PAN-AMERICAN NETWORK ON DRUG REGULATORY HARMONIZATION (PANDRH)

GOOD CLINICAL PRACTICES WORKGROUP

GUIDE FOR CONDUCTING CLINICAL STUDIES IN PEDIATRIC POPULATIONS

CONTENTS

1 – INTRODUCTION AND GENERAL PRINCIPLES

Providing adequate protection to vulnerable populations arouses special concern because such subjects may be less able to protect their own interests during studies with new medicines or pharmaceutical products. One such vulnerable group is children, where the limited capacity or freedom to consent requires the imposition of additional protections for their participation. Yet children are also vulnerable in being subjected to treatments that have often been evaluated only in adults, without scientific data to support the safety and efficacy of such treatments in their age group. As well, there are certain childhood diseases where few, if any, safe and effective medicines are yet to be developed. For these reasons, it may be appropriate and indeed not unfair to include children in clinical studies, provided such studies are conducted within the strictest scientific and ethical parameters.

In general, the Development Program of a medicinal product should include an evaluation of the pediatric population when the product is studies for a disease or condition in adults but where its use in children can be anticipated. Obtaining information from children should always be done without jeopardizing the welfare of the pediatric subjects participating in a clinical study. This responsibility must be shared by research institutions, regulatory authorities, medical professionals, and society as a whole.

1.1 OBJECTIVES

This guide's objective is to establish standards for clinical research of medicinal products in children, and to allow the development of pediatric studies in the Region of the Americas in a rigorous, scientific, and safe manner. It will address several critical issues in the development and evaluation of a drug for pediatric use, supporting safety, efficacy, and ethical conduct of clinical trials in children.

2- SCOPE OF THE GUIDE

Specific aspects of pediatric clinical trials include:

2.1 Considerations of when to start the Clinical Program in children during development of a new medical pharmaceutical product

2.1.1 Pediatric formulations

2.2 Timing of pediatric studies during product development

2.3 Types of studies: Pharmacokinetics-pharmacodynamics, efficacy and safety

2.4 Classification by age

2.5 Ethics in clinical research in children

2.6 Acceptability of complete information from studies conducted in childre in a country outside of the country where marketing authorization is sought

2.7 Need and requirements for additional clinical trials in children in the country were marketing authorization is sough due to insufficient data from studies in other countries.

This guide is not exhaustive, it should be supplemented with other guides form local and regional authorities and recommendations of pediatric societies

2.1 Considerations of when to Start the Clinical Program in Children during the Development of a New Medical Pharmaceutical Product

Information should be generated on the appropriate use of a pharmaceutical product in the pediatric population unless it is clearly inappropriate for this population. The approach and timing for commencement of the Clinical Program should be consulted with Regulatory Authorities at an early stage and then systematically and periodically reviewed during the entire process. The Clinical Program in children should not be delayed pending full results of testing in adults or availability of the product on the market, nor should it move ahead without sufficient scientific and ethical justification.

Factors influencing the decision to launch the Clinical Program in children and the nature of pediatric studies that are:

-- The prevalence of the underlying disease or condition of being treated in the pediatric population;
-- The seriousness or severity of the disease or condition to be treated;
-- The availability and appropriateness of alternative treatments for the pediatric condition in question, taking into account the efficacy, safety, and adverse event profile of current treatment(s);
-- The novelty of the product or whether it belongs to a class of compounds with well-known properties;
-- Whether the indication of the product is unique to the pediatric population;
-- The need to develop specific evaluation variables for the pediatric population;
-- The range of ages of pediatric patients likely to be treated with the medical pharmaceutical product;
-- Unique safety aspects of the pharmaceutical product for the pediatric population;
-- Potential need of developing a formulation for pediatric use.

Of these factors, the most important is the presence of a disease that is life-threatening and for which the product could represent an important advance in the treatment of the disease. This situation suggests a relative urgency in the early initiation of pediatric studies.

The preliminary information related to the safety of the product is most often obtained from information provided from adults. Pre-clinical information should also be available from repeated dose toxicity, genotoxicity, and reproductive toxicity studies. Studies should be undertaken in young animals if necessary, and it should be analyzed case by case according to the toxicity of the product.

2.1.1 Pediatric Formulations

New formulations must be obtained, more suitable for pediatric use, either to achieve a more simple, workable, and acceptable administration, or to adjust the doses and concentrations so that the product is safe and effective.

