EU Law Mandates Drug Testing in Children

By Gunjan Sinha

When it comes to access to the latest drugs, some scientists feel that sick children get a dodgy deal. Doctors have few safety or efficacy data to guide them; most drugs are never tested in children. To plug the data gap, the European Union has revamped its drug application process.

Starting in July 2008, any company that applies to the European Medicines Agency (EMEA) to market a new drug must include a pediatric investigation plan or obtain a waiver if a drug is not suitable for children. In return, the EMEA will extend patents on new drugs by 6 months.

The new regulation, called the Pediatric Rule, doesn’t stop there. It provides funding to study off-patent drugs in children and mandates that data from all trials conducted in children be publicly available.

The regulation is modeled on a law enacted in the U.S. in 2002 that rewards companies for studying their drugs in children in exchange for a patent extension. During the past 5 years, dozens of drugs in the U.S. have been relabeled to include information on prescribing to children. European physicians hope that the new EU legislation will be even more successful. Unlike the U.S. legislation, under which pediatric studies are voluntary, the EU legislation makes such studies mandatory—all new drugs fall under the law. “Generally speaking, the mandate is likely to work,” said Bruce Morland, M.D., consulting pediatric oncologist at Birmingham Children’s Hospital in England.

Pediatric oncologists are especially hopeful that the new law will provide children with the latest cancer drugs. Pediatric oncology is one area in which few drugs have gone through formal clinical trials in children. “Our handicap is that we have rare patients and rare tumors,” said Jochen Rössler, M.D., a consultant in pediatric oncology at the University of Freiburg in Germany. Consequently, industry has largely ignored the study of drugs to treat childhood cancers.

Academics have mostly picked up the slack. Today childhood cancers carry an average cure rate of 75%–80%. But cure rates for some rare cancers, such as advanced-stage neuroblastoma and sarcoma, remain low. Pediatricians would like to offer their patients newer, less toxic alternatives to standard chemotherapy and radiation. But these cancer therapies are rarely tested in children, even though preliminary data indicate that they may prove successful.

For example, Rössler has spent the past 10 years studying how pediatric tumor cells regulate angiogenesis. Childhood tumors are extremely vascularized, and many preclinical data indicate that angiogenesis inhibitors might be useful, he said. But there have been no formal clinical trials of angiogenesis inhibitors in children.

Under the Pediatric Rule, not only would any company applying to market a new angiogenesis inhibitor have to also test it in children, but the law also encourages companies to test angiogenesis inhibitors that are already on the market. European pediatric oncologists, in fact, are working with the drug company F. Hoffmann-La Roche AG to launch clinical trials of bevacizumab in children with metastatic sarcoma and relapsed brain tumors.

The lack of medicines that have been tested in children isn’t just a problem in cancer. Indeed, up to 75% of drugs taken by children have never been studied in their age group, according to the American Academy of Pediatrics. Children may therefore be overdosed, be underdosed, or receive treatment that is ineffective.

Medicines for Children in the U.S.

In the U.S., Congress responded to the situation by enacting the Best Pharmaceuticals for Children Act in 2002 and Pediatric Research Equity Act in 2003. The former grants companies a 6-month patent extension for studying an old or new drug in children; the latter authorizes the FDA to require pediatric studies on a new drug under certain circumstances and when the condition affects children.

Under the Best Pharmaceuticals for Children Act, pediatric studies are voluntary. Critics have argued that making them voluntary has enabled companies to selectively go after drugs that have large market share, just to get the extension, or drugs that are rarely prescribed to children, such as celecoxib—a nonsteroidal anti-inflammatory drug that brought in $278 million the first quarter that it hit the market.

But the FDA thinks long and hard about the public health benefit of a drug before granting a company a patent extension, according to Lisa Mathis, M.D., associate director in the office of new drugs for the pediatric and maternal health staff at the FDA. For celecoxib, “we looked at it for juvenile rheumatoid arthritis, and our position was that it was going to provide significant benefit in the pediatric population with rheumatoid arthritis.”
Moreover, blockbuster drugs made up a small percentage of drugs that were granted patent extensions under the law, she added. In the years since Congress enacted the Best Pharmaceuticals for Children Act, more than 132 medications have been studied and 115 drug labels have been changed to include prescribing information for children.

