseases unique to children; difficulties in multiple dosage.

The American Academy of Paediatrics already stated in 1977 that unethical to adhere to a system which forces off-label use. However, efficient measures to address the issue were only introduced at the end of the '90s. The results of the "Paediatric Exclusivity"

programme resulted in 295 Written Requests, involving 687 studies, with a total number of children of 42,939 involved in paediatric trials. It has allowed 85 new labels which give useful information.

The paediatric trials have allowed identifying unnecessary exposure to ineffective drugs; ineffective dosing of an effective drug; overdosing of an ineffective drug; undefined unique paediatric adverse events.

General findings include:
- Children are even more dynamic (PK) and variable than anticipated
- The new law was positive in fostering development of paediatric medicines
- Trial designs are being modified as we learn from experiences

Paediatric Advisory Subcommittee Meetings addressed:
- Patients vs. subjects in paediatric trials
- Placebo controlled studies
- Vulnerable paediatric populations

FDA supports the general principles laid down in the ICH E-11 guidance (including, not delaying adult studies or the availability of medicines. If a medicine has not been studied but is considered the standard of care, FDA seeks information and then considers if need to design a trial.

Agnès Saint-Raymond, EMEA
What are the hurdles today and why do we need a Regulation?

The consensus is that there is a need for the assessment of medicines in children. The situation has changed in the US, not yet in Europe. Centralised Procedure experience: few paediatric data have been submitted.

Currently some paediatric formulations are available in one or few MSs, not in all. Some problems are not assessed consistently from one MS to the other.

Impact of lack of paediatric information:
- dosing is different/PK different
- increased risk of ADRs
- risk of inefficacy
- delay to innovative medicines – because of different steps to be taken
- prescribers are left with unknowns

Dr Saint-Raymond mentioned that EMEA welcomes the introduction of measures to specifically paediatric investigations in orphan medicines. She raised some reservations regarding the Commission's proposal to rely on EUDRACT for the provision of information. Such database would be available to agencies only, not to investigators. There is need for broader information on paediatric studies to avoid replication of unnecessary trials and avoid exposing children to placebo if other treatments are available.

Hurdles in paediatric development:

- Research hurdles: clinical trials are more expensive – however, when there are sufficient incentives, such as in the US, it is possible to have the necessary trials.
- Funding hurdles: this is a true obstacle for academia. It affects old products, which may require expensive trials. However, uncontrolled trials or unguided prescription is unethical and remedies at Community and national level must be found.
- Regulatory hurdles: excess requirements?

EMEA has produced/will produce guidelines that serve as support to paediatric development: guidance on juvenile animals toxicity studies; demonstration of efficacy in children when already obtained in adults; numerous sub-populations; very long-term safety data.

There is a need for a Community Regulation to compensate for the lack of industrial interest and a situation that is potentially damaging for children (there is evidence to that effect), to ensure that the need for paediatric information is fulfilled.

Regarding the difficulties of conducting trials in paediatric sub-populations, Dr Saint-Raymond commented that from the experience with orphan medicines, there are means to conduct studies in heterogeneous populations. She also commented that off-label use would not disappear when the Regulation enters into force, and this should be so otherwise there will be a lack of treatments while some are being tested/developed in children.

Peter Arlett – European Commission
The Commission's Proposed Regulation

Dr Arlett gave an outline of the Commission's proposal:

- The proposal addresses three categories of products: newer medicines (new medicines and line extensions on medicines with IP); medicines already on the market, without IP protection.

- The creation of a Paediatric Committee ("PC") the key task of which is to agree on Paediatric Investigation Plans ("PIP").

- Paediatric Investigation Plans (these are different from the US Written Requests). There must be agreement on an initial plan, but the applicant will come back from time to time, adjusting/modifying the initial plan (a "living document"). A PIP will be conducted if the PC considers that it is in the interest of children, driven by public health, not by market interests. The PIP will serve as the basis to assess the data submitted when filing MAA.

- Regarding newer medicines: A requirement, which the EC chose to link to the submission of MAA (reportedly because this is the time when the regulators have the most power over the applicant). It is not clear for what proportion of products the PIP will be deferred (more than half? - unknown).

  The reward is linked to the submission of paediatric results. Information must be put in product information/leaflet – including negative data (this is a broader requirement than in the US). It grants a market monopoly for the new medicines. It will have an effect on government expenditures – at most, 0.25% increase of

European expenditures on medicines due to delay in entry of generics. And this figure does not consider benefits to public health and savings to budgets from improved treatments of children.

- Older Medicines: A Paediatric-Use Marketing Authorisation would be created. It would allow using the same name as the reference product in certain circumstances, therefore allowing for product recognition. The proposal would introduce amended data requirements, making it possible to refer to the adult medicine's data, complemented by the submission of paediatric data from a PIP. Dr Arlett commented that Member States will need to support the implementation of approved paediatric medicines (PUMA) to counter off-label use of medicines.

