SURVEY

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Draft EU regulation on paediatric medicines: some improvements but still far from perfect

- **In 2004, the European Commission proposed a draft European Regulation on paediatric medicines. This draft was more closely oriented towards defending drug companies' interests than with meeting children's medical needs.**

- **Despite pressure from drug companies and their allies, several major improvements were made to the draft at its first reading in the European Parliament, thanks especially to the efforts of the Medicines in Europe Forum.**

- **In particular, European deputies pushed for a better definition of children's needs and paediatric research priorities, greater transparency at various important stages of the market authorisation procedure, and strengthened pharmacovigilance.**

- **Yet the incentives and rewards offered to companies fail to take into account the notion of true therapeutic advantages and R&D expenditure.**

- **Unfortunately the Commission refused some important amendments and published a new draft proposal, which was accepted by the Council of Health Ministers at the end of 2005. The new draft will come before the Parliament for a second reading in 2006.**

For a variety of serious but relatively infrequent paediatric diseases, there are no suitably formulated drugs that have been adequately assessed in children, even in wealthy industrialised countries. As far back as 1989, *la revue Prescrire* pointed out that there was no scientific or ethical reason to justify the nearly total lack of studies in children. For example, the only betablocker approved for use in children in France had not been tested in paediatric trials (1).

This is why the Medicines in Europe Forum, of which *Prescrire* is a member, welcomed the European Commission's proposal to create a Regulation governing paediatric medicines (2).

The stated objective was to improve the health of children in Europe by encouraging drug companies to develop and evaluate drugs appropriate for children (3). However, the actual draft fell short of fulfilling these aims (2).

The draft Regulation focused to a greater extent on financial incentives and rewards for drug companies than on children's health needs. The draft was vague or even silent on points as important as the need for an inventory of paediatric drug requirements (and not simply drug companies' empirical practices and artificially created needs); the quality and pertinence of clinical evaluations (i.e. the risk-benefit balance); pharmacovigilance; the transparency of marketing authorisation procedures; and the quality of information provided to parents (access to assessment data, patient information leaflets). In addition, the draft recommended standard rewards for companies that develop paediatric drugs, rather than incentives commensurate with real R&D expenditure (2).

Too little time for debate

The Regulation has to go through the co-decision procedure involving the European Parliament and the Council of Health Ministers. However, unlike Directive 2004/27/EC and Regulation (EC) 726/2004 on medicines for human use, for which adequate time was provided for proper debate (4), the Regulation on paediatric drugs was rushed through the co-decision procedure.

Influential drug companies, the European Commission's Enterprise Directorate-General and certain member states (including France, the country that launched the initiative), were clearly in a hurry to achieve their goals. In 2005, a major campaign was conducted by drug company lobbyists (excepting generics manufacturers), with the help of patient (or parent) organisations and unions of healthcare professionals (especially paediatricians), based on a simplistic message: that drugs for children are lacking and that everything must be done, without delay, to remedy the situation (5-8).

In spring 2005, members of the Committee on Environment and Health proposed a total of 289 amendments to the draft Regulation, most of which were consistent with the positions of the Medicines in Europe Forum. The aim was to refocus the text on the interests of children and on public health (**a**) (9). This was an important contribution.

Unfortunately, the first reading during a plenary session of the European Parliament was rushed, and not enough time was allocated for a thorough debate. European deputies were given only a few days in late August 2005 in which to propose amendments, with the parliamentary vote scheduled for September 7. This meant that no further improvements could be made after the vote by the Committee on Environment and Health.

A draft refocused on children's interests

European deputies who were concerned with children's real needs managed to push through several positive amendments which were voted during the plenary session.

Refocusing on children's needs. Amendments were voted in order to focus the new marketing procedure for paediatric drugs on meeting "*needs which are not covered* and *research priorities*" (articles 2a, 2b and 7) (10). A specific European programme of drug research for the benefit of children was planned to support research activities in fields neglected thus far by drug companies (articles 39a, 47 and 47a).

The enlargement of the paediatric committee, which has a very important role throughout the procedure, should help to ensure that children's health needs are finally met. Amendments were voted so as to extend the committee and include: "*other physicians specialising in the treatment of children, general practitioners, pharmacists, pharmacovigilance and public health specialists*", as well as representatives of parent associations, as initially recommended (article 4).

Other amendments were voted to ensure that the results of paediatric trials already carried out in non-EU countries are taken into account, in order to avoid redundancy (article 7).

Greater transparency. A number of amendments were voted to ensure greater transparency concerning the opinions of the paediatric committee (article 5), committee members' conflicts of interest (article 6), waivers to the obligation to undertake paediatric research (article 15), patient information on drug indications (article 29) and adverse effects (article 35), and access to registries of paediatric trials and other studies (article 40).

Strengthened pharmacovigilance. The Regulation was amended to oblige companies to set up a risk management system for all paediatric drugs, and not only "*where there is particular cause for concern*" as proposed in the initial draft (article 35). An amendment required that adequate public funding was ensured for pharmacovigilance (article 35). Another amendment required that data on adverse effects collected before and after market release should be gathered together in a publicly accessible registry (article 35).

Missed opportunities

The main deficiencies to the current proposal concern incentives and added therapeutic value.

