DECISION

No. 6/29.02.2008

on approval of the Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population

The Scientific Council of the National Medicines Agency,
set up based on Order of the Minister of Health No. 485/09.05.2005, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 29.02.2008 in accordance with Article 10 of Government Ordinance No. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002, with further changes and completions, agrees on the following

DECISION

Single article. – The Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population is approved, according to the Annex which is integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE
on the role of pharmacokinetics in the development of medicinal products in the paediatric population

CHAPTER I
Introduction

Art. 1. - (1) This Guideline is a translation and adaptation of the European Guideline EMEA/CHMP/EWP/147013/2004/Corr.

(2) This guideline provides advice on the use of pharmacokinetic studies in paediatric drug development and on methodological issues concerning pharmacokinetic studies in paediatric patients.

Art. 2. - (1) An application for paediatric use of a medicinal product should include sufficient information to establish efficacy and safety.

(2) Paediatric patients have the same right to well investigated therapies as adults.

(3) There are, however, several reasons why it is more difficult to study a medicinal product in paediatric patients, particularly in very young patients.

(4) Hence, it is often unrealistic to expect the applicant to fully demonstrate efficacy and safety in paediatric patients in clinical studies.

(5) In such a situation pharmacokinetic data may be used to extrapolate efficacy and/or safety from data obtained in adults or in paediatric age groups other than the age groups applied for.

Art. 3. - (1) Special consideration is often necessary when performing pharmacokinetic studies in paediatric patients and it is important that the pharmacokinetic information available is presented and used in an optimal manner.

(2) A specific feature of very young paediatric patients is rapid maturation of organ functions important for drug absorption, distribution, and elimination of the medicinal product.

(3) Therefore changes in dose may be necessary for a patient over time, based on individual maturation.

Art. 4. - (1) It should be recognised that documenting a medicinal product for paediatric use involves a multitude of choices and that, at present, knowledge and experience in this field is limited.

(2) Sponsors are encouraged to explore new approaches in the development of medicinal products for the paediatric population.

Art. 5. - It is the objective of this Guideline to provide recommendations in the following areas:

a) use of pharmacokinetics and pharmacokinetic/pharmacodynamic relationships (PK/PD) in efficacy and safety assessments;

b) study design: stratification by age, specific age-related considerations, control groups;

c) data analysis, presentation and evaluation of the results;

d) description of the results in the Summary of Product Characteristics (SPC).

CHAPTER II
Scope

Art. 6. - This Guideline should be read in conjunction with Directive 2001/83/EC, as amended, and all other pertinent elements outlined in current and future EU and International Conference of Harmonisation (ICH) guidelines and regulations especially those on:

a) Clinical Investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99)

b) Pharmacokinetic Studies in Man (Notice to Applicant, Vol 3C, C3a, 1987)

c) Investigation of Chiral Active Substances (Notice to Applicant, Vol 3C, C29a, 1993)

d) The Investigation of Drug Interactions (CPMP/EWP/560/95)

e) Modified Release Oral and Transdermal Dosage Forms: Section II (Pharmacokinetic and Clinical Evaluation) (CPMP/EWP/96)

f) The Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98)

g) Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function CPMP/EWP/225/02

h) Validation of Analytical Procedures (ICH topic Q2A and Q2B)

i) Structure and Content of Clinical Study Reports (ICH topic E3)

j) Good Clinical Practice (ICH topic E6)

k) General Considerations for Clinical Trials (ICH topic E8)

Art. 7. - This Guideline is intended to assist applicants during development of medicinal products for paediatric patients.

CHAPTER III
Legal basis

Art. 8. - (1) This guideline applies to all new Marketing Authorisation Applications for human medicinal products submitted in accordance with Art. 702(4) of Law No. 95/2006 as amended.

(2) This guideline has to be read in conjunction with the Introduction and general principles paragraph (6) and Part I, Module 5 of the Annex to Minister of Public Health Order No. 906/2006 on approval of analytic, pharmacotoxicological and clinical norms and protocols concerning the testing of medicinal products.

