INTERNATIONAL COUNCIL ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM TO ICH E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

E11(R1)

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E11 (R1)

Draft ICH Consensus Guideline

Released for Consultation on 12 October 2016, at *Step 2* of the ICH

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1. INTRODUCTION

1.1 Scope and Objective of the ICH E11 Guideline Addendum (R1)

Pediatric drug development has evolved since the original ICH E11 Guideline (2000), requiring consideration of regulatory and scientific advances relevant to pediatric populations. This addendum does not alter the scope of the original guideline. ICH E11 (2000), including the present addendum (R1) is not intended to be comprehensive; other ICH guidelines, as well as documents from regulatory authorities worldwide, the World Health Organization (WHO) and pediatric societies, provide additional detail.

The purpose of the addendum is to complement and provide clarification and current regulatory perspective on topics in pediatric drug development. The use of the word "should" means that something is suggested or recommended, but not required, unless specific regulatory or statutory requirements are specified as advised by regulatory authorities worldwide.

In this addendum, section 2 on ETHICAL CONSIDERATIONS, section 4 on AGE CLASSIFICATION AND PEDIATRIC SUBGROUPS INCLUDING NEONATES, and section 7 on PEDIATRIC FORMULATIONS, supplement the content in ICH E11 (2000). Section 3 on COMMONALITY OF SCIENTIFIC APPROACH FOR PEDIATRIC DRUG DEVELOPMENT PROGRAMS addresses issues to aid scientific discussions at various stages of pediatric drug development in different regions. Section 5 on APPROACHES TO OPTIMIZE PEDIATRIC DRUG DEVELOPMENT includes enhancement to the topic of *Extrapolation*, and introduces *Modelling and Simulation (M&S)*. These sections describe essential considerations intended to provide high level guidance on the implementation of these important approaches in pediatric drug development, reflecting the evolving nature of these topics. This harmonized addendum will help to define the current recommendations and reduce the likelihood that substantial differences will exist among regions for the acceptance of data generated in pediatric global drug development programs and ensure timely access to medicines for children.

2. ETHICAL CONSIDERATIONS

ICH E11 (2000) Section 2.6 addresses relevant principles for the ethical conduct of pediatric studies including, the roles and responsibilities of the Institutional Review Board/Independent Ethics Committee (IRB/IEC), recruitment of study participants, parental (legal guardian) consent/permission and child assent, and minimization of risk and distress. These ethical principles are also defined in the current legal and regulatory framework of health authorities worldwide responsible for ensuring safeguards for the protection of children participating in research.

A fundamental principle in pediatric drug development requires that children should not be enrolled in a clinical study unless necessary to achieve an important pediatric public health need. When clinical studies are required to obtain information relevant to the use of a medicinal product, such studies should be conducted in pediatric populations having the disease or condition for which the investigational product is intended, unless an exception is justified. Without a prospect of clinical benefit from an experimental intervention or procedure, the foreseeable risks to which a pediatric participant would be exposed must be low. The burden of a procedure or an intended intervention should also be minimized. Experimental interventions or procedures that present greater than low risk must offer a sufficient prospect of clinical benefit to justify exposure of a pediatric population to such risk. Likewise, the balance of risk and anticipated clinical benefit must be at least comparable to the available alternative treatments. There should be a reasonable expectation that a clinical benefit resulting from the clinical study can be made available to this population in the future.

The general principles of ethical considerations for parental (legal guardian) consent/permission and child assent are outlined in ICH E11 (2000) Section 2.6.3 and continue to apply. Information regarding the clinical study and the process of parental (legal guardian) consent/permission and child assent should be provided to the parent (legal guardian) and/or child participant, as appropriate, at the time of enrollment, especially relating to long term studies or studies that may require sample retention. When obtaining child assent, relevant elements of informed consent should be provided appropriate to the child's capability to understand. Lack or absence of expression of dissent or objection must not be interpreted as assent. Over the course of a clinical study, it may be necessary to reassess the assent of a child in recognition of their evolving maturity and competency. During clinical studies there may be a requirement for obtaining adequate informed consent from pediatric participants once a child reaches the age of legal consent. Local regulations related to confidentiality and privacy of pediatric participants should be followed.

Policies that promote clinical research transparency are also relevant in pediatric clinical research. A fundamental principle of drug development is the public availability of objective and unbiased clinical study results to enhance clinical research, to avoid unnecessary clinical trials especially in children, and to inform clinical decisions in pediatric practice.

