

# The EU's new paediatric medicines legislation: serving children's needs?

Govin Permanand, Elias Mossialos, Martin McKee

*Arch Dis Child* 2007;**92**:808–811. doi: 10.1136/adc.2006.105692

In new legislation for paediatric medicines which came into effect on 26 January 2007, the European Union (EU) has attempted to address several unresolved issues relating to children's needs for medicines in Europe. This article reviews the legislation's main proposals and makes some comparisons with equivalent legislation in the USA. We argue that the legislation suffers from several gaps and uncertainties in relation to the specific proposals and their intended aims. As the establishment of new legislation in this area offered the EU an opportunity to set some clear guidelines and objectives, and had the potential to go beyond the equivalent American rules, we thus see the proposals as something of a disappointment.

The development and testing of drugs for children is far from satisfactory: many drugs used to treat children are only licensed for use in adults,<sup>1,2</sup> drugs are often unavailable in formats suitable for children<sup>3</sup> and clinical trials involving children raise complex ethical issues.<sup>4</sup> Further, the use of adult products at lower doses or on a less frequent basis may pose risks to children, as may the use of unlicensed and off-label medicines.<sup>5–7</sup> According to a detailed European survey conducted in 2000, the use of unlicensed drugs in paediatric wards was reported as widespread in Germany, Italy, the Netherlands, Sweden and the UK.<sup>8</sup> In 2005 the European Commission issued a revised set of proposals on paediatric medicines that sought to address these concerns,<sup>9</sup> and in a recent paper in this journal Choonara<sup>10</sup> identified a series of challenges arising from them. In this paper we argue that the challenges are even more wide-ranging and that the final legislation – Regulation 1901/2006,<sup>11</sup> which entered into force on 26 January 2007 – fails to clarify several uncertainties and leaves some gaps.

The regulation proposes a combination of incentives and obligations designed “to facilitate the development and accessibility of medicinal products for use in the paediatric population”. It further aims “to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations”. For the purposes of the European Union (EU), the paediatric population (0–18 years) consists of neonates (preterm and term), infants and toddlers (1–23 months), children (2–11 years) and adolescents

(12–16 or 18 years),<sup>12</sup> and accounts for approximately 25% of the EU's total population.<sup>13</sup> According to the European Commission's proposals, between 50% and 90% of the medicines currently administered to children have neither been tested on nor authorised for use in children. This does not necessarily suggest an established lack of therapies for paediatric conditions, although some age groups may be better served than others,<sup>14</sup> but it highlights the crucial need for more evaluation in children generally, particularly given the specific needs of each subgroup. Beyond a 1997 European Medicines Agency (EMA) guidance note on clinical investigations of medicinal products in children, which was superseded by the International Conference on Harmonisation's E11 guidance note in 2000,<sup>15</sup> this will be the first formal EU legislation focusing on medicines for children. Rather than offering a discussion on the relative merits of an incentive versus disincentive scheme to promote research into paediatric medicines, we review the regulation's main provisions and, drawing on equivalent US legislation, ask to what extent the European proposals will actually achieve their intended aims.

## EXTENDING PATENT PROTECTION

A central plank of the legislation is a 6 month extension of the Supplementary Protection Certificate (SPC) for products already available on the market where their use is to be extended to children. (The SPC, by adding up to 5 years additional protection upon patent expiry, prolongs a drug's effective patent-life up to a maximum of 15 years.) The extension is subject to the inclusion of paediatric clinical trial data in the Summary of Product Characteristics, which is submitted with the marketing authorisation application, and testing must have been aimed at the specific paediatric population targeted. For orphan drugs there is the possibility of an additional 2 year's market exclusivity. As evidence of testing on children is now to

See end of article for authors' affiliations

Correspondence to: Govin Permanand, LSE Health and European Observatory on Health Systems and Policies, London School of Economics and Political Science, Houghton Street, London WC2A 2AE, UK; g.permanand@lse.ac.uk

