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MEDICINES IN EUROPE

Application of the European regulation on paediatric drugs: remain vigilant!

- **The European regulation on paediatric drugs, first drafted by the European Commission in 2004, focused more on BigPharma's profitability than on children's therapeutic needs.**
- **The draft was subsequently improved, notably due to the actions of the Medicines in Europe Forum.**
- **Despite a number of flaws, the final text adopted by the European Parliament and Council focuses more on children's needs, introduces more transparency, and strengthens pharmacovigilance of paediatric drugs.**
- **The economic incentives for companies that develop paediatric drugs bear no relation to therapeutic advance or to the true costs of research and development.**
- **The Paediatric Committee of the European Medicines Agency will play a key role in ensuring that the regulation improves treatment of sick children. The Committee will be able to set priorities based on children's real needs and to make sure that paediatric indications are only approved if they represent a tangible therapeutic advance.**
- **Application of the paediatric regulation has already given rise to a welcome definition of 'significant therapeutic benefit'.**

In late 2006 the European Union adopted a regulation intended to encourage the pharmaceutical industry to study and develop drugs specifically designed for children. The Regulation (EC) n° 1901/2006 on medicinal products for paediatric use will be implemented gradually, between 2007 and 2009 (**a**)(1,2). This review examines the major provisions, as well as the opportunities and pitfalls, of the regulation.

A first draft too focused on industry concerns

The stated objective of the European Commission – to improve the health of children in Europe by encouraging drug companies to develop and evaluate drugs suitable for children – was commendable (3). In fact, there is a lack of suitable drugs, including drugs specifically evaluated in the paediatric setting, for some severe illnesses in children. However, there is a risk that this need for paediatric drugs will be seen solely in terms of market opportunity by drug companies, leading to over-medicating of children and adolescents, the vast majority of whom are in good health.

Prescrire, and the Medicines in Europe Forum, of which we are an active member, welcomed the European Commission's proposal to draft a regulation on drugs for paediatric use (**b**)(4).

However, the Commission's first draft, made public in 2004, focused too much on financial incentives for drug companies and too little on the real needs of sick children. The draft text dealt inadequately with several issues, including: the quality and relevance of clinical trials; pharmacovigilance; transparency of marketing authorisation procedures; and the quality of information for parents (information leaflet, access to assessment data) (5). The draft regulation also stated that all paediatric studies would be rewarded, regardless of the cost of research or the drug's therapeutic benefit (3).

Some requirements, in exchange for major economic incentives

After having been debated (and improved) by the European Parliament and Council (see inset page 40), the draft regulation on drugs for paediatric use imposed a number of obligations on drug companies, albeit in return for major financial rewards.

New drugs: paediatric studies required as of 2008, barring waivers. Starting on 26 July 2008, all marketing applications for new drugs will have to include data concerning the use of the drug in children, based on studies outlined in a "paediatric investigation plan" approved by the European Medicines Agency (EMEA) (**c**). However, in some circumstances, EMEA may waive such studies (**d**), or allow them to be conducted at a later date (**e**)(1).

These requirements, as well as those applying to new indications, new formulations or new routes of administration, and to paediatric marketing authorisation, concern all EU marketing authorisation procedures, not only the centralised procedure (1).

New indications, pharmaceutical formulations or routes of administration for patented drugs: paediatric studies required as of 2009, barring waivers. As of 26 January 2009, the above-mentioned requirements for new drugs will be extended to new market applications for indications for all drugs that are still protected by patents or by 'supplementary protection certificates', as well as to all new pharmaceutical forms and new routes of administration (1).

Existing drugs: marketing authorisation for paediatric use. Since 26 July 2007, companies selling drugs that are already on the market, specifically drugs that are no longer protected by patents or by supplementary protection certificates, have been able to apply for 'paediatric use marketing authorisation' (PUMA). In this case the company must provide "*the particulars and documents necessary to establish quality, safety and efficacy in the paediatric population, including any specific data needed to support an appropriate strength, pharmaceutical form or route of administration for the product, in accordance with an agreed paediatric investigation plan*" (1). Here too, the marketing application must include an EMEA-approved paediatric investigation plan (1).

