

# Paediatric Labelling: A Different Point of View

**Peter R Joiner of Madeira Therapeutics discusses the difficulties in overcoming the various challenges facing paediatric drug labelling**

Despite legislative attempts to provide increased incentives, there are still several challenges that paediatric drug developers need to overcome. Today, only about a quarter of all prescription medicine contains labelling information for children, and more than two-thirds of medicine that is prescribed to children has not been studied and labelled for paediatric use.

While it's true that in almost all cases, developing paediatric medicine is more complicated and less remunerative than adult formulations, legislation is now in place that requires the development of an 'age-appropriate formulation' if the medicine under development is suitable for children.

The barriers to paediatric drug development include the logistical complexity of paediatric clinical trials; medicine dosage for a wide range of ages, weights and endocrine (puberty) statuses; and the palatability of the finished product to ensure compliance throughout the course of treatment. However, experience developing products for the paediatric market proves that while these considerations are challenging, they are far from insurmountable.

To improve the percentage of medicines labelled for paediatric use, I believe three mechanisms should be explored:

- ◆ A publicity programme to raise awareness of the paediatric off-labelling issue to physicians and the general public
- ◆ An international registry for the collection and dissemination of baseline data on morbidities, treatments and other paediatric research parameters
- ◆ A method to vastly expand the pool of available candidates for paediatric clinical trials

The future of paediatric drug development is impossible to predict, but we can envision a future in which children are safer, and manufacturers have the tools to make paediatric drug research more effective and efficient.

## THE LEGISLATIVE HISTORY

In recognition of the need for paediatric labelling instructions in the US, Congress included incentives for conducting

paediatric studies in the FDA Modernization Act of 1997 (FDAMA). When this failed to have a significant impact, Congress passed the Best Pharmaceuticals for Children Act (BPCA) in January 2002, which provided innovators with a six-month extension of exclusivity if prescribed studies were performed. Later, in 2003, Congress passed the Paediatric Research Equity Act (PREA), which allowed the use of bridging data from adult studies for the approval of paediatric medicines. In September 2007, the Food and Drug Administration Amendments Act (FDAAA) reauthorised both the BPCA and the PREA until 2012.

In pharmaceuticals, as in any industry, product development is driven by economics. The reality is that in evaluating the profit potential of the paediatric population, pharmaceutical companies take into account the facts that children grow up, their metabolism rates change as they grow, and that before long, they will outgrow the medicine. Thus, it is unlikely there will ever be a blockbuster drug in this category – and that is what large pharmaceutical companies are looking for.

However, for a smaller pharmaceutical company, it can become a niche area and provide an economic incentive for servicing this specialised market.

## THE ETHICS OF OFF-LABEL PRESCRIBING

With so few paediatric medications containing adequate labelling information to guide their use, off-label use of medicines has become, unfortunately, an accepted part of paediatric medical practice. Off-label prescribing includes the use of medicine for unapproved indications or with a different age group, dosage, frequency or route of administration. It also includes the administration of extemporaneous formulations (such as oral suspensions made from adult tablets) with untested bioavailability and stability.



When paediatricians prescribe an adult medication to a child by, in effect, guessing at the appropriate dosage and method of administration, are they doing the right thing? On the one hand, they are offering a treatment or analgesic to a patient who may have no other option. On the other, they may be subjecting their patient to a significant risk based on inappropriate dosing or inadequate consideration of the differences in childhood metabolism and therefore the pharmacokinetics of the medication.

Penicillamine is a good example of a less-than-optimum formulation being prescribed off-label for paediatric use. Penicillamine tablets are large and must be crushed to administer them to children, leading to uncertainty of the actual dose delivered. Dosing of penicillamine is also required for extended periods of time, and the crushed tablet is foul smelling with an unpalatable taste.

Children deserve palatable, tested drugs, just like adults, and they also deserve to benefit from scientific and pharmaceutical progress. However, because issues of growth and development must be taken into account, because the trials are more complex, because of informed consent in working with minors and because the overall market is smaller, paediatric drug development has been delayed.

### THE POWER OF PUBLIC OPINION

Given a choice, the vast majority of paediatricians would prefer to stop prescribing off-label – it puts both them and their patients at unnecessary risk for uncertain benefit. If consumers, especially parents, were more aware of the problems associated with off-label prescribing for children, it is a virtual certainty that concerns would be voiced.