Accepted 29 January 2007

**Abbreviations:** BPCA, Best Pharmaceuticals for Children Act; CHMP, Committee on Human Medicines; EFPIA, European Federation of Pharmaceutical Industries and Associations; EGA, European Generic Medicines Association; EMA, European Medicines Agency; EU, European Union; Eurordis, European Organization for Rare Diseases; FDA, Food and Drug Administration; MHRA, Medicines and Healthcare products Agency; MICE, Medicines Investigation for the Children of Europe; NICHD, National Institute of Child Health and Human Development; NIH, National Institutes of Health; PDCA, Paediatric Committee; PIP, Paediatric Investigation Plan; PREA, Pediatric Research Equity Act; PUMA, Paediatric Use Marketing Authorisation; SPC, Supplementary Protection Certificate

be provided as part of all applications, the extension is being offered as compensation to companies for the potential extra costs and difficulties in undertaking paediatric trials. Manufacturers may themselves seek to extend a product's existing indications to paediatric use, and undertake the requisite testing, but it is one of the tasks of a new paediatric committee (see below) to decide on which products should be considered. It is important to note that the product need not be granted a paediatric indication to qualify for the extension as was the requirement in the previous draft of the legislation. Instead, an extension will be granted where the company has undertaken paediatric testing of its product, whether it is successful or not, and covers all indications.

The patent extension is largely based on a similar US provision in the 1997 Food and Drug Administration (FDA) Modernisation Act. The American "pediatric exclusivity" provision provides a 6 month patent extension for companies willing to perform paediatric clinical investigations at the request of the FDA. Initially due to run for only 5 years, during which time it was credited with having stimulated paediatric clinical trials and increased paediatric labelling (with 56 drugs receiving exclusivity status),<sup>16</sup> it has since been extended for another 5 years. In 2001 it was said to have resulted in studies being undertaken on over 70 diseases and conditions specific to children, with 32% of these studies covering neonates and infants.<sup>17</sup> According to the FDA, "the pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date",<sup>18</sup> a conclusion echoed in a later independent study.<sup>19</sup>

The USA has since enacted two further pieces of legislation: the 2002 Best Pharmaceuticals for Children Act (BPACA) and the 2003 Pediatric Research Equity Act (PREA). The former extended the paediatric exclusivity provision and provided incentives for off-patent products, while the latter granted the FDA the authority to demand that companies provide paediatric studies in specific cases, changing what had been a voluntary scheme. The three instruments are together credited with increasing knowledge of paediatric prescribing (eg, addressing dosage issues, appropriate administration formats) and the number of products specifically for children in the USA, thereby also reducing potential risks for children.<sup>20</sup> On 19 December 2005, the anti-convulsant medication Trileptal became the 100th medicine with specific paediatric information to be approved in the USA.<sup>21</sup>

Lower medicine prices in Europe, however, may mean that the patent extension will not have the same effect as the exclusivity clause has had in the USA.<sup>22</sup> Indeed, the research industry's trade body, the European Federation of Pharmaceutical Industries and Associations (EFPIA) views a 6 month extension as a minimum given the cost, length and complexities of paediatric research.<sup>23</sup> That said, an independent review estimates that paediatric testing will add only 0.2–0.7% of industrial costs,<sup>24</sup> with most research into paediatric medicines focused on dosage issues, formulations and side-effects rather than basic research.<sup>25</sup> The European Generic Medicines Association (EGA), although not a disinterested party, has estimated that the extension will amount to €100 million in annual sales for "mid-range" products and €500 million for "blockbusters".<sup>26</sup> Such a potential windfall would seem disproportionate for what is essentially compliance with new mandatory paediatric testing rules. Moreover, the US extension resulted in a host of studies for patent-expiring products on children, particularly regarding anti-hypertensive drugs. Some of these will have been genuinely directed at serving children's needs. However, with cardiovascular conditions not among the major causes of morbidity in children,<sup>27</sup> it

seems reasonable to assume that several were directed towards extending the patent protection in the companies' own interests. It will be important to ensure that this is not replicated in the EU.