Common rules. For all new or existing drugs, regardless of patent protection status, paediatric investigation plans will have to cover all age classes from 0 through 17 years, unless this requirement is waived by the paediatric committee (for one or several age classes) (1).

Submission of a paediatric investigation

plan does not guarantee that the requested paediatric indication will be approved. However, whether or not paediatric approval is granted, the results of all paediatric studies will be included in the summary of product characteristics, "*and, if appropriate, in the package leaflet of the medicinal product, provided that the competent authority deems the information to be of use to patients*" (1).

Obviously, drugs exempted from paediatric studies will not be granted paediatric indications.

By 26 January 2010 at the latest, all drugs approved in paediatric indications will bear a specific symbol on the label that will be explained in the patient information leaflet (1).

Major economic incentives for firms. Marketing authorisation for paediatric use will automatically protect the data utilised to obtain the authorisation for a 10-year period, which basically means 10 year market exclusivity (1). And this exclusivity will last 12 years for orphan drugs (1).

When a company applies for marketing authorisation for a new drug, a new indication, a new form or a new route of administration, and provides results in line with the paediatric investigation plan approved by the paediatric committee, the market exclusivity will be prolonged by 6 months (even for the non paediatric indications), whether or not the paediatric indications are ultimately granted (1).

Application of the regulation: key points to watch

The European Regulation includes both opportunities and pitfalls: everything will depend on how it is put into practice.

EMEA paediatric committee: important responsibilities. A paediatric committee (PDCO), created in July 2007, is charged with providing the EMEA with an opinion on the contents of paediatric investigation plans and on requests for waivers or deferral (see notes c, d and e). When requested to do so by a drug regulatory agency examining a marketing application, the committee must also provide an opinion on whether the submitted studies are in accordance with the approved paediatric investigation plan; it must also provide an opinion on the quality, safety and efficacy of the drug intended for the paediatric population (1).

The committee is also responsible for establishing an inventory of paediatric drug requirements and managing a network of European researchers specialising in paediatric studies (**f**)(1).

It is clear that the paediatric committee has a crucial role in guaranteeing that, in practice, the regulation ensures that children's real needs are met.

The paediatric committee includes: five members (and their deputies) appointed by the EMEA licensing committee (CHMP), a representative (and deputy) of each member state not represented by the five EMEA-appointed members (1), as well as three healthcare professionals and three patient representatives (**g**)(6). On 27 November 2007, these latter six members had not yet been appointed. We hope they will be chosen wisely and, above all, that there will be no financial conflicts of interest with industry.

Attention to ethics of paediatric trials. The regulation is designed to increase the number of drugs evaluated and developed for paediatric use. This will therefore lead to more paediatric trials, which is often viewed as a delicate and worrying perspective. The paediatric committee will be responsible for waiving the need for paediatric studies when the indication sought by the company does not concern children, or when the drug "*is likely to be ineffective or unsafe*", or "*does not represent a significant therapeutic benefit over existing treatments for paediatric patients*" (1).

The European Commission considered it necessary to restate the conditions under which paediatric trials must be conducted in different age classes (7). The Commission considers some research, such as comparisons with treatments known to be inferior to existing options, to be unethical (7). The Commission insists that ethics committees charged with approving paediatric trial protocols must also take their scientific validity into account (**h**)(7).

These welcome measures aimed at protecting children raise an obvious question: why are adults not offered the same protection?

Paediatric needs. The regulation still focuses less on children's needs than on incentives for drug companies. For ►►

Significant therapeutic benefit: why only for children?

Application of the regulation on drugs for paediatric use provided an opportunity for the European Commission to define what it means by a "significant therapeutic benefit":

"*Significant therapeutic benefit could be based on:*

- *Expected improved efficacy in a paediatric population compared to the current standard of care for the treatment, diagnosis or prevention of the condition concerned.*
- *Expected substantial improvement in safety in relation to either adverse events or potential medication errors.*
- *Improved dosing scheme or method of administration (number of doses per day, oral compared to intravenous administration, reduced treatment duration) leading to improved safety, efficacy or compliance.*
- *Availability of a new clinically relevant age-appropriate formulation.*
- *Availability of clinically relevant and new therapeutic knowledge for the use of the medicinal product in the paediatric population leading to improved efficacy or safety of the medicinal product in the paediatric population.*
- *Different mechanism of action with potential advantage for the paediatric population(s) in terms of improved efficacy or safety*" (1).