The analysis of the excipients and their safety is another element to consider. In some cases, failure to consider such issues has brought fatal consequences, such as death by kidney failure in 107 children in 1938 due to the excipient diethylene glycol in sulfanilamide.

In general, these formulations should be in accordance with internationally harmonized standards for excipients and for the validation of procedures.

2.2 Timing of the Studies

During the clinical development of the product, the timing of pediatric studies will depend on the type of disease, the safety of the product as well as the safety and efficacy of available treatments.
If the development of a new formulation is required, it should be considered early in the development of the product.

2.2.1 Products for Diseases Prevalent in Children or with Exclusive Appearance in the Pediatric Population

In these cases, the Clinical Studies Program will be conducted completely in the pediatric population with exception of the initial safety data which will often be obtained from adults. This information may be impossible to obtain from adults due to its limited helpfulness, for the target population could be neonates undergoing maturation of some systems and organs, or because the product could pose too much risk for adults. Some examples include surfactant in respiratory distress syndrome of the newborn and genetic diseases of exclusive manifestation in the pediatric population.

2.2.2 Products for Serious Diseases Threatening the Lives of Both Adults and Children, for Which There Are No Therapeutic Options or They Are Very Limited

The presence of such conditions would argue for starting studies in the pediatric population as early as possible following initial assessment of safety and reasonable evidence of potential benefit of the product.

2.2.3 Products That Attempt to Treat Other Diseases

For such products, studies in children should begin in the later stages of the studies in adults or in some cases, once the product is registered and its marketing is launched, and with substantial experience in adults.

Laboratories should have a Clinical Development Program for the pediatric population, which in such diseases would not generally be initiated before the end of phase II or III in adults. Taking into account that many studies of Phase II do not reach valid conclusions, children should not be submitted to a product that can have no benefit. The risk of the benefit must be balanced in every program of the development of the product in order to make a decision of when to begin.

2.3 Types of Studies

When a medical pharmaceutical product is studied in pediatric patients of a region, the extrapolation of the results of this study to other regions should take into account both intrinsic (for example, pharmacogenetic) and extrinsic factors (for example, diet), that could have an impact on the extrapolation of the data.

When attempting to use a medical pharmaceutical product in the pediatric population for the same indication studied and approved in adults, the process of the disease is similar in both populations and it is likely that the results of therapy studies are comparable, it may be appropriate to extrapolate to the children the data of efficacy obtained in adults. In such case, pharmacokinetic studies in all the different age ranges for pediatric patients likely to receive the medical pharmaceutical product, coupled with safety studies, could provide adequate information for use of the product, allowing this way, the selection of pediatric doses that would yield optimal therapeutic levels of the product in blood. If this approach is used, pharmacokinetic data from adults must be available for the design of pediatric studies.

When it is intended to use a medical pharmaceutical product in younger pediatric patients for the same indication that was studied and approved in older pediatric patients, the

process of the disease is similar, and it is likely possible that the treatment results are comparable, it can be possible that the extrapolation of efficacy data from older pediatric patients, if already reached in these patients, the maturation processes of those major organs, that participate in the process of metabolism and excretion of medicines. If this maturation is still not reached, the pharmacokinetic studies in younger pediatric patients destined to receive the product, together with safety studies, could provide adequate information for their use of the product.

An approach based on pharmacokinetics may be insufficient: 1) for pharmaceutical products in which it is known or expected that blood levels do not match with efficacy, 2) if there is a possibility that the concentration-response relationship may differ between pediatric and adult populations. In such cases, clinical studies or evaluation of the pharmacological effect of the product must be conducted.

In those cases where it is expected that the course of the disease or the response to therapy in the pediatric patient is similar to that obtained in adults, even though the appropriate blood levels are not clear, it is possible to use measurements of the pharmacodynamic effect related to clinical efficacy for the purpose of confirming the expectations of effectiveness and to define the doses and concentrations necessary to achieve the pharmacodynamic effect in children. Such studies could provide a high confidence in reaching a given exposure of the drug in pediatric patients will produce the desired therapeutic response. So a PK/PD approach combined with safety and other relevant studies could avoid the need for clinical studies of efficacy.