CHAPTER IV
Main Guideline text

IV.1.Use of pharmacokinetics in paediatric drug development

Art. 9. - (1) Pharmacokinetic information may be used to extrapolate clinical efficacy and safety from adult to paediatric patients as well as between paediatric patients of different ages.

(2) Different approaches may be taken and the applicant should justify the choice of a certain strategy.

Art. 10. - (1) The relevance of efficacy data obtained in adults for the paediatric population for systemically acting drugs depends on a number of factors such as the aetiology and course of the disease, as well as the mechanism of action of the medicinal product in adult and paediatric patients.

(2) Provided that data from adults are considered relevant, pharmacokinetic information can be used to extrapolate efficacy to the paediatric population.

(3) If similar exposure in adult and paediatric patients can be assumed to produce similar efficacy, pharmacokinetic data alone can be used to extrapolate efficacy.

(4) If a similar relationship between concentration and clinical efficacy cannot be assumed, paediatric PK/PD (biomarker) data can be used to extrapolate efficacy. In this case, the predictability of the biomarker should have been documented. If this has been performed in adults only, its value for the paediatric population should be adequately justified.

(5) Evaluation of the PK-PD relationship in dose-ranging studies or multiple dose level studies is encouraged, as such information may be very valuable for dose-selection.

(6) The same approaches may be used when extrapolating efficacy between paediatric age groups.

Art. 11. – Further information on how pharmacokinetics can be used for efficacy extrapolations is available in several of the separate EWP guidance documents for specific indications.

Art. 12. - (1) The paediatric development program is often restricted in terms of the number of patients included.

(2) Therefore, the safety assessment for systemically as well as locally acting medicinal products often has to be extrapolated from data obtained in adults or from a different target group within the paediatric population.

(3) However, the underlying assumption, that the exposure-adverse event relationship is similar in adults and paediatric patients, should be recognised.

(4) The possibility of a marked difference in incidence of side effects should be discussed, taking into account the preclinical and clinical pharmacology of the drug and, if possible, known effects of substances with a similar pharmacological profile.

Art. 13. - (1) Even if clinical efficacy and safety have been sufficiently documented for the paediatric population as a group, the clinical studies may not have sufficient power to detect differences in efficacy and safety in sub-groups within the studied age interval.

(2) Pharmacokinetic data will then be important for identification of sub-groups in which the exposure differs from the overall study population to a clinically relevant extent.

Art. 14. – Pharmacokinetic information from one indication can be extrapolated to another indication if it can be assumed that the diseases and commonly used concomitant medications are not affecting the pharmacokinetics of the medicinal product.

Art. 15. - (1) In addition, recognising the methodological and ethical difficulties with pharmacokinetic studies in the paediatric population, it may be possible to obtain such knowledge from other medicinal products.

(2) For example, information on the pharmacokinetics in various age groups for a medicinal product excreted solely through renal filtration may partly or entirely be based on drugs with similar pharmacokinetic and chemical characteristics.

Art. 16. - (1) Bioequivalence studies for bridging paediatric clinical documentation between two formulations should preferably be performed in adults, but the applicant should justify that the study results can be extrapolated to the paediatric population.

(2) If there are reasons to believe that the absorption from a formulation may be significantly different in certain paediatric age-groups, supportive data in the paediatric population may be needed.

Art. 17. - The exposure of active substances in paediatric patients should be discussed in comparison with exposures in non-clinical studies, including juvenile toxicity studies if available.

IV.2. Study design

Art. 18. - The design of pharmacokinetic and PK/PD studies in paediatric patients should be based on a number of factors including the known pharmacokinetic characteristics (dose- and time-dependency of pharmacokinetics, route of elimination, presence of active metabolites, protein binding, etc), route of administration, therapeutic index, paediatric group investigated, possibility to collect blood samples, sensitivity of the analytical method, method for the pharmacokinetic data analysis, desired use of the pharmacokinetic data, etc.

Hereafter some particular aspects of study design and methodology in paediatric pharmacokinetic and PK/PD studies will be discussed.