3. COMMONALITY OF SCIENTIFIC APPROACH FOR PEDIATRIC DRUG DEVELOPMENT PROGRAMS

General principles outlined in ICH E11 (2000) Section 1.4 continue to apply. Pediatric drug development programs are increasingly multiregional. Multiregional pediatric drug development programs face specific challenges due to regional differences in pediatric regulatory requirements, operational practicalities, and cultural expectations. These regional differences in some instances limit the ability of health authorities to align regulatory processes. Thus, timely and efficient drug development requires a common scientific approach for which the following key questions should be addressed:

1. What is the medical need in one or more pediatric populations that the drug could address?
2. Who are the appropriate pediatric populations or subgroups that could be considered?
3. What objectives(s) for the pediatric development program could be considered?
4. Based on the existing knowledge, including developmental physiology, disease pathophysiology, nonclinical data, data in adult or pediatric populations or subgroups, or data from related compounds, what are the knowledge gaps?
5. Are specific juvenile animal studies needed?
6. What clinical studies and/or methodological approaches could be considered?
7. What pediatric-specific clinical study design elements could be considered?
8. Are there different formulations/dosage forms that will be needed for specific pediatric subgroups, both to facilitate an optimal dose-finding strategy, and for treatment of pediatric patients in different subgroups?

A common scientific approach should consider input from stakeholders, (e.g., clinicians, patients, experts from academia), and should be based on scientific advances and up-to-date knowledge.

Early consideration of pediatric populations during drug development planning, along with early interactions between drug developers and regulatory authorities worldwide can facilitate agreement on a common scientific approach. When differences are identified, established regulatory pathways to minimize the impact of these differences can be utilized. Therefore, a common scientific approach, not common regional requirements, is at the cornerstone of efficient pediatric drug development and timely delivery of safe and effective medicines for children.

4. AGE CLASSIFICATION AND PEDIATRIC SUBGROUPS, INCLUDING NEONATES

A rationale for the selection of the pediatric population to be included in clinical studies should be provided. Chronologic age alone may not serve as an adequate categorical determinant to define developmental subgroups in pediatric studies. Physiological development and maturity of organs, pathophysiology of disease or condition, and the pharmacology of the investigational product are factors to be considered in determining the subgroups in pediatric studies. Further, the arbitrary division of pediatric subgroups by chronological age for some conditions may have no scientific basis and could unnecessarily delay development of medicines for children by limiting the population for study. Depending on the condition and treatment, it may be justifiable to include pediatric subpopulations in adult studies or adult subpopulations in pediatric studies.

Advances in medical care have led to better survival of high risk newborn infants, especially preterm newborn infants, which makes drug development research in newborn infants or "neonates" increasingly important. Neonates include both term and pre-term newborn infants. The neonatal period for term newborn infants is defined as birth plus 27 days. The neonatal period for preterm newborn infants is defined as beginning at birth and ending at the expected date of delivery plus 27 days. As the neonatal population represents a broad maturational range, the conditions that affect this population can vary considerably. A rationale for the selection of a neonatal population in clinical studies should be provided.

5. APPROACHES TO OPTIMIZE PEDIATRIC DRUG DEVELOPMENT

The concepts presented in ICH E11 (2000) Section 2.4 still apply. The principles outlined in ICH E4, E5, E6, E9, and E10 should be consulted. The number of pediatric studies and knowledge in the field of pediatrics has increased since ICH E11 (2000). Respective regulations for pediatric drug development worldwide have also evolved. However, drug development in pediatrics continues to present challenges and opportunities. In some cases, there are difficulties with generating data across a pediatric population due to a variety of ethical considerations and feasibility issues. Alternative approaches may provide opportunities to address these issues when structured and integrated into the development program as per the principles outlined in this addendum. Early multi-disciplinary dialogue regarding the acceptability of such approaches with regulatory authorities is recommended. The planning for development of the drug for children should not begin when development in adults reaches its conclusion.

5.1 Use of Existing Knowledge in Pediatric Drug Development

To better inform the design of a pediatric drug development program, there is an opportunity to utilize existing knowledge. Existing knowledge includes evidence already or concurrently generated with the drug under development in adult and pediatric populations with the same disease or condition. Existing knowledge also integrates nonclinical data, data about related compounds, disease pathophysiology, as well as consideration of the developmental physiology of the pediatric population or subgroup. Use of such information can optimize pediatric drug development programs without reducing evidentiary standards. Safety and risk consideration based on the existing knowledge should guide the decision whether specific mitigation, such as staggered enrollment based on age group, is necessary. However, any uncertainties related to the use of existing knowledge must be identified and managed prospectively. As data are generated through the drug development cycle, it is possible that the assumptions behind the parameters that have gone into the development strategy and methodology may need to be revisited to take new information into account. This new information will continue to inform the strategy and present an opportunity to further address uncertainties.

