

Pediatric Research

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Quintiles Assesses Regulations for Clinical Studies in Pediatric Patients in the European Union

EXECUTIVE SUMMARY

In 2006, the European Council (EC) and the European Parliament adopted a regulation that created major changes in the way clinical studies in pediatric patients would be planned and conducted in the European Union (EU). For many years, the clinical evaluations of drugs and biologics were conducted primarily in adults because it was simpler than conducting studies in children and because it raised fewer ethical concerns than studies in children. Nevertheless, the use of these products to treat children often followed their regulatory approval for use in adults, despite the lack of clinical trials in children. Physicians often used an empirically selected lower dose based on the weight of the child. In some cases, this could have resulted in exposure to unsafe or ineffective doses because children may metabolize a drug or biologic differently than do adults.

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In September 2004, based on the success of pediatric drug laws in the US, the EC adopted a proposal to develop regulations for pediatric investigations for Europe. The EC passed Pediatric Regulation (EC) No. 1901/2006 in 2006, later amended by Regulation (EC) No. 1902/2006, to require clinical studies for pediatric drug development in the EU. The regulation took effect on January 26, 2007.

Major Provisions of the European Pediatric Regulation

The European Pediatric Regulation and its amendment required that manufacturers submit a Paediatric Investigation Plan (PIP) for all new products and line extensions (new indication, new formulation, new dosage form, etc.) for existing products. The PIP had to outline studies to be performed or state the reasons why a waiver or deferral should be granted and “should be submitted early during product development, in time for studies to be conducted ... before marketing authorization applications are submitted.” However, it has been recommended that a PIP be submitted when pharmacokinetic studies have been completed, effectively at the end of Phase I studies in most cases.

The regulation also specified that PIPs must address all pediatric age groups, and Marketing Authorization Applications (MAA) must contain data for use of products in each of the different pediatric age groups unless waived or deferred. Pediatric age groups were defined in ICH Guidance E11 “Clinical Investigation of Medicinal Products in the Pediatric Population,” as:

- > *Preterm newborn infants*
- > *Term newborn infants (0 to 27 days)*
- > *Infants and toddlers (28 days to 23 months)*
- > *Children (2 to 11 years)*
- > *Adolescents (12 to 16-18 years, depending on the geographic region)*

If needed, a deferral or waiver should be requested as part of the PIP. The PIP must be approved by the Paediatric Committee (sometimes abbreviated as PDCO), and once it has been approved, it is binding on the manufacturer unless it is formally revised due to the availability of new information. Because the PIP is usually submitted very early in the course of clinical development of the product, amendments are often necessary. The Paediatric Committee also reviews all PIP amendments, and all of its decisions are posted on a public Web site.

Other Provisions of the European Pediatric Regulation

The regulation provided for waivers from the requirement for pediatric studies if the product is unlikely to benefit a pediatric age group. It provided for deferrals to delay pediatric studies until preliminary data on adults suggest it would be safe to proceed in children, until an age-appropriate formulation is available, or merely to avoid undue delay in making the product available for adult patients. The regulation established an expert Paediatric Committee within the European Medicines Agency (EMA, previously called EMEA) to review PIPs, waivers, and deferrals.

The regulation provided incentives for doing studies in pediatric patients, including a six-month extension of the supplementary protection certificate for products covered by such a certificate and approved under an MAA. In order to encourage pediatric studies for orphan indications, the regulation provided for a total of twelve years of marketing exclusivity for doing pediatric studies rather than the ten years provided in Europe for orphan indications in adults.

For products for use in adults that are already on the market and not covered by a patent or a supplementary protection certificate, the regulation created a mechanism (the Paediatric-Use Marketing Authorization, or PUMA). Under PUMA, pediatric labeling could be obtained based on pediatric studies in the literature or studies in dossiers of other approved products, as well as by new clinical studies. This was intended to provide an incentive for small and mid-size companies to develop products for use in children. The regulation permitted the use of the EU Centralized Procedure for MAAs with pediatric indications or for PUMAs, and provided 10 years of market protection as a reward for conducting clinical trials in pediatric patients for products approved under a PUMA.

The regulation established a system of optional free scientific advice from the EMA for studies in pediatric patients. It also created a public database for listing of pediatric studies.

The regulation established an expert Paediatric Committee within the European Medicines Agency (EMA, previously called EMEA) to review PIPs, waivers, and deferrals.