The same rewards for all… For drug companies and the European Commission, a 6-month patent extension was the cornerstone of the draft Regulation. The Medicines in Europe Forum and concerned European deputies from across the political spectrum failed to ensure that incentives and rewards would be proportional either to added therapeutic value or to true R&D costs.

However, according to an adopted amendment, after a 6-year period the EU Commission "*shall carry out an analysis of the incentive and reward operations (…) with a financial assessment relating to the research costs and profits resulting from such incentives*", which could lead to updating the Regulation (article 49) if the incentives mechanism is found to be ill-suited to children's health needs.

We also welcome the adoption of several amendments designed to avoid the accumulation of both paediatric incentives and other types of protection (article 36 and 37), and rewards for trials already carried out (article 55).

Insufficient attention to therapeutic advantage. The Commission presented the draft Regulation as a response to the lack of development or testing of drugs to ensure that they meet children's health needs (3). The Medicines in Europe Forum considered it logical that, when a drug is already approved for a paediatric indication, any new drugs with the same indication should be compared with it. Unfortunately, amendments intended to ensure such comparative evaluations of paediatric drugs were rejected.

However, the paediatric committee will still have a major role when it comes to establishing the list of waivers regarding the obligation to conduct paediatric studies, and approving drug companies' "*paediatric investigation plans*". The Regulation states that: "*in all its work, the paediatric committee should make sure that studies in children have potential significant therapeutic benefits for paediatric patients*" (3).

The Commission has refused or partly refused some important amendments adopted by the members of Parliament after first reading. The Commission has published a new draft proposal (with a selection of amendments) that has been accepted by the Council of Health Ministers. The new draft will have to go before the Parliament for a second reading in 2006.

a- *See www.prescrire.org for more details.*

1- Prescrire Rédaction "Le "parent pauvre"" *Rev Prescrire* 1989; **9** (84): 152.
2- Prescrire Rédaction "La proposition de Règlement européen relative aux médicaments "pédiatriques" est trop loin des besoins des enfants" *Rev Prescrire* 2005; **25** (259): 226-227.
3- "Proposal for a regulation of the European parliament and of the council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/83/EC and Regulation (EC) No 726/2004 (presented by the Commission)" 29 September 2004: 57 pages.
4- Prescrire Rédaction "Europe et médicament: les succès obtenus par les citoyens" *Rev Prescrire* 2004; **24** (252): 542-548.
5- "Industry pushes for adoption of European legislation on paediatric trials" *Scrip* 2005; (3068): 2-3.
6- European Federation of Pharmaceutical Industries and Associations "To the attention of members of the EP Environment Committee" 29 June 2005: 4 pages, signed by 36 company directors.
7- "UE/Médicaments: les ministres de la santé soutiennent l'octroi d'une protection supplémentaire de six mois pour les indications pédiatriques - La parole est au Parlement" *Bulletin Quotidien Europe* 2005; (8963): 13.
8- Confederation of European Specialists in Paediatrics "More paediatric research needed in Europe to improve children's health" 10 December 2004: 2 pages.
9- "Europe et médicaments pédiatriques" *Rev Prescrire* 2005; **25** (263): page III of "Lettre aux Abonnés".
10- "Medicinal products for paediatric use- European Parliament legislative resolution on the proposal for a regulation of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/83/EC and Regulation (EC) No 726/2004 (COM(2004)0599–C6-0159/2004–2004/0217(COD)) - P6_TA-PROV(2005)0331'': 28 pages.

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The French regulatory agency: where do its true priorities lie?

The French regulatory agency (Afssaps) rarely supports its decisions with solid and precise data. This will soon have to change, when European Directive 2004/27/EC on human medicines is transposed into French law. For the moment, however, the Afssaps director general provides little or no information on the reasons for his decisions.

As a result, the French public can only watch and wonder. In certain cases an intriguing relationship appears to exist between the sales figures of a drug with a negative risk-benefit balance and the time taken to withdraw it from the market. For example, the Agency demanded the market withdrawal of local antibiotics (delivered intranasally or to the oropharynx), but took several years to enforce its decision; bizarrely, the drugs with the most sales were among the last to be withdrawn (see the example of Locabiotal° (fusafungine) (**a**)).

The Agency has performed even worse when it comes to dextropropoxyphene + paracetamol combinations, which are far more popular than local antibiotics. It claims that these combinations, which are unnecessary, do not carry the same risks in France as in Sweden or the United Kingdom, where market withdrawal is planned for the end of 2005 (see page 20).

When drugs that have long been known to have negative risk-benefit balances, such as benfluorex and veralipride, are withdrawn from the Spanish market, the French Agency remains silent and sales continue unabated.

And when the drugs in question are new, expensive, and widely prescribed, the French agency not only allows them to remain on the market, but also ensures that information on the associated dangers is released very slowly. The slow release of information on adverse effects of the cox-2 inhibitors was but one example of this chronic failure to act.

In the near future, the French Agency will have to emerge from the shadows, and we will see where its true priorities lie!

a- *According to the French national health insurer (Caisse nationale d'assurance maladie des travailleurs salariés), which handles about 72% of drug reimbursements in France, 3 547 190 boxes of Locabiotal°, 15 309 475 boxes of Di-Antalvic° (dextropropoxyphene - paracetamol combination), 6 165 196 boxes of Mediator° (benfluorex), and 929 951 boxes of Agreal° (veralipride) were reimbursed in 2003.*