Concerns over potential profits to manufacturers (and burdens on health care budgets) saw variations on the blanket 6 month extension discussed during early consultations. Of particular note was the idea of "variable SPCs" forwarded by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK.<sup>28</sup> This was to tie the extension period to volume sales on a product-by-product basis. In principle this was perhaps not a bad idea (it has also been said of the US approach that it could be better targeted according to demonstrable impact<sup>29</sup>), but it was rejected by other member (EU) states as too cumbersome and bureaucratic a scheme to operationalise. Indeed, as there are financial impacts on national healthcare systems,<sup>24, 30</sup> particularly in terms of delaying the entry of generics (the EGA has further calculated that the extension will cost already-stretched EU healthcare systems an extra €2 billion a year), some member states have called for a shorter extension. This may, however, also be intended to support their generics industry.

## PROMOTING OFF-PATENT PRODUCTS AND PUBLIC RESEARCH

The proposals also seek to encourage companies to consider paediatric uses for off-patent products. Under a Paediatric Use Marketing Authorisation (PUMA) scheme, manufacturers will be granted a right to 10 years of data exclusivity when new studies are carried out on older drugs. The product retains its brand name, with a symbol added to indicate that it has been tested in children. Although the symbol has yet to be decided upon, this new labelling requirement is likely to be of use to pharmacists and those who administer the medicines. However, as the PUMA does not ensure market exclusivity (other companies will be able to conduct their own studies on the same product and themselves apply for a PUMA), it is questionable whether the scheme will prove an adequate incentive for generic companies. As studies will need to be carried out by each manufacturer seeking a PUMA, and it is not clear how many entrants in a given class of drug will be permitted, there are, therefore, practical and ethical concerns regarding the potential duplication of trials in children.<sup>31</sup> Moreover, even if the PUMA scheme has the desired effect, it may actually promote research investment in areas that are seen as most profitable rather than where therapies might be most needed. By comparison, the corresponding American legislation mandates evaluation of both off- and on-patent drugs that the industry is not interested in.

Interestingly, the proposal to create a Medicines Investigation for the Children of Europe (MICE) fund to promote independent research into the use of substances not covered by patent or an SPC, which appeared in the previous draft of the proposals, no longer appears in the final regulation. As funding for the scheme was never made explicit, a contributory factor was that it was not obvious that it could have been financed from the Commission's existing research budget.<sup>32</sup> Notwithstanding valid concerns that the market for the relevant products may not be sufficiently attractive to encourage research investment,<sup>33</sup> such funding of public research was seen as a good idea in principle.

In contrast, the US government explicitly supports paediatric drug development in the USA and worldwide through the National Institute of Child Health and Human Development (NICHD). A similar mechanism could potentially facilitate better targeting of research in areas of genuine clinical need (the EMEA's Committee on Human Medicinal Products has a

Paediatric Working Party which is looking at this issue). Moreover, the EU legislation does not provide for any formal coordination with the long-standing activities of the NICHD, which would help to avoid overlaps and support cooperation between European and US drug regulators. Co-operation between the EU and US in the area of paediatric medicines is needed, particularly as the FDA and EMEA have on occasion expressed different opinions about the same clinical trials.<sup>34</sup> The simultaneous submission of paediatric plans to the EMEA and FDA would seem desirable, but the regulation makes no commitment to collaboration.

## MARKETING AUTHORISATION AND THE PAEDIATRIC MEDICINES COMMITTEE

Companies' submissions for evaluation of new medicinal products are to take the form of a new Paediatric Investigation Plan (PIP). The detailed content and format has yet to be developed, but it will probably cover all aspects of the development and the likely formulation (given that only substance properties will have been identified by this time). The timing also needs to be finalised, and is it expected that the PIP will need to be accepted before an application is made for marketing authorisation.<sup>31</sup> Submission of a PIP does not require that paediatric testing already be underway, but it does potentially allow for early testing on children. While clearance of the PIP may be at the time of marketing authorisation application, submission of the plan itself is likely to be at the time of phase II clinical trials in adults. Although adult safety cannot be relied upon as an indicator of the safety of medicines in children, and notwithstanding the E11 statement that "some products may be reasonably studied only in the paediatric population even in the initial phases", it may be that from an overall safety point of view, the later the PIP submission the better. The paediatric committee ought to provide guidance here. Not only will it be desirable that some studies for children-specific conditions be undertaken even earlier, but there are examples of adult drugs which can be used for other indications in children. This question of timing also raises potential ethical concerns about undertaking trials in children when the results in adults have not been favourable, but a waiver and deferral scheme for medicines unlikely to be of benefit to children and to prevent unnecessary testing, may address this. Consequently, there is a need for close scrutiny of the PIP and any applications for waivers or deferrals, and also to ensure that the deferral provision is not (mis)used to speed the approval of adult formulations.