It remains to be seen whether this definition will have any real impact on marketing authorisation of drugs for paediatric use. In any case, it is high time for the same concept of therapeutic benefit to be introduced in the assessment of drugs for adults.

1- "Commission guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies" European Commission January 2007: 19 pages.

a- *The Regulation (ref 1) was immediately amended (ref 2) in order to adapt it to changes in the functioning of European institutions.*

b- *Our website (www.prescrire.org) provides documents in its "Medicines in Europe" pages, notably on the paediatric regulation and the Medicines in Europe Forum.*

c- *"The paediatric investigation plan shall specify the timing and the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned". This plan, or a waiver request, must be submitted, at the latest, by the date when the adult pharmacokinetic studies end (ref 1).*

d- *Waivers for a drug or class of drugs can be granted by the paediatric committee in response to a company's request, or be established at the committee's initiative. These waivers are granted if the drug is "likely to be ineffective or unsafe in part or all of the paediatric population", if the condition does not exist in children, or if the drug "does not represent a significant therapeutic benefit over existing treatments for paediatric patients" (ref 1).*

e- *When submitting its paediatric investigation plan, a company can request a deferral for the submission of study results (to be submitted later than the main application for market authorisation), for "scientific and technical reasons", and "on scientific and technical grounds or on grounds related to public health" (ref 1). The paediatric committee may accept or reject these requests, and monitor their implementation.*

f- *In July 2007, EMEA published a plan for the creation of this network; the objectives of the network will be "to coordinate studies relating to paediatric medicinal products, to build up the necessary scientific and administrative competences at European level, and to avoid duplication of studies and testing in children" (ref 18).*

g- *The French regulator AFSSAPS has a paediatric orientation committee and a paediatric drugs unit (ref 19).*

h- *Prescrire contributed to the public consultation on the draft guideline concerning paediatric trials. We found the proposal acceptable overall, but recommended certain changes aimed at protecting children's safety (ref 20).*

A better regulation, thanks to public lobbying

In the spring of 2005, members of the European Parliament's Environment, Public Health and Food Safety Committee submitted 289 amendments, which generally corresponded to the position statement of the Medicines in Europe Forum seeking to re-focus the draft paediatric regulation on children's needs and public health (1,2). After a heated debate several important amendments were finally adopted (3). Although some of the amendments were watered down when the draft regulation came before Parliament and the Council, the regulation that was finally adopted in 2006 is a significant improvement over the Commission's initial proposal.

Re-focusing on children's needs. The research programme on possible paediatric indications for drugs that are no longer protected by a patent or by a supplementary protection certificate was adopted thanks to public lobbying (4). And, while the cornerstone of the regulation is the financial incentive represented by the 6-month extension of the marketing exclusivity in all indications, this publicly funded research programme will not have to take commercial interests into account.

Another important improvement is that the composition of the paediatric committee has been extended to cover "*the scientific areas relevant to paediatric medicinal products, and including at least: pharmaceutical development, paediatric medicine, general practitioners, paediatric pharmacy, paediatric pharmacology, paediatric research, pharmacovigilance, ethics and public health*" (4).

Other amendments ensure that paediatric trials already conducted in non-EU countries will be taken into account, thus avoiding unnecessary trials (4).

More transparency. The final version of the regulation guarantees more transparency concerning conflicts of interest among members of the paediatric committee, access to the committee's opinions and to the list of waivers for paediatric studies, and partial access to the database of paediatric trials (4).

Pharmacovigilance: small advances. The draft regulation initially stated that the EMEA could ask firms to provide a risk management plan "*where there is particular cause for concern*". This is now a requirement (4). The Commission did not want to make these risk management plans obligatory in every case, but the regulation now states that the paediatric committee can ask for "additional reports" (4).

