Position Statement by the Medicines in Europe Forum

On the draft regulation prepared by the European Parliament and European Council on medicines for paediatric use

The Medicines in Europe Forum welcomes the EU initiative aimed at making appropriate drugs available for children and their caregivers. The Forum has closely examined the draft regulation on paediatric drugs presented by the European Commission in autumn 2004.

The draft regulation mentions several measures aimed at encouraging the funding of paediatric drug development:
– drug substances protected by patents or by supplementary protection certificates: a "paediatric investigation plan" must be submitted at the same time as the marketing application (except for drugs that do not concern children); the data protection is automatically extended if the plan is implemented, even if authorisation for paediatric use is not granted;
– drug substances that are no longer protected: creation of a specific marketing authorisation for paediatric use, with major rewards in terms of the duration of data protection.

However, as usual for a draft proposed by the Enterprise Directorate-General of the European Commission, the project centres on the financial concerns of pharmaceutical firms and on technical measures intended to meet these concerns. It leaves the initiative entirely in the hands of drug companies and neglects the overriding public health objective, which is to provide every possible means of treating children better.

If the draft regulation on paediatric drugs were to be adopted as it currently stands, it would result in a paediatric medicines market that fails to meet the needs of those children lacking new treatments, and would also increase paediatric consumption of useless and risky drugs.

The Medicines in Europe Forum considers that the text must be refocused on the initial public health objective, which is to improve the health of all children in the European Union. A thorough inventory of real needs must be conducted by an independent, publicly funded authority, in order to orient research efforts most efficiently. Research incentives must be available to both the public and the private sector. The initiative must not be left simply to the goodwill of private drug companies. The rules of the game must be clear, so as to avoid abuse and misappropriation of incentives and funds. Rewards must be proportional to spending on research and development of really needed drugs. Pharmacovigilance must be reinforced in the paediatric clinical trial setting.

The Medicines in Europe Forum has several proposals to make on the EU draft regulation for paediatric drugs, all aimed at refocusing the text on the claimed public health objective. Amendments corresponding to each proposal will be put by the Forum before the text is examined by the European Parliament and Council.

Preliminary note: the concept of marketing authorisation for paediatric use has always existed

It has always been possible to market drugs specifically designed for children, and also drugs for use by both adults and children (sometimes different preparations, dose strengths or formulations). Many companies have marketed paediatric medicines in Europe without being specifically encouraged to do so. And regulatory agencies have not expressed the opinion that the marketing applications for these drugs are particularly inadequate.

The concept of paediatric drugs is therefore not a new one. What is sought now is a new impetus for paediatric research, aimed at developing drugs for unfulfilled needs.

The announcement of a "Medicines Investigation for the Children of Europe" (MICE), on the use of drug substances not covered by patents, is therefore particularly welcome. Surprisingly, however, this initiative is reported in the presentation of the draft regulation on paediatric drugs but not in the main body of the text.

The Medicines in Europe Forum proposes that an article of the regulation should explicitly deal with the launch of the MICE programme, specifying the timetable and public funding modalities, and taking into account other existing EU programmes. **(*Amendment 1 proposed by the Forum*)**

The starting point must be the real needs of children who currently lack appropriate treatments

According to the European Commission's communiqué presenting the draft regulation, the objective is *"to improve the health of European children (…)"*. If this is indeed the objective, then there is no need to increase the number of paediatric drugs available in fields already covered by adequate preventive or curative methods, or to encourage pharmaceutical firms to create spurious needs, as they do for adults. The objective should rather to encourage and facilitate the development of preventive and curative means for specific areas in which children and caregivers have no options whatsoever.

Most European children are in good health and do not need new drugs. Most of the 100 million children living in the European ▶▶

► Union are in good health, thanks notably to antenatal and postnatal monitoring, vaccination, and access to clean drinking water, and many hardly need drugs at all. The priority for such children is primary prevention, including dietary measures, to avoid obesity and the risk of diabetes for example.

Many childhood health problems necessitating drug therapy are covered by products already available on the European market. There is no "therapeutic desert", contrary to some media claims surrounding the launch of the European initiative on paediatric medicines. Some drugs are excessively used, or poorly used: excessive use of antibiotics in some countries increases the risk of bacterial resistance; antiasthmatics are sometimes prescribed at increasingly high doses, after approximate diagnoses, with a risk of adverse effects; antidepressants are increasingly used in children, with a risk of self-harm and even suicide; while methylphenidate is increasingly used even when the diagnosis of hyperactivity is poorly established. In such areas the priority is to improve the rational use of existing treatments.

Don't confuse pharmaceutical form and complex clinical evaluation. For some age groups we still lack appropriate paediatric forms, dose strengths or preparations based on substances with a positive balance of benefits versus harm in children. Development of well-adapted drugs must be encouraged in these situations. This is based on pharmaceutical technology or pharmacokinetic studies, but does not require further clinical evaluation. It is therefore relatively cheap.

Drugs are used empirically in other groups of children, without relevant clinical evaluation. Intensive fundamental research is needed in other areas in which the underlying disease mechanisms are unknown and no effective treatments are available. Research and paediatric evaluation requires in these circumstances more human and financial resources and should be strongly encouraged.