Finally, a crucial element in the legislation is the creation of a paediatric committee within the EMEA; to be established by July 2007. The committee (PDCO) will evaluate the PIP, decide on the number and type of studies required, in which groups they are to take place, and the applicability of waivers or deferrals. The European Parliament, in its review of the legislation, placed great emphasis on the committee's role in this regard.<sup>35</sup> Safety, quality and efficacy evaluation, as for adult medicines, will still lie with the Committee on Human Medicinal Products (CHMP), and marketing authorisation can be withdrawn if the product is not placed on the market within 2 years of approval; the corresponding figure for conventional products is 3 years.<sup>36</sup> The paediatric committee's evaluation role will therefore be crucial, and it is to be hoped that the EMEA's broader function in providing pre-application scientific advice to manufacturers will not interfere.

Additionally, the PDCO will also establish and maintain "an inventory of public health needs based on existing uses for medicinal products in the paediatric population". While the details again have yet to be elaborated, this is a positive step. It is nevertheless only a surveillance mechanism, and could be

strengthened by proactive identification of unmet medical needs (the regulation does not call for even a preliminary identification of needs). Indeed, the European Organization for Rare Diseases (Eurordis) has suggested that the paediatric committee's role should extend to publishing "targeted calls for PIPs aimed at addressing critical unmet medical needs".<sup>37</sup> By comparison, under the Best Pharmaceuticals for Children Act in the US, the FDA works closely with the National Institutes of Health (NIH) to develop a "List of Drugs for which Pediatric Studies are Needed", with input from various FDA and NIH divisions and others, including the American Academy of Pediatrics. The EU inventory will include input from member state authorities and relevant health and medical associations but, given differing national priorities and requirements, it remains to be seen whether a single coherent register will be possible.

## AN UNCERTAIN FUTURE

Much like the US legislation, the EU proposals are a combination of incentives and obligations aimed at improving the health of children by promoting research into paediatric medicines and testing on children generally. Member state governments are also encouraged to create their own incentives, and even to invest in clinical trials centres and training health professionals to conduct trials. Yet, as we have highlighted, there are still many uncertainties and gaps in the legislation and, according to the EU Committee of the British House of Lords "... it is impossible to judge... whether these arrangements are likely to provide the necessary incentives to industry, whether they are likely to be equitable and proportionate, or whether they may give rise to excessive profits, penalise the health services of Member States or create unacceptable disadvantages for the manufacturers of generic products".<sup>30</sup> Indeed, the incentives – SPC extension versus PUMA – would appear to favour first-movers in the market rather than generic producers, while accurate predictions of costs to healthcare systems and profits to companies are uncertain. It is perhaps worth noting that a limited study found that paediatric licensing is greater in the US than in the UK, Australia and New Zealand where such paediatric incentives are not in place, but that this is only true for preparations for children over 6 years of age.<sup>38</sup> This may be due to a lack of perceived utility and small patient numbers at younger ages, perhaps coupled with the comparative ease in recruiting older trial participants.