As usual, the Commission strongly resisted attempts to make pharmacovigilance more transparent, and data on adverse events will therefore remain locked away from public scrutiny (**a**)(5).

The concept of therapeutic benefits. The Commission claimed that the primary objective of the draft regulation was to prevent the "*non-availability to the paediatric population of therapeutic advances*", and the paediatric committee was responsible for considering "*the potential significant therapeutic benefits of studies in children*" (4).

The Medicines in Europe Forum requested that the manufacturers bear responsibility for demonstrating added therapeutic value be placed on the applicant (1). Most members of the EU Parliament and Council thought this excessive, but the paediatric committee must take added therapeutic value into account when it considers "*whether or not any proposed studies can be expected to be of significant therapeutic benefit to and/or fulfil a therapeutic need of the paediatric population*" (4).

The Commission's definition of "significant therapeutic benefit" provides the paediatric committee with the means to ensure that it takes children's best interests into account when granting waivers for paediatric studies and when examining drug companies' paediatric investigation plans (see inset page 39) (6). We hope that the paediatric committee will fully seize these opportunities.

a- *A draft recommendation released by the EMEA in January 2007 on paediatric pharmacovigilance nevertheless mentions the existence of particular concerns in this area (ref 7).*

1- Medicines in Europe Forum "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" December 2004. www.prescrire.org accessed 9 August 2007: 4 pages.
2- Prescrire Rédaction "Europe et médicaments pédiatriques" *Rev Prescrire* 2005; **25** (263): page III of the Letter to Subscribers.
3- Prescrire Editorial Staff "Draft EU regulation on paediatric medicines: some improvements but still far from perfect" *Prescrire Int* 2006; **15** (81): 32-33.
4- "Regulation (EC) N° 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004" *Official Journal of the European Union* 27 December 2006: L 378/1-L 378/19.
5- "Prescrire Editorial Staff "Medicines in Europe: The most important changes in the new legislation". *Prescrire Int* 1 July 2004. www.prescrire.org/aLaUne/dossierEuropeSynthese2En.php
6- "Commission guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies" European Commission January 2007: 19 pages.
7- EMEA "Guideline on conduct of pharmacovigilance for medicines used by the paediatric population" 25 January 2007. www.emea.europa.eu accessed 27 August 2007: 13 pages.

▶ example, the paediatric committee must compile an inventory of therapeutic needs (by 26 January 2010, three years after the regulation comes into effect) "*with a view to identifying research priorities*" (1). But the regulation states that this inventory will be based on "*available data on all existing uses of medicinal products in the paediatric population*", which member states must provide to the EMEA by 26 January 2009 at the latest (1).

In the meantime, the committee uses lists established by the EMEA paediatric task force. The EMEA has published lists of therapeutic needs as well as priorities among drugs that are no longer under patent (8,9). The list of needs actually became an inventory of drugs that are indicated for adults and also used in children (albeit off-label), or drugs with paediatric marketing authorisation in some countries (**i**). The second list is a non prioritised list of existing drugs with very different risk-benefit balances.

It is logical to begin an inventory of needs by collecting information on current practices, but some of these practices are not evidence based, others may be useless or even harmful, while some needs are not covered. The amendment proposed by the Medicines in Europe Forum, intended to extend the inventory to cover unmet needs, was ultimately rejected, but there is nothing to stop the paediatric committee from simply preparing an inventory of existing practices (4).

Drugs with known or suspected serious adverse effects in adults should not be evaluated in children. Only drugs with well-documented efficacy in adults should be studied in children, unless there are valid arguments to suggest that a product that is ineffective in adults might be effective in children. The first priority for paediatric studies should be to focus on drugs from each pharmacotherapeutic class that have the best risk-benefit balances and are considered standard treatments for adults (10).

At last, the concept of significant therapeutic benefit! One key point in the regulation is that the paediatric committee can, either on its own initiative or in response to a request from a company, waive the need for paediatric investigation plans for drugs or drug classes, if

they "*do not represent a significant therapeutic benefit over existing treatments*" (1). This should limit the number of drugs that need to be evaluated in children, and strengthen efficacy requirements in clinical trials.