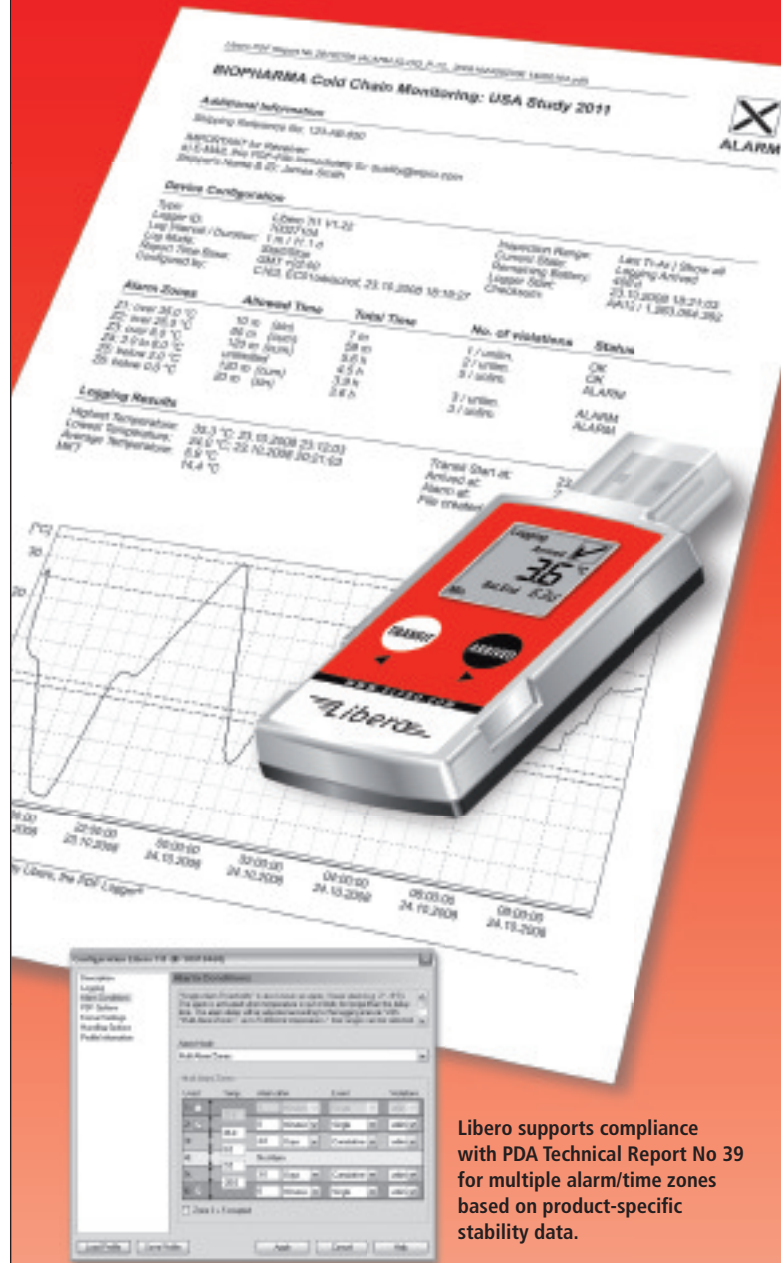
A concerted, nationwide effort to inform the public – especially parents and physicians – about the dangers of off-label prescribing could be an effective way to bring about change. Utilising a public relations and advertising programme or a consumer advocate campaign could make parents more aware of the medicines being prescribed off-label for their children – for example, imagine what a segment on a morning TV show might do.

If parents voice their concerns to doctors and doctors voice their concerns to drug representatives, it could create a stronger market demand for paediatric pharmaceuticals and a positive incentive for manufacturers to respond to that demand.

Raising awareness to harness public opinion can be a powerful tool in the effort to improve paediatric drug development, but it cannot stand alone.

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## THE VALUE OF A CONSORTIUM

Improving labelling for children's medicines is just a single aspect of improving paediatric care, and fortunately, there are many in our industry who are deeply concerned with this patient group.

One such organisation is the Institute for Paediatric Innovation, a consortium of some of the most innovative and well respected children's hospitals in the US, including Children's Mercy Hospital, Missouri; Children's Hospital, Colorado; Phoenix Children's Hospital, Arizona; Children's Hospital of Wisconsin, Wisconsin; Lucille Packard Children's Hospital, California; and the Rainbow Babies and Children's Hospital, Ohio. The group seeks to improve paediatric care by stimulating the development of medical products and medications designed specifically for babies and children.

Building on the concept of such a consortium, entities from all parts of the research spectrum – pharmaceutical manufacturers, biotech companies, academia and CROs – could combine their efforts to accomplish together what none are able to do alone.

Owing to the history and nature of paediatric drug development so far, nowhere near the amount of baseline medical information exists for children as it does for adults. Using a consortium as a nexus for the activity, an online clearinghouse to capture demographics, medical histories, morbidities, range and efficacy of treatments and baseline data on healthy individuals could be established. This information could be made available for free or via subscription to entities seeking data to support

Investigational New Drug and other regulatory applications involving paediatric formulations.

## THE CLINICAL TRIALS CANDIDATE SHORTAGE

Paediatric clinical trials are typically more complicated and expensive than adult trials, often involving different endpoints and requiring a greater number of participants. Additionally, clinical trials involving children mean recruiters must essentially recruit two people – a child and parent – for each available slot.

Any clinical trial is facilitated by the existence of a database of willing participants, especially one that has been pre-screened and medically qualified. One can only imagine the immense benefit of a nationwide pool comprising hundreds of thousands of searchable candidates for paediatric trials.

Developing and maintaining such a database is well beyond the resources of most single entities. In addition to rigorous promotion to raise awareness about the need in order to convince parents and children to participate, the programme would likely require additional incentives, both for registration and for participation in a trial. However, because the benefits of such a large paediatric database could be widespread and significant, a consortium of industry, government and academia to undertake such a project seems very feasible.

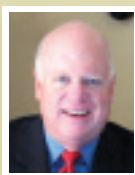
## A FUTURE TO WORK TOWARD

The FDA and the National Institutes of Health (NIH) have a list of about 400 compounds for which they would like to have paediatric labelling information. Congress and the FDA have enacted legislation over many years, but few pharmaceutical companies have chosen to enter this marketplace.

By building market demand for compliance with paediatric labelling requirements while simultaneously providing research tools to streamline the development process, a wide variety of appropriately labelled paediatric medicines could be made available.

Although developing medicine for children is more complex, this does not remove the moral obligation for drug development companies and doctors to provide medications that are safe and effective, even for their smallest patients.

### About the author



**Peter R Joiner** is President and CEO of Madeira Therapeutics. Peter has 30 years of experience in sales, sales management and marketing for pharmaceutical companies. These have included executive-level sales force management, pharmaceutical company strategic business planning/analysis and large customer account management. He has launched over 15 major pharmaceutical products and established significant partnerships and relationships with key organisations in the healthcare industry.

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