Art. 19. – (1) Information from other sources, on organ maturation and/or on paediatric pharmacokinetics of medicinal products with similar pharmacokinetic properties (hepatic extraction ratio, enzymes involved in main metabolic pathway(s), mode and extent of renal excretion, etc), can be used when designing the study.

(2) Two alternative approaches can be taken:

a) The first approach focuses on inclusion of paediatric patients in the age of particular importance. Depending on the therapeutic index of the medicinal product and available data from additional sources, the study may focus on age interval(s) where the most noticeable difference in exposure compared to the reference population is expected. It may be possible to exclude (or minimise the number of) patients in certain age intervals, where a reliable prediction of the pharmacokinetics can be made.

b) In the second approach, which is the most common, the pharmacokinetic data should cover and be evenly distributed over the whole target age range intended for treatment. If feasible, effort should be made to balance the study population for factors predicted to affect the pharmacokinetics of the specific medicinal product e.g. age/weight, renal or hepatic function or disease state, etc. The number of individual patients should be sufficient to give an appropriate estimate of the inter-individual variability in each sub group.

Art. 20. - (1) For ethical reasons, paediatric pharmacokinetic studies are often performed in patients who may potentially benefit from the treatment.

(2) The design of pharmacokinetic studies performed should reflect the information needed for an adequate assessment of efficacy and/or safety.

Art. 21. - (1) If there are pharmacologically active metabolites significantly contributing to the efficacy or safety, the pharmacokinetics of such metabolites should be studied, unless it may be assumed that the exposure ratio of metabolite to parent medicinal product is similar to the ratio in the "reference age group".

(2) Blood sampling may be difficult and the number of samples is usually limited, especially in younger age groups.

(3) Effort should be put into optimising study design and use of the available data as well as further developing the analytical methods to allow for small sample volumes to be used.

(4) If a medicinal product is not metabolised and elimination is predominantly renal, or if the medicinal product is partly eliminated through renal excretion in a dose-linear fashion, data on urinary excretion may be used to describe elimination capacity.

IV.2.1. Age classification

Art. 22. - (1) The following age classification is suggested in the ICH and CPMP guidelines: preterm newborn infants, term newborn infants (0 – 27 days), infants and toddlers (28 days – 23 month), children (2 – 11 years) and adolescents (12 to 17 years).

(2) Some specifically important issues related to pharmacokinetic studies in each of these age groups are described in this Guideline.

(3) It should be noted that this classification is used to discuss characteristics of the paediatric population in different developmental stages.

(4) Some age classes are wide and include a large range of maturation levels.

(5) The identification of which age range to study should be medicinal product-specific and justified.

(6) The assessment of efficacy and safety should not be based on the specific age classes *per se*, but on the available documentation within each studied age range.

(7) In addition to age, the classification of the population may be based on other variables such as gestational age, renal function, metabolic function etc.

IV.2.2. Specific considerations for preterm and term newborn infants, infants and toddlers

Art. 23. - (1) These groups present the largest pharmacokinetic challenges.

(2) Rapid developmental changes in absorption, distribution, metabolism and excretion, combined with all possible disease processes that might interfere with the developmental changes, necessitate a study design that is tailored to these populations.

(3) It is important to consider that there may be large pharmacokinetic and pharmacodynamic differences among preterm infants and within infants over time, depending on their gestational or postconceptional age (gestational age + postnatal age).

(4) It is highly recommended that effort is put into finding markers correlated to maturation-related changes in pharmacokinetics, making individualisation of the dose possible between individuals, as well as within an individual over time.

(5) Therefore, it is advisable to include factors such as gestational age, postnatal age, birth and body weight, renal function, S-albumin, concomitant medication, other diseases, etc, in pharmacokinetic studies within the paediatric population.

(6) The possibility of therapeutic monitoring of the medicinal product should be considered.

(7) Determining the protein binding of highly bound medicinal products and active metabolites should be considered when studying newborns.

IV.2.3. Specific considerations in children

Art. 24. - (1) This group consists of children aged 2-11 years.

(2) The pharmacokinetics in children aged 2-4 years is probably the least predictable within this group.

(3) With increasing knowledge about liver maturation at the enzyme level, further extrapolations might be possible based on the relationship between liver and body weight, especially in the older children.