The draft guideline prepared by the European Commission, specifying the conditions for the application of the regulation, provides the paediatric committee with a solid base from which to work (11). In fact, the Commission specifies that "*to enable the paediatric committee to make its assessment the applicant should provide a comparison of the medicinal product which is the subject of the application with the current standard of care for the treatment, diagnosis or prevention of the diseases / conditions that are the subject of the intended indication in children*" (11). We are particularly pleased to see that the Commission has defined the concept of "significant therapeutic benefit" for children, especially as the Commission was fiercely opposed to comparative assessments during the revision of the Directive and Regulation adopted in 2004 (see inset page 39) (12).

It will be necessary to remain vigilant here as well: in some cases, the applicant can simply provide "*well-justified and plausible assumptions*" or refer to the inventory of therapeutic needs established by the paediatric committee (11).

Missed opportunities

The Regulation has several limitations and pitfalls.

Uniform financial rewards. Granting a 6-month extension of market exclusivity for all approved paediatric investigation plans is a regrettable waste of public funds. This 6-month exclusivity represents extremely variable amounts of extra income for the companies concerned, depending on the drug. It does not reflect the cost of paediatric research or the therapeutic benefit for children.

The Medicines in Europe Forum lobbied, in vain, for these incentives to reflect the real endeavours undertaken by the company (13).

However, this measure was at the core of the proposed regulation, which in fact sought to offer drug companies the same advantages in Europe as they have enjoyed in the United States since 1997 (14).

One American study showed that the economic return that a company realised for developing a paediatric drug (i.e. the difference between 6 months of supplementary sales and the specific costs of paediatric R&D) ranged from -9 to +509 million dollars (14).

A reduction of the market exclusivity period from 6 months to 3 months has been debated in the United States; the US Senate has officially proposed that the incentive be limited to an extra 3 months of market exclusivity for drugs with annual sales of over one billion dollars (14,15).

Some European members of Parliament proposed a 3-month exclusivity period, but this proposal was not adopted. This is particularly regrettable as the incentives offered in Europe will be added to those available in the United States, often for the same set of paediatric studies.

It is also unfortunate that the incentives will not be counteracted by lower prices for paediatric drugs.

Omissions and pitfalls. For drugs that are already on the market, companies are only required to conduct paediatric studies if they are seeking approval for a new indication, a new pharmaceutical form, or a new route of administration. It is unlikely that such studies will be conducted for drugs with small sales figures (16).

For all new marketing authorisations granted after 26 July 2008, companies will have to provide, unless this requirement is waived, the results of a paediatric investigation plan. There is a danger that some firms will be tempted to apply for a paediatric indication in a single, narrow age class (qualifying them for the reward) and to apply for a waiver in other age classes in which studies could be more difficult or expensive (17). The paediatric committee must be ready to counter these strategies.

Finally, the regulation states that drug regulatory agencies will be able to modify summaries of drug characteristics on the basis of paediatric studies that were already available when the regulation came into effect (1). Here again, the paediatric committee must verify that such modifications are based on robust data.

Keep an eye on the paediatric committee and on drug regulatory agencies. This regulation encouraging better drug evaluation in children is welcome, as it should improve the treatment of serious diseases – or at least those qualifying for drug therapy. But the regulation must not be turned into a Trojan horse for the pharmaceutical industry, leading to overmedication of children and adolescents.

It will be the responsibility of the paediatric committee, along with the drug regulatory agencies, to ensure that only drugs likely to represent a significant therapeutic benefit for children are approved. This calls for vigilance on the part of healthcare professionals and parents.

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i- Prescrire informed the paediatric committee of our concerns regarding the draft list of paediatric therapeutic needs (ref 10).

Selected references from Prescrire's literature search.

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12- Prescrire Editorial Staff "Medicines in Europe: the most important changes in the new legislation" *Prescrire Int* 1 July 2004. www.prescrire.org/aLaUne/dossierEuropeSynthese2 En.php

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