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Children's medicines

"Bonne Année", "Gutes Neues Jahr"? Will 2007 be a "Happy New Year" for children's medicines in Europe?

T Stephenson

New European legislation has the potential to have an enormous impact on how paediatric medicines are studied and used

New European Union (EU) paediatric regulations to encourage more research on children's medicines became law on 26 January 2007.¹ The main proposals are as follows. First, there will be incentives to encourage the pharmaceutical industry to test products for use in children. Secondly, the European Agency for the Evaluation of Medicinal Products (EMA) will host an expert paediatric committee to oversee and assess paediatric investigation plans for developing medicines for children. Thirdly, a European clinical trials network will be set up to foster collaboration on paediatric studies throughout the EU. Fourthly, medicines licensed for paediatric use should be sold with a special label indicating that fact.

This legislation has the potential to have an enormous impact on how paediatric medicines, both old and new, are studied and used. Is this good news for Europe's 140 million children?

THE DRIVERS FOR THE NEW EUROPEAN LEGISLATION

Evidence-based prescribing for children is compromised by lack of sufficient data on many drugs.²⁻⁴ Although there is an elaborate system for testing drugs before they are used in adults, many drugs given to children have not been tested in this population at all, even though children can react differently to drugs.⁵ Moreover, it is often financially unrewarding to conduct research on medicines for children because the children's market is smaller than that of adults.

If evidence for the safety, efficacy and acceptable risk/benefit of a drug exists, then that drug can be licensed for use as a medicine with indications, doses and side-effect warnings. However, prescribing can also be unlicensed (eg, the

medicine is given as a liquid whereas the licence is for a tablet) or outside the terms of the licence (off-label; eg, a different dose for a different age group). Half of prescriptions for children and 90% of prescriptions for neonates are for drugs which have not been licensed for that use.⁶⁻⁸ Every day, paediatricians face the dilemma of whether it is more unethical to prescribe a drug that has not been tested or to deny treatment to a sick child.

Whether a medicine is beneficial and safe in children is best determined by studying it in children. Where the market is large (eg, antibiotics) or the price is high (eg, surfactant), companies do conduct well planned studies in children and secure licences, suggesting that the industry can overcome ethical problems⁹⁻¹⁰ and litigation risks if the price is right.¹¹ However, because of the cost of developing drugs¹² and the small market in children, recouping research costs before the patent expires is uncertain.

THE US EXPERIENCE

The "paediatric exclusivity" provision in the Food and Drug Administration Modernisation Act 1997 provided an incentive (6 months added to market exclusivity or patent protection on the active drug) for companies who performed clinical studies in children.¹³ The incentive was granted irrespective of whether the results demonstrated safety and efficacy in children or, equally importantly, suggested the drug should not be used in children.

As of 2004, the data generated had led to revised labelling (ie, new dose, route or indication) for 63 medicines and 661 studies had been requested. The incentives have therefore been successful in the US in stimulating paediatric studies and ensuring that more paediatric data are

available to prescribers, although not always for the most important medicines.¹⁴⁻¹⁵ The largest category considered for paediatric studies was cardiovascular drugs (n = 36), including 22 anti-hypertensives, suggesting choice was not due to paediatric need.¹⁵ The financial gains were higher for "blockbuster" drugs since the 6 months' extension of patent protection applied to all formulations of the drug type, whether appropriate for paediatric use or not. The current US regulations have a "sunset" clause in 2007 unless renewed by Congress.

The US measures brought little benefit to European children. International companies appear unwilling to voluntarily submit US data to support authorisation for children in the EU, presumably because of the lack of financial incentives in Europe. Progress in Europe appeared unlikely without legislation.

THE NEW EUROPEAN LEGISLATION

The key measures included in the new European paediatric regulations cover both older and newer medicines.

For newer medicines

All applications for a marketing authorisation for a new medicine, including orphan medicines, must contain the results of all studies and information required in a previously agreed paediatric investigation plan (PIP). The PIP will contain a full proposal of all the studies (and their timings) necessary to support the paediatric use of an individual product and will cover all paediatric age groups and all necessary age-appropriate formulations. This is the default position of the regulation.

There is a system of waivers for medicines unlikely to benefit children so that children are not studied unnecessarily. There is also a system of deferrals of the requirement to study the childhood population to ensure that medicines are tested in children only when it is safe to do so and to prevent the requirements delaying the authorisation of medicines for adults. In this case, the paediatric data will be provided after the initial marketing authorisation has been granted. But unless a deferral or a waiver has been granted, paediatric data must be provided in all applications for the authorisation of new medicinal products. This applies from 26 July 2008.