Nevertheless, to address the issue of companies’ sidestepping pediatric studies, Congress later enacted the Pediatric Research Equity Act, which gives the FDA more authority over the types of drugs that are developed for children. Under the law, the FDA can require companies to conduct pediatric studies when the agency declares that the drug might benefit sick children. The law also allows the FDA to require studies when a new-drug application is for a new indication, a new active ingredient in an already marketed drug, a new drug dosage, or a new delivery route.

Moreover, under both acts, there is continual dialogue between companies and the FDA regarding pediatric studies, Mathis said. The FDA issues written requests for pediatric studies that specify the types of data and other parameters required to ensure that each drug is well studied. If a company does not adhere to the written request, the FDA can deny their patent extension or their drug application, Mathis said. Companies can, however, apply for deferrals or waivers.

In September 2007, Congress amended and renewed both acts. One amendment, for example, requires the FDA to set up an internal review committee that evaluates all drugs that apply to pediatrics. Another requires the agency to make more data from pediatric submissions publicly available on the agency’s Web site—for example, the FDA’s written requests and reviews of the data would be available; previously, only data summaries were released.

Setting up a review committee is “a huge step in the right direction,” commented Rich Gorman, M.D., chair of the American Academy of Pediatrics section on clinical pharmacology and therapeutics. The new committee will look at all agents for possible pediatric applications and will review all pediatric studies for adequacy. “That will speed up the process and make it better.”

But the amended rules don’t go far enough, Gorman said. For one, generic drugs get short shift. Under the Best Pharmaceuticals for Children Act, the FDA can ask companies to conduct pediatric studies on off-patent drugs. If a company refuses, the FDA can send a research request to a division of the National Institutes of Health to conduct the appropriate research. To date, there have been 40 drugs placed on the off-patent priority list for pediatric studies, but only seven have been studied. None have yet been relabeled for pediatric use.

The main problem is that Congress has not appropriated NIH any funding to carry out more research. “They have done an amazing job with no budget,” Gorman said. But he said that work has been done slowly, and providing funds would speed up the research.

**How Does Europe Compare?**

The EU legislation gives the EMEA a heavier hand and enables the agency to be transparent. Not only are pediatric studies on all drugs mandated, but the EMEA plans to make available all clinical trial results from studies in children—positive, negative, or terminated—in a database that will be available to the public. There is no equivalent database in the U.S. The EMEA also has a final say on pediatric drug labeling, whereas the FDA negotiates drug labels with companies, although an amendment now allows the FDA’s advisory committee to require language on a label and to publicly discuss the issue.

Also, the European Commission has made available €30 million ($45 million) for research on off-patent drugs in children—a small sum but better than nothing, researchers said.

Despite the EU’s seemingly comprehensive approach, there is a potential loophole. “We have to be careful about the issue of waivers,” Morland added. A company might be developing a drug for breast cancer, for example, and apply for a waiver by arguing that breast cancer doesn’t occur in children. However, a drug that targets a known breast cancer protein might also work on some pediatric cancers. Consequently, waivers need to be directed toward protein targets and not diseases, Morland said. The EMEA is aware of the issue, but only time will tell if waivers really become a problem.

Europe has also started up a new clinical trial committee of the Innovative Therapies for Children with Cancer Consortium, a group founded in 2004 with funding from several EU countries. ITCC brings together pediatric oncologists in six EU countries. Morland cochairs the committee.

With the new regulation in place, the consortium hopes that more companies will come to them to conduct cancer clinical trials in children. And while it’s too early to tell how effective the new mandatory law will be, Morland cautioned, “the number of pharmaceutical companies approaching [Innovative Therapies for Children with Cancer] about testing cancer drugs in children has already increased.”

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