Finally, the Commission's proposals talk about children's "needs" without actually defining what these are, and there is only vague reference to funding, via the Community's 7th Framework Programmes for Research, Technological Development and Demonstration Activities, "or any other Community initiatives for the funding of research". An underlying concern, therefore, is that the legislation seeks to increase the number of paediatric medicines on the market as an end in itself, rather than being needs driven. Here, however, the potential strength of the paediatric committee in setting norms and obliging companies to perform paediatric tests is to be commended. While the EU legislation may result in more clinical trials, new medicines, a reduction in adverse events and safer prescribing for children,<sup>28 39</sup> this is a long-term goal. Moreover, it reflects an EU approach which, rather than developing and building on the US experience, instead hopes to emulate it.

## ACKNOWLEDGEMENTS

The authors wish to acknowledge the helpful and constructive comments provided by two reviewers on an earlier draft of this paper.

**Authors' affiliations**

**Govin Permanand, Elias Mossialos**, LSE Health and European Observatory on Health Systems and Policies, London School of Economics and Political Science, London, UK

**Martin McKee**, European Centre on Health of Societies in Transition and European Observatory on Health Systems and Policies, London School of Hygiene and Tropical Medicine, London, UK

Competing interests: None.

**REFERENCES**

- 1 't Jong GW, Eland IA, Sturkenboom MC, *et al.* Unlicensed and off-label prescription of respiratory drugs to children. *Eur Respir J* 2004;**23**:310–13.
- 2 Pandolfini C, Impicciatore P, Provasi D, *et al.* Off-label use of drugs in Italy: a prospective, observational and multicentre study. *Acta Paediatr* 2002;**91**:339–47.
- 3 Standing JF, Tuleu C. Paediatric formulations--getting to the heart of the problem. *Int J Pharm* 2005;**300**:56–66.
- 4 Saint Raymond A, Brasseur D. Development of medicines for children in Europe: ethical implications. *Paediatr Respir Rev* 2005;**6**:45–51.
- 5 Stephenson T. Medicines for children – the last century and the next. *Arch Dis Child* 2001;**85**:177–9.
- 6 Nunn T. Using unlicensed and off-label medicines. *Pharmacy Management* 2002;**18**(4):64–7.
- 7 Pandolfini C, Bonati M. A literature review on off-label drug use in children. *Eur J Pediatr* 2005;**164**:552–8.
- 8 Conroy S, Choonara I, Impicciatore P, *et al.* Survey of unlicensed and off label drug use in paediatric wards in European countries. *BMJ* 2000;**320**:79–82.
- 9 **Communication of the European Commission.** Amended proposal for a regulation on paediatric products for medicinal use and amending Regulation (EEC) 1768/92, Directive 2001/83/EC and Regulation (EC) No 726/2004. 577 final, 10.11. 2005.
- 10 Choonara I. Improving children's medicines. *Arch Dis Child* 2006;**91**:550–1.
- 11 **Commission of the European Communities.** Regulation (EC) No 1901/2006 on medicinal products for paediatric use and amending Regulation (EC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. *Official Journal of the European Communities* L378 27/12/, 2006:1–19.
- 12 **Committee on Human Medicinal Products.** CHMP reflection paper: formulation of choice for the paediatric population, EMEA/CHMP/PEG/194810/2005. London: European Medicines Agency, 2005.
- 13 Watson R. EU supports testing for children's drugs. *BMJ* 2005;**330**:1348.
- 14 **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. Available at <http://www.prescrire.org/docus/euMedPedEn.pdf> (accessed 20 March 2007) Brussels: MiEF, 2004.
- 15 **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.** ICH harmonised tripartite guideline: clinical investigation of medicinal products in the pediatric population E11. Available at <http://www.ich.org/LOB/media/MEDIA487.pdf> (accessed 20 March 2007).
- 16 Weschler J. FDA, Congress spur pediatric drug development. *Applied Clinical Trials*, 2002, July 1. Available via <http://www.actmagazine.com/appliedclinicaltrials> (accessed 20 March 2007).