The requirement also applies to applications to add a new indication, new formulation or new route of

administration for medicines still covered by patent protection. In these cases, the requirement applies from 26 January 2009.

If a pharmaceutical company undertakes appropriate and ethical research on children during the development of a new drug as previously agreed in a PIP, the company can receive a 6-month extension to the duration of the supplementary protection certificate (6-month patent extension on the active moiety). Before research on children is undertaken, the research plan (the PIP) must be agreed in advance with a newly constituted Paediatric Committee of the EMEA. Scientific advice on the optimum way of conducting trials in children to minimise painful procedures and measure appropriate outcomes will be freely available with the help of the EMEA. The incentive of 6-month patent extension applies irrespective of whether or not the results demonstrate safety and efficacy of the drug in children provided that the product literature includes relevant trial information (positive or negative).

If the drug fulfils the criteria of an orphan medicine, an additional 2 years of market exclusivity will be added to the existing 10 years awarded under the EU orphan regulation.

For older medicines

For medicines which are already beyond the period of their patent, obviously a further 6 months' exclusivity cannot be granted. However, if a pharmaceutical company undertakes studies in children on an older unlicensed drug (or a licensed medicine without authorised paediatric indications or formulations) which provide new data on safety or efficacy and an age-appropriate formulation, a new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA), will become available. This allows 10 years of data protection for the paediatric use of that medicine. Therefore, whilst other companies can continue to manufacture and promote the drug for adults, they cannot do so for children since they cannot cite these new paediatric data in support of their product.

The legislation contains a plan for an EU paediatric study program funded from the European Community Framework Programme. Originally called Medicines Investigation for the Children of Europe (MICE) in the draft legislation, it is intended to fund research on off-patent medicines for children. For the first 2 years €30 million has been set aside for this purpose. This Community funding for the research and development of off-patent medicines will significantly benefit children.¹⁶

For old and new medicines

The regulation includes the establishment of

- measures to increase the pharmacovigilance (safety monitoring) of medicines for children,
- a requirement for industry to submit study reports they already hold on use of their medicines in children – these will be made public,
- an EU inventory of the therapeutic needs of children to focus research, development and authorisation of medicines,
- an EU network of investigators and trial centres to conduct research on medicines for children,
- a database of paediatric studies (protocols and results), accessible to the public.

UKCRN, MCRN and the new EU legislation

The United Kingdom Clinical Research Network (UKCRN) provides infrastructure and networks to enable clinical studies in targeted medical fields (eg, stroke medicine, diabetes, medicines for children). The key purpose of the UKCRN Medicines for Children Research Network (MCRN) is to facilitate the conduct of randomised trials and other well designed studies of medicines for children.¹⁷

A common misconception is that MCRN will fund drug trials in children. Investigators will still need to obtain funding from government, EU, charities or industry to undertake the research – the MCRN ensures the trials are undertaken to the highest standards and that adequate numbers of children are recruited on time.

Six local research networks throughout England and Wales will each receive approximately £0.5 million/year (Professor RL Smyth, personal communication) to provide research nurses and expertise to support multicentre studies. These six networks cover 6 million children. MCRN is timely since if the experience in Europe follows that in the United States, the pharmaceutical industry may be queuing up to undertake studies for the benefit of Europe's children.

CONCLUSION

As Baroness Howarth stated¹⁸:

Without the intervention of this directive [sic], children's medicines will be developed by market forces rather than any altruism or proper concern for our most precious asset: our

Summary of the new European regulation

For newer medicines

- a requirement at the time of licensing new medicines for data on the use of the medicine in children
- an incentive for compliance with this requirement in the form of 6-month patent extension on the active moiety

For older medicines

- a new Paediatric Use Marketing Authorisation which allows 10 years of data protection for medicines which are solely for paediatric use

For old and new medicines

- a requirement for industry to submit study reports they already hold on use of their medicines in children
- an EU network of investigators and trial centres to conduct research on medicines for children and a database of paediatric studies
- a system of free scientific advice for the industry, provided by the European Medicines Agency
- increased pharmacovigilance (safety monitoring) for medicines marketed for children

children. That is why the directive is vital.

The EU legislation is now a regulation and, unlike a directive, passes unamended into the laws of the member states.

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