The specific needs of particular groups of children must therefore be precisely identified in order to prioritise available resources and to find solutions as rapidly as possible.

Providing for a well-conducted inventory. The draft regulation does not call for a preliminary identification of needs. The principle of an "*inventory*" (and not a true analysis of needs) only appears in article 41 of a draft that counts 56 articles. Article 41 stipulates that the Paediatric Committee will be charged with compiling this inventory, and it will also examine marketing applications. The Committee's affiliation to the European Medicines Evaluation Agency (financed mainly by pharmaceutical firms) will be made official. Thus, the same authority will be required to make an inventory of public health needs, and to act as a service provider for pharmaceutical firms. Indeed, marketing authorisation has become over the years a service to industry. In addition, according to articles 41 and 42, the inventory will be based on data collected in Member States on "*existing uses of medicinal products in the paediatric population*". This data collection is clearly necessary, and has been underway for several years, but not all habits are well founded. Common practices must be compared with the most reliable international data, and especially with epidemiological data.

The Medicines in Europe Forum considers that this inventory of needs must be launched immediately (without waiting the three years stipulated in article 41) by a publicly funded, independent scientific authority including, in addition to paediatricians, public health specialists and epidemiologists, general practitioners and specialists in other fields involved in child management, representatives of parent organisations, health insurers, and specialists in pharmacovigilance. This inventory should be regularly updated and establish a list of important needs towards which research efforts should be oriented by providing incentives for both public research institutions and private companies.

The Forum proposes that article 1 of the regulation, which mentions the "*specific therapeutic needs of the paediatric population*", present the inventory of needs (currently in article 41) as the framework on which incentives for the development of paediatric drugs should be based. ***(Amendment 2 of the Forum)***

Comments on the proposed technical measures: making resources available for real needs; preventing abuses

The European Regulation on orphan drugs, which has been in effect for 4 years, was designed to promote the development of drugs for patients with rare diseases and no available treatments. Some positive effects have already been felt: small groups of patients now benefit from drugs that improve their daily lives, even if they are not curative. But there have also been negative effects, such as orphan drug status (and high prices) being granted for drugs used to treat far larger patient populations than initially intended; widely used and profitable drugs (such as *celecoxib* or *sildenafil*) for which companies have requested orphan drug status in other indications; and flawed examination of some marketing applications (e.g. *agalsidase*).

The Medicines in Europe Forum considers that the regulation on paediatric drugs should take into account problems encountered with the regulation on orphan drugs, and proposes the following modifications or precisions.

Transparency of procedures and decisions. Regulation 726/2004 on European marketing authorisation offers major guarantees with regard to data transparency and access, even if they are still inadequate in the field of pharmacovigilance. The draft regulation on paediatric drugs mentions Regulation 726/2004 and should therefore offer the same guarantees. However, some of the draft articles are not sufficiently clear or precise.

Draft article 5, which deals with the functioning of the Paediatric Committee of the European Medicines Evaluation Agency, stipulates that if a consensus opinion is not reached, "*the opinion will consist of the position of the majority of members and divergent positions, with the grounds on which they were based*".

The Forum considers that a clearer wording is needed, in order to guarantee that voting details are made public at the same time as the final decision. **(*Amendment 3 of the Forum*)**

Draft article 15 indicates that the European Medicines Evaluation Agency *shall maintain a list of all waivers*, i.e. all cases in which a company does not need to provide paediatric data because the drug has no interest for children. This list, being an administrative document belonging to the Agency, should theoretically be made public, but the draft does explicitly mention this requirement.

The Forum considers that the article should contain

words to the effect that *This regularly updated list shall be made public.* **(*Amendment 4 of the Forum*)**

Precise endpoints. The presentation of the draft regulation states that: "*studies must be done only if one can expect a therapeutic advantage for children (avoiding dual use)*". But according to article 7.1.d of the draft regulation, the Paediatric Committee that evaluates the paediatric investigation plan will offer an opinion "*on the quality, safety and efficacy*" of the drug. Thus, the body of the text no longer contains the notion of demonstrating therapeutic advance for the children concerned. According to the draft text, if a therapeutic advantage over existing means was sought but not demonstrated, the Committee would nevertheless be able to give a favourable opinion, considering the drug to be effective and safe. True, article 7.2 stipulates that the Committee will examine "*whether or not any proposed studies can be expected to be of significant therapeutic benefit to the paediatric population*" and article 12.1.c waives the need to present paediatric data if "*the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients*", but the word "significant" is vague.

The Forum considers that there is no reason to reward a company for a drug that offers children no advantages relative to existing therapeutic options. The risk is that in the paediatric setting, as in adult medicine, there will be an increase in very similar drugs, creating a source of confusion, over-consumption, and harms. Added therapeutic value must be taken into account when rewarding the development of a paediatric drug. **(*Amendment 5 of the Forum*)**

Time allowed for application examination. Draft article 18 is precisely worded with regard to the time allocated for examining the paediatric investigation plan, and on its prolongation if supplementary information is requested. In contrast, draft article 23, concerning modifications of these investigation plans, is far too vague. Paediatric trials are difficult to conduct, and investigation plans often need to be modified as a result. The Paediatric Committee must have sufficient time to examine proposed modifications and their possible consequences for the quality and pertinence of the paediatric investigation.