Comparison of Regulations for Studies in Pediatric Patients in the EU and the US

There are many similarities but also some significant differences between pediatric study requirements in the EU and the US, as shown in this table.

| EU Pediatric Drug Development | US Pediatric Drug Development |
|--|--|
| Covered under a regulation, (EC) No. 1901/2006 (amended by 1902/2006), covering all aspects of pediatric drug development. | Covered by two separate but complementary laws, Pediatric Research Equity Act (PREA) requiring pediatric studies, and Best Pharmaceuticals for Children Act (BPCA) providing for additional marketing exclusivity. |
| PIP recommended for submission before start of Phase II and must be approved before submission of MAA. It can be amended. | Pediatric development plan must be submitted with or before submission of the New Drug Application. |
| All PIPs are reviewed by PDCO. | All pediatric development plans are reviewed by the review division for the disease area being studied. All Pediatric Study Requests issued by FDA, as well as deferrals and waivers for pediatric studies, must be approved by an internal but central FDA Pediatric Committee. |
| Free scientific advice available for pediatric studies. | All scientific advice provided by FDA is free. |
| Provides 6 months additional marketing exclusivity for products for which pediatric information has been added to labeling based on studies. Two years of additional marketing exclusivity are provided for orphan products for pediatric patients (in addition to the 10 years for orphan products for adults). | Provides for 6 months additional marketing exclusivity if studies in pediatric patients are completed in accordance with a written Pediatric Study Request issued by FDA, but only as an extension of other granted exclusivity. |
| 10-year exclusivity available for off-patent drugs developed for pediatric patients; does not need to be an extension of other exclusivity. | No exclusivity available for developing off-patent drugs <i>per se</i> . |
| Research grants available for pediatric drug development. | Research grants available for pediatric drug development. |

REFERENCES

Regulation EC No 1901/2006 on Medicinal Products for Paediatric Use:

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

Amending Regulation EC No 1902/2006 on Medicinal Products for Paediatric Use:

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2006_1902/reg_2006_1902_en.pdf

Public Web site for posting of decisions on PIPs:

<http://www.ema.europa.eu/htms/human/paediatrics/decisions.htm>

ICH Guidance E11: "Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population" (CPMP/ICH/2711/99)

<http://www.ema.europa.eu/pdfs/human/ich/271199en.pdf>

ABOUT THE AUTHORS

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Dr. Raj Kishore has over 23 years of experience in regulatory affairs, including ten years at FDA and more than 11 years working for multinational pharmaceutical companies. Dr. Kishore worked as Assoc. Director of Regulatory-CMC at Otsuka Pharmaceuticals, Director of Regulatory-CMC at Shire Pharmaceuticals, Senior Director of Regulatory-Clinical at Shire Pharmaceuticals and Director of Regulatory Strategy at EMD Pharmaceuticals. He has served as the primary contact for these companies with the FDA for his projects and has led sponsor teams at FDA meetings. Dr. Kishore joined Quintiles in October 2007. Dr. Kishore's therapeutic areas of experience include oncology, neurology, and cardiovascular indications.

He received his PhD in Nuclear Chemistry from Clark University in Worcester, MA, and was a postdoctoral fellow at the University of California, Irvine, at Brookhaven National Laboratory, and at Harvard Medical School. He spent 12 years at the Albany VA Hospital as the director of their radioimmunoassay laboratory with the rank of Associate Professor at Albany Medical College and one sabbatical year as a visiting scientist at the University of Washington, Seattle, where he worked on radiolabeling of anti-cancer monoclonal antibodies. He then joined FDA as a reviewing chemist and became the Supervisory Chemist in the FDA Office of Generic Drugs.

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Dr. Edward Tabor is currently Vice President and Head of Global Regulatory Strategy at Quintiles. He joined Quintiles in July 2005. He had been Associate Director for Medical Affairs in the Office of Blood Research and Review at the U.S. Food and Drug Administration (FDA) from 1999 to June 2005, and a Division Director of two FDA divisions prior to that.

Dr. Tabor obtained his undergraduate degree from Harvard University, his M.D. from Columbia University, and did a residency in pediatrics at Columbia University (Columbia-Presbyterian Medical Center). At FDA, Dr. Tabor was a Division Director in both CBER and CDER, where he led the review and approval of numerous products, including the first treatment for human immunodeficiency virus (azidothymidine), as well as antibiotic, dermatologic, and ophthalmic drug products, and in vitro tests to detect viruses. He led the development of the antiviral regulatory policy and created an anti-viral review group that formed the basis of FDA's Division of Antiviral Drug Products. Dr. Tabor participated in the development of many FDA policies and policy documents. In addition, he managed an active laboratory-based research program. At the National Institutes of Health (NIH) he was Associate Director for Biological Carcinogenesis, National Cancer Institute, supervising six large intramural research laboratories.

Dr. Tabor is an internationally known expert on the hepatitis viruses and liver cancer. He is an author of more than 300 publications on viral hepatitis and other infections transmitted by blood transfusion, has written or edited six scientific books, and has seven U.S. patents (on behalf of the U.S. government). During his years at NIH and FDA, Dr. Tabor received 19 DHHS, FDA, and U.S. Public Health Service (USPHS) awards, including the USPHS Meritorious Service Medal and the USPHS Outstanding Service Medal.

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