Tripartite meeting. Paediatric regulatory guidelines: do they help in optimizing dose selection for children?

N. S. Baber

MHRA, Market Towers, 1 Nine Elms Road, Vauxhall SW8 5NQ

Correspondence

N.S. Baber, MHRA, Market Towers, 1
Nine Elms Road, Vauxhall SW8 5NQ
E-mail: Nigel.Baber@mhra.gsi.gov.uk

Introduction

Establishing a safe and effective dose or dose range for a given medicinal product is difficult. It is at the centre of clinical development programmes leading to marketing authorization (licensing). Pharmaceutical companies are, naturally, keen to define a limited range of doses that will be taken forward into full-scale development and manufacture; it is unrealistic to expect an unlimited number of strengths and formulations produced to the standards of Good Clinical and Laboratory practice to be made available.

The variables that affect dose–response in a given disease state are legion. They are frequently, if simplistically, placed into extrinsic and intrinsic categories but more usefully considered under headings of genetic control or influenced by environmental and behavioural factors. Knowledge of these variables is fragmentary at the time of marketing application, and drug hunters, be they from academia or industry, must discern between two extremes of drug profiles in clinical practice – ‘one size fits all’ or the ‘right drug for the right patient, at the right dose’. In general, the promise of pharmacogenetics to ‘individualize’ or ‘personalize’ medicines has not, so far, been fulfilled [1]. Yet the achievements in discovering new medicines and the advances in clinical trial methodology to examine critically their clinical usefulness are remarkable. Unsurprisingly, the practical applications of these advances are predominantly in

evaluation of adult medicines, and, with the exceptions of some diseases specific to children, such as acute lymphoblastic leukaemia, the study of dose–response and end point definition in paediatric populations has been neglected. There are many reasons for this, which have been well rehearsed [2].

Four major difficulties stand out which make the study of medicines in children more challenging than in adults. First, the comparative rarity of many diseases in children, leading to recruitment difficulties for pivotal trials. Second, the inhomogeneity of children defined in this convenient collective term. Third, real (or perceived) ethical problems in conducting placebo-controlled, or even positive-controlled trials in children. Finally, problems of definition of end points for establishing efficacy and safety. All of these and others are discussed in subsequent papers.

Guidelines

The primary guidelines for paediatric drug development, including advice on dose definition, are:

(a) In Europe.

- Clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99).
- Clinical investigation of medicinal products in children (CPMP/EWP/462/95).
- Note for guidance on evaluation of anti-cancer

medicinal products in man: Addendum on Paediatric Oncology (EMA/CPMP/EWP/569/02) – operational date January 2004.

(b) In the USA.

- ICH guidelines, especially Clinical Investigation of Medicinal Products in the Paediatric Population.
- General Considerations for Paediatric Pharmacokinetic Studies for Drugs and Biological Products Draft Guidance, November 1998.
- Guidelines for the Clinical Evaluation of Psycho-Active Drugs in Infants and Children (July 1979).
- Non-clinical Safety Evaluation of Paediatric Drug Products (February 2003).
- General Considerations for the Clinical Evaluation of Drugs in Infants and Children (September 1977).

Supportive guidelines in Europe include:

- Pharmacokinetic studies in man.
- Dose–response studies to support drug registration (ICH E4).
- Investigation of drug interactions.
- Good clinical practice (ICH topic E6).
- General consideration for clinical trials (ICH topic E8).

There are disease-specific guidelines that also make reference to children, for example in Europe, where extrapolation from pharmacokinetic data in adults to children may support dose definition:

- On HIV (CPMP/EWP/633/02).
- On nociceptive pain (CPMP/EWP/612/00).
- On allergic rhino-conjunctivitis (CPMP/EWP/2455/02).
- On antibacterial products (CPMP/EWP/2655/99).

All of these guidelines are available on the EMA and FDA websites (<http://www.ema.eu.int> and <http://www.fda.gov>, respectively).

How useful are these guidelines in giving advice to companies for defining paediatric doses during phase I–III clinical trial development? First, there are some helpful general statements. There is recognition that it is unrealistic to expect applicants to ‘fully demonstrate’ efficacy and safety in children in clinical studies. Whilst this is not expanded upon, it does give some leeway to the impossible task a company would face in having to pin down a dose for every age band, and for a totally comprehensive safety package (if that should ever be possible) at the time of marketing authorization. The need to develop paediatric-specific end points and the valuable, if artificial, chronological banding now adopted by regulatory authorities are recognized.