(4) The onset of puberty differs markedly between individual children.

IV.2.4. Specific considerations for adolescents

Art. 25. - (1) The pharmacokinetics in adolescent patients is often similar to the pharmacokinetics in adults.

(2) In several cases, limited confirmatory pharmacokinetic data are sufficient in this group.

(3) Monitoring the onset of puberty could be considered if it is suspected that inter-individual variability in maturation may be of importance for individualising the dose.

(4) Stratification of the patient group according to sex could also be considered in case gender differences are expected.

IV.2.5. The choice of control group

Art. 26. - (1) The drug exposure of the control (reference) group should reflect the exposure of the population for which clinical efficacy and safety has been documented.

(2) If no differences in study specific factors are expected to influence the results, e.g. bio-analytical methods or study conditions, then a historical control group can be used.

(3) The choice of historical controls should be justified and the relevance should be discussed.

(4) The historical control group should be pre-specified and of sufficient size (e.g. pooled pharmacokinetic data of adequate quality from phase II and III trials).

IV.2.6. Population pharmacokinetics

Art. 27. - (1) Population pharmacokinetic analysis, using non-linear mixed effects models, is an appropriate methodology for obtaining pharmacokinetic information in paediatric trials both from a practical and ethical point of view.

(2) Mean and variances are estimated and information from all individuals is merged making it possible to use sparse sampling schemes.

(3) Both parametric and non-parametric estimation methods can be considered depending on the underlying distributions of the parameters.

Art. 28. - (1) The population approach may replace conventionally designed pharmacokinetic studies with rich sampling.

(2) Simulations or theoretical optimal design approaches, based on prior knowledge (see Section 2), should be considered as tools for the selection of sampling times and number of subjects.

Art. 29. - (1) A population approach offers the possibility of estimating the typical pharmacokinetics in the population and quantifying variability components, i.e., noise (residual error) and variability due to real biological differences between individuals (inter-individual variability), simultaneously.

(2) Interoccasion variability can be estimated if observations are available from more than one occasion.

(3) Patient specific characteristics (covariates) can be included to explain variability between and within individuals.

(4) The use of statistical as well as clinical significance criteria for the covariate inclusion is recommended.

Art. 30. - Adult data may be used as prior information and may be included in the analysis as long as the predictions in children are satisfactory.

IV.2.7. Interactions

Art. 31. - (1) Conventional interaction studies are not expected to be performed in children.

(2) The interaction data can often be extrapolated from adults.

(3) However, in younger children, where the liver is not fully developed, data on interactions may be more difficult to estimate by extrapolation.

(4) The applicant should discuss whether an extrapolation of the interaction data from adults to the paediatric target age group is adequate.

(5) If differences in enzyme contribution/mode of elimination or protein binding are expected, the consequences should be discussed.

(6) In these cases, the effect of common concomitantly used medicinal products and vice versa could possibly be studied in population PK analyses, taking into account the limitations of the analysis in these aspects.

(7) If unexpected interactions are observed, or if detailed information is needed to recommend dose-adjustments, further supportive studies may be needed.

(8) Such studies may be of conventional design but may also be model-based using sparse sampling.

(9) Data on urinary excretion can be used in place of or in supplement to plasma samples.

IV.2.8. Special populations: impaired organ function and pharmacogenetics

Art. 32. - (1) As mentioned in section 4.2.7, the impact of a reduced drug elimination through a specific pathway may be different in young children as compared to adults, depending on the degree of maturation of the drug eliminating organs.

(2) Therefore the effect of genetic polymorphisms in genes coding for drug metabolising enzymes, as well as hepatic or renal impairment on the pharmacokinetics within the paediatric age group, may be different from the effect in adults.

Art. 33. - (1) The applicant should discuss the need for separate paediatric recommendations in the SPC.

(2) If needed and feasible, the effect of these factors should be investigated.

(3) This could be performed using population pharmacokinetic analysis.

IV.3. Data analysis

Art. 34. - The primary intent of the data analysis is:

a) estimation of pharmacokinetic parameters;

b) evaluation of the relationship between different covariates and the pharmacokinetic parameters;

c) development of dosing recommendations.