Additional approaches to optimize pediatric drug development may include, but are not limited to, statistical and pharmacometric methods, including M&S that integrate and leverage existing knowledge, as well as extrapolation of information from other populations (adults or pediatric subgroups).

5.1.1 The Use of Extrapolation in Pediatric Drug Development

The concept of "extrapolation" is used in different ways in drug development. "Pediatric Extrapolation" is defined as an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) population.

When a drug is studied in a pediatric population, consider all factors which may result in different drug responses, such as intrinsic (e.g., developmental) and extrinsic (e.g., geographic) factors that could impact on the extrapolation of data from one population to the other.

Where an extrapolation approach is scientifically justifiable, it should be a dynamic process that examines several factors including disease pathogenesis, criteria for disease diagnosis and classification, measures of disease progression, and pathophysiological, histopathological, and pathobiological characteristics that support the assumptions of similarity of disease and similarity of response to therapy between the pediatric and the reference populations. A thorough understanding of the differences between pediatric and reference populations is required relative to the pathophysiology of the disease, available biomarker/endpoints, organ systems physiology (i.e., renal, hepatic, central nervous system, skeletal, and immune systems), as well as clinical context of therapeutics, and pharmacological behavior of the drug.

Support for the assumptions of similarity of disease and response to therapy, including exposure-response relationship, and prediction of an effective dose for the intended population, may be derived from existing data, published literature, expert panels and consensus documents, or previous experience with other products in the same therapeutic class. All data and information gathered can either confirm the extrapolation approach or inform how it might be improved. Ultimately, the exercise should identify if there is sufficient data to support extrapolation, or if additional clinical information is needed.

When efficacy in the pediatric population can be extrapolated from data obtained in the reference populations, leveraging of safety data from the reference to the pediatric population may be utilized; however, additional pediatric safety data are usually required, as data in adults may only provide some information about potential safety concerns related to the use of a drug in the pediatric population. [ICH E11 (2000) Section 2.4].

When extrapolation is considered in a pediatric drug development strategy, the following framework of questions should be discussed to assess what additional supportive data are needed:

1. What evidence supports a common pathophysiology of disease, natural history, and similarity of the disease course between the reference and pediatric population(s)?

2. What is the strength of the evidence of efficacy in the reference populations?

3. Is there a biomarker or surrogate endpoint in the reference populations that is relevant in the pediatric population?

4. What evidence supports a similar exposure-response between the reference and intended populations?

5. What uncertainties do the existing data (e.g., clinical or historical data and published literature) have, and what uncertainties about the pediatric population remain?

6. If uncertainties remain, what additional information should be generated (e.g., information from M&S, animal, adult, pediatric subgroup studies) in order to inform the acceptability of the extrapolation approach?

As evidence builds, the acceptability of the proposed extrapolation approach will need to be reassessed and it may be appropriate to change the extrapolation approach.

5.1.2 The Use of Modelling and Simulation in Pediatric Drug Development

Advancement in clinical pharmacology and quantitative modelling and simulation (M&S) techniques has enabled progress in utilizing model-informed approaches (e.g., mathematical/statistical models and simulations based on physiology, pathology and pharmacology) in drug development. M&S can help quantify available information and assist in defining the design of pediatric clinical studies and/or the dosing strategy. Considering the limited ability to collect data in the pediatric population, pediatric drug development requires tools to address knowledge gaps. M&S is one such a tool that can help avoid unnecessary pediatric studies and help ensure appropriate data are generated from the smallest number of pediatric patients. The usefulness of M&S in pediatric drug development includes, but is not limited to, clinical trial simulation, dose selection, choice and optimization of study design, endpoint selection, and extrapolation. With M&S, quantitative mathematical models are built with all available and relevant sources of existing knowledge. Provided well conducted, M&S can inform on the pharmacokinetics, pharmacodynamics, efficacy and safety of a drug.

The incorporation of M&S into pediatric drug development should be based on a strategic plan established through multidisciplinary discussions outlining objectives, methods, assumptions, deliverables and timelines. When building a model, several criteria should be considered, including the intended use of the model itself, the quality and the extent of the existing data, and the assumptions made. Assumptions are usually structured around five main areas: clinical pharmacology (the compound and the patient), physiology, disease considerations, existing data, as well as the mathematical and statistical assumptions underpinning the model.