- 17 Milne C-P. The paediatric studies incentive: equal medicines for all. White Paper of the Tufts Center for the Study of Drug Development (TCSDD). Boston, MA: Tufts University, 2001.
- 18 **Food and Drug Administration.** The pediatric exclusivity provision: January 2001 status report to Congress. Washington, DC: FDA, Department of Health and Human Services, 2001.
- 19 Roberts R, Rodriguez W, Murphy D, *et al.* Pediatric drug labelling – improving the safety and efficacy of pediatric therapies. *JAMA* 2003;**290**(7):905–11.
- 20 Davies A, Bateman M, Yates A, *et al.* Paediatric regulation in Europe and the US. *Regulatory Affairs Focus*, 2005;May, 118–21.
- 21 **Food and Drug Administration.** FDA joins children's health groups to mark historic milestone for pediatric drugs – 100 drug labels have new pediatric information since 1997. FDA Press Release, 19 December, 2005.
- 22 Charlish P. What's the verdict, so far? *Good Clinical Practice Journal* 2004;**11**(12):8–9.
- 23 **European Federation of Pharmaceutical Industries and Associations.** Industry leaders urge MEPs to keep paediatrics legislation effective and simple. EPFIA Press Release, 5 July. Brussels: EFPIA, 2005.
- 24 **RAND.** *Extended impact assessment of a draft regulation on medicinal products for paediatric use.* Leiden: RAND Europe, 2004.
- 25 **Association Internationale de la Mutualité.** *AIM opinion on the draft regulation on paediatric medicines*, 7 April 2005. Luxembourg: AIM, 2005.
- 26 **European Generic Medicines Association.** EU paediatric medicines proposal: EGA urges measures to maximise benefits to children. Press release, 29 September 2004. Brussels: EGA, 2004.
- 27 't Jong G, van den Anker J, Choonara I. FDAMA's written request list. *Lancet* 2001;**357**:398.
- 28 **Medicines and Healthcare Products Regulatory Agency.** Consultation of the European Commission's Proposal for a Regulation of the European Parliament and of the Council on Medicinal Products for Paediatric Use and Amending Council Regulation (EEC) Number 1768/92, Directive 2001/83/EC and Regulation (EC) 726/2004. 25 May 2005. Document reference MLX 323.
- 29 Balakrishnan K, Grieve J, Tordoff J, *et al.* Pediatric licensing status and the availability of suitable formulations for new medical entities approved in the United States between 1998 and 2002. *J Clin Pharmacol* 2006;**46**:1038–43.
- 30 **UK House of Lords.** *Paediatric medicines: proposed EU regulation – report with evidence*, European Union Committee Report (20th Report Session 2005–06). London: Stationery Office, 2006.
- 31 Harman R. Paediatric medicines – the new regulation: Daniel Brasseur interviewed by Robin Harman. *Regulatory Rapporteur* 2005;**2**(5):2–7.
- 32 O'Donnell P. Pediatrics and ethics predominating in 2005. Applied clinical trials 2005; May 1. Available via <http://www.actmagazine.com/appliedclinicaltrials> (accessed 20 March 2007).
- 33 Saint-Raymond A, Seigneuret N. Medicines for children: time for Europe to act. *Paediatr Perinat Drug Ther* 2005;**6**(3):142–6.
- 34 Ceci A, Felisi M, Catapano P, *et al.* Medicines for children licensed by the European Agency for the Evaluation of Medicinal Products. *Eur J Clin Pharmacol* 2002;**58**:495–500.
- 35 **European Parliament.** Report 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)). Strasbourg: European Parliament, 2005.
- 36 **Commission of the European Communities.** Regulation (EC) No 726/2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Directive 2004/27/EC amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. Directive 2004/28/EC amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products. Directive 2004/24/EC amending, as regards traditional herbal medicinal products. Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Official Journal of the European Communities* L31 30/04/, 2004:1–90.
- 37 **European Organisation for Rare Diseases.** *Medicines for children, better, more and faster*, EURORDIS position paper on the proposal for a regulation on medicinal products for paediatric use. Paris: EURORDIS, 2005.
- 38 Grieve J, Tordoff J, Reith D, *et al.* Effect of the pediatric exclusivity provision on children's access to medicines. *Br J Clin Pharmacol* 2005;**59**:730–5.
- 39 Marcovitch H. Safer prescribing for children. *BMJ* 2005;**331**:646–7.