However, it is in the sections on pharmacokinetics and dynamics that the guidelines are most helpful.

Statements from relevant guidelines

Where the disease process is similar in adults and children, where the achievement of plasma concentration, AUC and C_{max} is similar to that in an adult population, and where the drug is effective in all age ranges likely to receive the drug, this may be considered sufficient evidence provided dose selection will produce similar blood levels to that in adults.

Extrapolation of efficacy from older to younger children may be possible where the disease process is similar and the outcome of therapy is likely to be comparable.

A PK-only approach is unlikely to be sufficient where plasma concentration and effect do not correspond, or concentration–response relationships are different between adults and children.

Where comparability of disease course or outcome of therapy in children and adults is similar, but there is no clinical effect, then plasma concentration relation, measurement of pharmacodynamic effect related to clinical effectiveness and confirmation of concentration needed to obtain that pharmacodynamic effect, may suffice. Thus a PK/PD approach combined with safety and other relevant studies could avoid the need for clinical efficacy studies.

Where a pharmacokinetic approach is not applicable, e.g. topical products, extrapolation of efficacy from one population to another may be based on pharmacodynamic end points and/or alternative assessments.

Behind these statements is the recognition that large, phase III, randomized controlled trials, with long-term safety follow-up, in all relevant age ranges, is just not feasible. A key word in these guidelines is ‘similar’. The variability around the plasma concentration, which has been shown to be associated with a satisfactory therapeutic ratio in adults, or the variability of a dynamic response will be the point of discussion in a marketing application that takes this route. The other key phrase is that a PK/PD approach combined with safety studies could avoid the need for clinical studies. Thus, the linking of plasma concentration (or other relevant kinetic variable) to dynamic (surrogate) response related to clinical effectiveness in adults, could lead to a waiver of, or modification to, phase III pivotal trial programmes.

The guideline is firm that where novel paediatric indications are sought, or disease outcomes for children and adults are different, then clinical efficacy trials will be needed.

Further kinetic advice is given elsewhere in the guidelines; for example, to support formulation development and to advise that steady-state studies may be needed where kinetics are nonlinear in adults, or the duration of effect is different between single and repeated dosing.

The 1999 CPMP/ICH guideline also recognizes that most dosing in children in early development is done on a mg kg⁻¹ basis, and that difficulties in conducting PK (or PK/PD) studies in cohorts of patients may be overcome by use of population pharmacokinetics and sparse sampling approaches.

Four questions arise from a consideration of guidelines referring to dose definition in clinical trials:

- Are the current guidelines sufficiently comprehensive to cover all contingencies?
- Do they embrace recent advances in PK/PD modelling and biosimulations?
- Is there sufficient guidance on trial design and sample size?
- To what extent should dose-defining guidelines be disease specific?

It must be remembered that a guideline is just that. It is not a directive, implying 'follow this and success in your application is assured', nor does it imply 'if you do not follow this you will fail'. So guidelines must run the gauntlet between being too general to be useful and too specific to be exclusive.

A further consideration is that new European guidelines are under development. Two are relevant: 'Points to consider' on the evaluation of pharmacokinetics of medicinal products in paediatric populations, and a concept paper on 'guidance on formulations of choice for paediatric populations'.

It is hoped that with contributions from academics, industry and regulators, the first can include advice

embracing biosimulation and virtual modelling techniques which are now being used by industry and, we understand, considered by the FDA (see contribution by Dr T. Johnston).

Two other points should also be made. The European Commission is finalizing its document on a paediatric strategy. This will include the requirement for companies to submit a Paediatric Investigation Plan with any marketing authorization unless there is a specific waiver, or no paediatric indication possible. This should increase the use of current guidelines and may trigger the development of new ones. Second, companies planning for paediatric indications or variations to their licence can seek scientific advice from the EMEA or a national authority. This would argue against guidelines being too specific or restrictive, as novel drugs or indications can be readily encompassed within existing regulations.

In summary, the paediatric guidelines and other guidelines on drug development and clinical trials are adequate to cover modern and traditional approaches to drug development. New guidelines under evaluation can be modified as required. The wider challenge is for companies, academics and regulators to work together on trial designs, surrogate endpoints and dose-defining approaches that will at least determine a limited range of doses to be tested in formal phase III trials or, in selected instances, replace the need for conducting them.

References

- 1 Tucker G. Pharmacogenetics – expectations and reality. *BMJ* 2004; 329: 4–6.
- 2 Baber N, Pritchard D. Dose estimation in children. *Br J Clin Pharmacol* 2003; 56: 489–93.