IV.3.1. Parameter estimation

Art. 35. - (1) Plasma concentration data (and urinary excretion data if collected) should be analysed to estimate parameters describing the pharmacokinetics of the drug and its active metabolites.

(2) The choice of pivotal pharmacokinetic parameters to be used in dosage adjustment strategies should be justified by considering knowledge available on the concentration-effect and concentration-toxicity relationships.

(3) The parameters can be estimated using either non-compartmental analysis or a model-dependent approach, for example non-linear mixed effects models.

IV.3.2. Presentation of results

Art. 36. - (1) The data presentation should enable assessment of variability at different maturational stages and facilitate the identification of cut-off points for posology adjustments.

(2) If a conventional noncompartmental analysis has been performed, the results should be presented as descriptive statistics (e.g. mean, SD, range, median) of pharmacokinetic parameters in different age groups, as well as graphical description of the relationship between different covariates (e.g. age, body weight, BSA etc) and individual observed pharmacokinetics parameters.

Art. 37. - The pharmacokinetic parameters of interest are usually AUC, Cmax, Cmin, CL, t1/2 or time over an established effective drug concentration.

Art. 38. - (1) If population pharmacokinetic analysis has been undertaken, a prospectively defined analysis plan, a detailed description of

the data, the methodology used, the model selection criteria and an overview of the main model development steps (run record) should be included.

(2) Proper graphical diagnostics (goodness of fit, parameter distributions, etc.) should be included wherein any stratification by age/maturation, relevant descriptors of size, etc, should be visible.

(3) Typical parameter estimates (standard error or confidence intervals) should be accurately presented.

(4) Influence of relevant descriptors of size and age/maturation, etc, on relevant pharmacokinetic parameters should also be presented graphically.

(5) Proper model validation should be undertaken.

IV.4. Development of dosing recommendations

Art. 39. - (1) The aim is to develop dosing recommendations that will ensure that the patients will obtain an exposure which is considered effective and safe.

(2) This should be based on information available on PK/PD relationships, or conventional documentation of exposure *vs*. efficacy and safety in the reference group and paediatric population.

(3) Target criteria should specify what change in exposure would justify a posology adjustment.

(4) The target criteria should be justified and based on the main concern (adverse events or lack of efficacy) for the specific product.

(5) Comparisons of the exposure in the paediatric population, with the exposure in the reference group associated with satisfactory efficacy and safety, should take into account that the clinical studies most probably have not been powered to detect statistically significant differences in efficacy and safety at the extreme ends of the exposure range.

Art. 40. - (1) If steady state plasma concentrations have not been determined at the recommended doses simulations of the predicted exposure during treatment should be provided.

(2) The simulations should include graphical description of concentration over time and the predicted variability in the population.

(3) Graphical descriptions of observed or predicted relevant steady state exposure parameters versus age, weight or other suitable covariates, including appropriate measures for variability, should also be presented.

(4) If the half-life of the drug is very long, which may be the case in the newborn, and a fast onset of action is needed, the possibility of a loading dose should be considered.

Art. 41. - (1) Dosing recommendations, including the covariate used for dosing, such as age, weight, body surface or renal function, etc, should be based on the above analysis rather than the age range set in the inclusion criteria of the clinical studies.

(2) The choice of covariate used in the dose recommendations should be carefully considered.

(3) If dosing by bodyweight is considered, the risk of overexposure in overweight children and the frequency of overweight children in the patient population should be considered.

(4) The study population that forms the basis for the dosage recommendation should be large enough to reflect the inter-subject variability.

(5) This is of most importance in the ages where the pharmacokinetics is more difficult to predict, i.e., usually the lower part of an age range.

IV.4. Labelling

Art. 42. - (1) The pharmacokinetic data for the different age groups should be presented in section 5.2 (Pharmacokinetic Properties), including existing information on the effects of covariates on the pharmacokinetics of the medicinal product.

(2) The dosing recommendations in the paediatric population should be given under Section 4.2 (Posology).