Complexity in M&S requires a careful assessment of the impact of each of the above assumptions because the impact of each one can vary between populations. In pediatrics, it is particularly critical to consider the maturation of organ systems with the understanding that data from older subgroups may not necessarily be informative for the younger subgroups. Once assumptions are set, different scenarios should be defined to support the analysis of the impact of potential uncertainty in existing knowledge.

Emerging knowledge is incorporated into the model in an iterative approach to revisit and improve the model. A series of "learn and confirm" cycles should be used for model building and simulation/prediction, and be confirmed as soon as new information is generated. Several models may be needed to support a given pediatric drug development program depending on the question(s) to be addressed, the confidence in the model, and the emerging data generated.

Risk assessment is a critical part of M&S. The clinical and statistical consequences of a specific approach should be discussed with experts to define the risks to be handled. The risks associated with accepting the M&S assumptions should accordingly be assessed and weighed against the confidence in the model predictions and the validity of the assumptions.

6. PRACTICALITIES IN THE DESIGN AND EXECUTION OF PEDIATRIC CLINICAL TRIALS

Before deciding which types of methodological approaches are to be used in clinical trial design and execution, one should consider several practical factors that influence the design and execution of pediatric clinical trials. Three key practical factors to consider are feasibility, outcome assessments, and long-term clinical aspects, including safety.

6.1 Feasibility

Pediatric drug development faces unique feasibility issues, including a small number of eligible children for clinical research, limited pediatric specific resources at research centers, and the lack of dedicated pediatric trial networks. Consideration should be given to the available centers willing to participate that have access to eligible pediatric participants. When studying pediatric conditions, it may be necessary to consider implementing clinical trial operational strategies, including, but not limited to, the use of pediatric research coordinating centers, the development of master protocols for clinical trials planned and conducted in a collaborative manner to evaluate multiple therapies for the same disease or condition with a single control arm, and the enhancement of pediatric clinical research networks. These operational strategies may be challenging to implement, but may result in improved feasibility and increase timely and efficient pediatric drug development.

The expectations of children and their guardians, including the emotional and physical burden, and the convenience of participation, should be considered. Current standards of care can influence physician/patient treatment choices that may impact pediatric clinical trial design. Strategies that foster input from children, their caregivers, and the advocacy communities can facilitate participation, recruitment, and acceptability of a clinical study.

6.2 Outcome Assessments

As stated in the ICH E11 (2000) Section 2.4.2, it may be necessary to develop, validate, and employ different endpoints for specific age and developmental subgroups. The relevant endpoints and outcome measures for the pediatric population should be identified as early as possible. It is important to include protocol design features that allow pediatric participants at appropriate ages to contribute directly in these measures when possible. Where relevant, it may be prudent to assess potential pediatric endpoints in the adult development program.

6.3 Long-term Clinical Aspects, including Safety

The concepts on safety presented in ICH E11 (2000) Section 2.4.3 and Section 2.4.4 still apply. It is acknowledged that rare events may not be identifiable in pre-registration development, and that pediatric-specific adverse events are unlikely to be detected in development programs that are limited in size and duration. Planned collection of safety data in nonclinical studies, adult clinical studies regardless of dose or indication, or data from other sources (e.g., M&S), should serve to improve the design of pediatric studies and pharmacovigilance activities to address specific pediatric safety concerns.

Long-term effects of drug treatment in children can include impacts on development, growth, and/or maturation of organ/system function. Therefore, adequate baseline assessments of growth/development and organ function, and regular follow-up measurements should be planned. Early planning for follow-up in a development program offers the opportunity to systematically capture and evaluate long-term effects in a disease or condition, and increase data interpretability.

7. PEDIATRIC FORMULATIONS

Principal considerations for the development of age-appropriate pediatric formulations to allow for safe and accurate use of pediatric medicines as outlined in ICH E11 (2000) Section 2.2 continue to apply. Additional considerations for pediatric formulations to optimize efficacy and reduce the risk for medication and dosing errors should include age-appropriate dosage forms, ease of preparations and instructions for use for caregivers, acceptability (e.g., palatability, tablet size), choice and amount of excipients, delivery systems, and appropriate packaging.