The Forum considers that precise time periods must be added to article 23. **(*Amendment 6 of the Forum*)**

Time to effective drug availability. Draft article 34 indicates that, when a drug has already been placed on the market in other indications (in adults), and the company is granted a paediatric indication, it must place the drug with the paediatric indication on the market within two years following the authorisation. But this period makes no sense if the paediatric authorisation was granted because the drug offers children an advantage. Marketing should take place as soon as possible once authorisation is granted.

This article needs to be clarified. **(*The Forum requests clarification*)**

Public access to evaluation data. Draft article 29.1 stipulates that the results of studies done according to the paediatric investigation plan "*shall be included in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product, whether or not all the paediatric indications concerned were approved*". It is indeed important for health care professionals and patients to have access to evaluation data, but this wording calls for two comments.

On the one hand, the same information (results of clinical trials, but also the trial protocols) must be made public and the words "*if appropriate*" must be removed. Even if the wording of a package leaflet must be clear, concise and comprehensible, it must not hide some of the data.

In addition, data that accompanied a successful marketing application should be clearly distinguished from data provided in support of unsuccessful applications. The current trend is for companies to exploit all their data for promotional purposes, through ambiguous and blurred presentation of the different sections of summaries of product characteristics.

The Forum considers that article 29.1 must be more precisely and strictly worded. **(*Amendment 7 of the Forum*)**

Reinforced pharmacovigilance. The presentation of the draft regulation is intended to reassure the public that pharmacovigilance of paediatric drugs will be reinforced. But draft article 35 relating to pharmacovigilance mentions few new measures relative to what already exists for drugs used in adults.

The applicant is simply required to detail (...) the "*measures to ensure the follow-up of efficacy and possible adverse reactions*". The competent authority can also demand specific post-marketing studies, or a "*risk management system*". Draft article 35.4 states that the European Medicines Evaluation Agency will be charged with establishing guidelines relating to implementation of this article.

The Forum considers this article far too vague. Pharmacovigilance affairs are on the increase, and this call for a real change in attitudes leading to reinforced surveillance and prevention of adverse effects. The planned guidelines should be integrated now into the draft regulation, and all short-term and long-term demands accompanying marketing authorisation of paediatric drugs must be made public. **(*Amendment 8 of the Forum*)**

Another article should deal with the collation of adverse events during clinical investigation, and with the public accessibility of these data once the drug is marketed. **(*Amendment 9 of the Forum)***

Finally, article 33 of the draft regulation, concerning the identification of drugs for paediatric use as such on the packaging, should include an obligation to clearly mention warnings and treatment precautions on the packaging when the drug exposes to serious adverse effects. **(*Amendment 10 of the Forum*)**

Financial incentives in line with research expenditure. Close examination of evaluation data of paediatric drugs already available on the European market shows very large variations. In some cases the company only manufactured a pharmaceutical form and conducted a bioequivalence study. Others undertook more or less complex clinical trials of various sizes and durations.

Research efforts should be rewarded financially, but this reward must be proportional to the work actually undertaken. A levelling of rewards, as anticipated in the draft regulation (an extra 6 months of data protection for drugs that are still protected, an extra 2 years for orphan drugs (already protected for 10 years), and 8 + 2 years for drugs that are no longer protected) carries a double risk: first, a bias in favour of drugs with the biggest sales figures, which are still protected and whose manufacturers wish to extend the period of data protection; and a trend towards lower-quality evaluations. ►►

► The Forum considers that draft articles 36, 37 and 38 should include measures aimed at fine-tuning rewards according to the paediatric investigation plan rather than the global sales figure. **(*Amendment 11 of the Forum*)**

For the record, the Forum reminds that, in article 14.11 of Regulation 726/2004 (to which article 38 of the project refers), the lengthening of the duration of data protection for new indications only applies if the indication is considered to offer *"a significant clinical benefit in comparison with existing therapies"*. This principle should also apply to new paediatric indications.

The Forum also considers that, if companies continue to demand more than the financial incentives currently proposed, as suggested by recent position statements from big-pharma representatives, then we will have reached the limits of confiding drug research to the private sector. Available incentives will in this case have to be redirected towards public research institutions. At all events, research incentives must be attributed in total transparency, and the results of the research thus funded must be analysed in the same way.

In conclusion

The Medicines in Europe Forum wishes to underlines that, while the draft regulation seeks to answer a true need, which is limited in scope but important, it will be necessary to begin by analysing the precise needs of European children and their caregivers, and to define priorities. R&D incentives will have to be attributed according to these priorities. They should be open to both the public and private research sectors, and be proportional to real research and development spending. Research must be done in strict transparency, especially regarding adverse effects that occur in clinical trials, and that should be proactively detected.

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