  The PUMA will be awarded an incentive in the form of Regulatory Data Protection (8+2 year on the paediatric data). The EC believes this should be sufficient to stimulate paediatric research into medicines already on the market.

  Special paediatric fund – there is no specific reference in the Regulation text, only in the Explanatory Memorandum. Funding and operation of this incentive are still being investigated – it will be difficult to reach agreement amongst EU Member States. A separate legislation will come later.

Also:
Scientific advice – it will involve paediatricians.
Inventory - the EMEA and PC will identify gaps in medicines available and therapeutic needs.
Paediatric clinical trials network – not building from scratch, but organising and coordinating the existing ones. If a company wants to initiate studies in certain disease fields, it would come to the EMEA and ask whom they should contact, and the Agency will provide them with names of paediatricians who may be their investigators.

Brian Ager – European Federation of Pharmaceutical Industries and Associations

"EFPIA" is the trade association representing the research-based pharmaceutical industry at Community level, before EU institutions. It is composed of national associations/companies. It includes a specialised group, the European Vaccines Manufacturers (Europe is source of 90% of vaccines worldwide).

EFPIA welcomes the EC proposal. It is a win-win solution if Europe gets it right. It should improve the pharmaceutical research-based for Europe, and help counter the sliding towards other world regions.

Due to time constraints, Mr Ager focused on:
- the conditions of the requirement provisions in the proposal, emphasizing the fact that these should not delay adult forms of medicines – otherwise, this would be a deficiency of the proposal. We must make sure that the way the legislation is drafted it will set the right conditions.
- the incentives to be introduced, which should allow compensating for the delay in introducing measures for the EU. The US will have already benefited from successful measures for 10 years when the EU Regulation will come into force. There are significant differences in the market place. 6 months of paediatric extension in the EU is not the

same reward as 6 months in the US. EFPIA raises the same question mark as the CESP regarding the level of incentive in the Commission's proposal.
The EU initiative will mean opportunities for SMEs. It will also create a cascade of opportunities for generics once the incentive for a specific product has elapsed.
- there is also a lot to do on paediatric research frameworks in Europe. The Commission mentioned that these are "patchy", and therefore it would require giving Europe the means to achieve a true paediatric R&D environment.

Ijsbrand Poortman - EPPOSI
Majority of patient representatives

Mr Poortman reported that they are pleased with the increased collaboration with EMEA, EC, Paediatricians, EFPIA and other interested parties. Unfortunately, the importance of research in children is not reflected in current public budgets for paediatric research, which are much too low. Greater public awareness is crucial in this debate – and patient organisations are key in this.

Harrie Seeverens – Dutch Government and EU Presidency

Mr Seeverens reported that the Dutch government has a positive view on the Commission's proposal, but that it will obviously require discussing. He reported the following points which were discussed by Member States:

- Ethics for children: agreed Good Clinical Practice standards should cover all trials in children. Concretely, it will be the national IRBs which will decide on the acceptability of a specific protocol.
- Consequences to budgets: costs are difficult to assess, and positive social gains (such as better public health) are even more difficult to assess. Member States will make their own calculations. The Dutch government are currently doing their own assessment and they believe there will only be a slight/moderate increase in the costs of medicines.

Francis Crawley – EFGCP

There is a need for an ethical framework for paediatric research. EP will require convincing that Regulation will not result in unwarranted, premature paediatric testing. Avoid "human (children) guinea pig" label in the debate will be a true concern.

Question Period:

Question on the proposal's Paediatric Committee: the proposal provides for membership mostly made up of pharmacologists. Paediatric specialists should have arole in the PC activities. There should be at least one representative from each of the 11 sub-sections of specialists at CESP in PC. There needs to be a large panel in PC to come up with a European consensus.
Response from EMEA: Regarding the expertise of the proposed PC, the aim is to have experts who may coordinate work in the PC, but these will go back to the relevant experts when required. Note: the PC is not intended as an ethics committee. It does not advise on ethics but advises on paediatric investigation. The Commission believes ethics in children should be dealt with in the framework on Dir. 2001/20.

Question on long-term surveillance studies in the proposal.

Response from Commission: There are specific legal provisions to address these.

Question on how to address the need for resources in clinical wards where trials must be conducted, and on how to ensure sufficient funding for infrastructures.
Response from Commission: Community may act only whereand to the extent it is allowed according to the Treaty. The proposal includes robust measures to foster clinical research in Europe. The Commission is also committed categorically to introduce the special paediatric fund. But overall, this will also require complementary actions from Member State measures.

Question regarding vaccines: are there specific measures envisaged in the proposal to ensure their efficacy and effectiveness?
Response from Commission: All of the measures anticipated in the proposal will apply to vaccines.