Adult dosage forms are not always appropriate for use in the pediatric population, and if a preparation for adults is used, it may pose a safety risk. When pediatric considerations are not addressed early during the development process, the final medicinal product may require such manipulation for use in children that it increases the likelihood for inaccurate dosing and changes in stability or bioavailability. Examples of this include multiple small volume acquisitions from a vial designed for a single adult use, use of an opened adult capsule formulation or crushed tablets to administer a pediatric dose mixed with food, and breaking tablets that do not have a score line. Therefore, planning for development of age-appropriate dosage forms for pediatric populations should be incorporated into the earliest stages of product development. When manipulations of the available form are unavoidable, measures to minimize the impact on dose accuracy, stability and bioavailability must be addressed.

7.1 Dosage and Administration

In order to achieve the targeted drug exposure, more than one dosage form of the active pharmaceutical ingredient (API) or its strength may be needed to cover the range of pediatric populations intended to receive the medicinal product. For pediatric drugs, the environment where the product is likely to be administered should be considered when selecting the formulation for development. For example, long acting formulations may be of importance in settings where the caregiver is not available (e.g., school, nursery). Further, certain dosage forms that reduce the requirements for handling and storage may be more appropriate than others.

In developing a formulation for pediatric use, considerations should include the ease of accurate measurement and capability to deliver small volumes to minimize the risk for dosing error, especially in neonates, infants and young children. Such approaches could include clearly marked administration devices designed for accurate measurement of the smallest dose volume and dose increments.

7.2 Excipients

Excipients may lead to adverse reactions in children that are not observed (or not to the same extent) in adults. Thus, the use of excipients in pediatric medicines should take into account factors such as pediatric age group (e.g., term and preterm newborns related to their physiologic development), frequency of dosing, and intended duration of treatment. The number of excipients and their quantity in a formulation should be kept to the minimum required to ensure product performance, stability, palatability, microbial control, and dose uniformity. Alternatives to excipients that pose a significant risk to children should always be considered, and the risk posed by the excipient weighed against the severity of the disease and availability of alternative treatments. When selecting excipients, one should always consider the potential impact on absorption and bioavailability of the active ingredient.

7.3 Palatability and Acceptability

Orally administered pediatric medicines must be palatable to ensure dose acceptance and regimen adherence. A formulation strategy for developing palatable drugs includes minimizing/eliminating aversive attributes of the API and formulation of favorable flavor attributes. Taste masking is often needed to improve the palatability of the medicine. As pediatric drug development can benefit global populations, the target for taste masking should not only be focused on ensuring a medicine does not taste unpleasant; it should also ensure that the taste has broad cultural acceptance.

Alternative dose administration strategies should be considered for pediatric populations who cannot be accommodated by the intended dosage form (e.g., segmenting or crushing tablets, co-administration with food or liquids). Appropriateness of the alternative strategy for a pediatric population, including patient and caregiver aspects (e.g., taste/palatability, ease and accuracy of manipulation, and potential changes in bioavailability due to a variety of factors) should be investigated prior to selection of the final market image formulation. Understanding real-world use behaviors in administering pediatric dosage forms and the mitigation of associated risks will contribute to the development of a formulation that allows for safe dose administration.

7.4 Neonates

Formulation requirements for neonates warrant special attention, such as its effects on electrolyte, fluid or nutritional balance. Intramuscular injections should be avoided where possible and the tolerability of subcutaneous and intravenous injections evaluated. For neonates, environmental conditions (e.g., temperature, light) and equipment used for drug administration (e.g., enteral feeding tubes) may have an effect on drug delivery and bioavailability. When developing a parenteral dosage form, compatibility with other commonly administered parenteral medicines or parenteral nutrition should also be investigated, as intravenous access is often limited in this population.

8. GLOSSARY

Parental (legal guardian) consent/permission:

Expression of understanding and agreement by fully informed parent(s) or legal guardian to permit the investigator/sponsor of a clinical study to enroll a child in a clinical investigation. The choice of the terms parental consent or parental permission in different regions may reflect local legal/regulatory and ethical considerations.

Child assent:

The affirmative agreement of a child to participate in research or to undergo a medical intervention. Lack or absence of expression of dissent or objection must not be interpreted as assent.

Modelling and Simulation (M&S):

A range of quantitative approaches, including pharmacometrics/systems pharmacology and other mathematical/statistical approaches based on physiology, pathology and pharmacology to quantitatively characterize the interactions between a drug and an organic system which could predict quantitative outcomes of the drug and/or system's behavior in future experiments. In modelling and simulation, existing knowledge is often referred to as "prior" knowledge.