In other situations where the pharmacokinetic approach can not be applied, as in the case of medical pharmaceutical products for topical use, the extrapolation of the efficacy from one patient population to another may be based on studies with pharmacodynamic endpoints and/or other appropriate assessment alternatives, such as local tolerance studies. It may be important to determine concentrations in blood and effects at the systemic level for the product in order to be able to assess its safety.

When seeking new indications for a pharmaceutical product in pediatric patients, or when the course of the disease and the results of therapy are different between the adult and pediatric patients, it is generally necessary to conduct clinical studies of efficacy in the pediatric population.

2.3.1 Pharmacokinetics

Generally pharmacokinetic studies should be done for the purpose of supporting development of the formulation and for determining the pharmacokinetic parameters in different age groups to support the recommended dosage. Overall, the comparisons of relative bioavailability of pediatric formulations with oral formulations in adults should be done on adults. However, when seeking to select the dose for different age ranges of pediatric patients in whom the medicine is likely to be used, final pharmacokinetic studies should be conducted in pediatric populations, and usually performed in patients with the disease. The former may lead to higher inter-subject variability than in studies with healthy volunteers, but the data better reflect clinical use.

For products that show linear pharmacokinetics in adults, single-dose pharmacokinetic studies in the pediatric population may be sufficient to provide information for the selection of dosage. Conversely, if the kinetics are non-linear in the uptake, distribution and/or elimination, or if there is any difference in duration of effect between single dosing and

repeated dosing in adults, it is necessary to conduct steady state studies in the pediatric population.

The selection of approach is facilitated if pharmacokinetic parameters in adults and the clearance path of the drug are known and the possible changes in these processes associated with age are understood, all those of great utility in the design of pediatric studies.

The dosing recommendations for the majority of medical pharmaceutical products used in the pediatric population are given in milligram (mg) per kilogram (kg) of body weight up to the maximum adult dose. Although many prefer the dosage based on mg/m^2 body surface area, clinical experience suggests that it is common for errors to occur in measuring the height or length of the body and in calculating body surface area, particularly in infants and young children. For some medications (for example, medicines with a narrow therapeutic index, such as in oncology), dosing by surface area may be required, and extreme care must be exercised to ensure the proper dose calculation.

2.3.1.1 Practical Considerations for Facilitating Pharmacokinetic Studies

The volume of blood to be drawn in pediatric studies should be minimized and should be justified in the protocol(s). The Independent Ethics Committees/Institutional Review Committees (IEC/IRC) could review and determine the maximum amount of blood that can be drawn for research purposes (usually in ml/kg or percentage based on total volume of blood). Various approaches can be used to minimize the amount of blood drawn and/or the number of punctures for the extractions. For example, the use of laboratory techniques for small samples, the collection of analysis at the same time as routine clinical testing, and the use of special catheters to make the extraction process less intrusive.

2.3.2 Efficacy

The aspects concerning design, selection of control group, and statistical considerations in studies of adults are generally applicable to pediatric studies. However, there are some specific features for the pediatric population, in which cases it is not possible to infer for the children, the results of efficacy performed on adults.
When these studies are required, it is necessary to develop, validate and employ response evaluation variables appropriate for the child's stage of development. The measurement of certain subjective symptoms, such as pain, require specific assessment tools for patients of different ages.
In pediatric patients with chronic diseases, the response to a drug can vary among patients not only depending on the duration of the disease, but also depending on the stage of child development.
Many diseases that appear in term-born and pre-term infants are unique or have manifestations that do not permit extrapolation from older patients and therefore require new methods of assessment in this population.

2.3.3 Safety

The concepts of safety documentation that collect the descriptions and reports of adverse events are applicable to pediatric studies. The laboratory values and clinical measurements must be normalized for age, and must be used on the adverse events report.

Ingestion of a drug inadvertently, by accident, can sometimes provide safety information of potential adverse events and in some cases, contribute with elements of pharmacokinetics to a better understanding of the relationship between dose and adverse events or side effects.

Some products may affect physical and/or cognitive growth and development of the child. The profile of these events will differ among different age groups since the developing systems respond differently according to the maturing of organs and therefore, adverse events may appear in children that did not show up or were not identified in studies of adults.
Additionally, because of the dynamics of the process of maturation and growth, an adverse event may not manifest in acute form but only in the long term, as it affects the process of child development.
Follow-up studies over the medium and long term as well as pharmacovigilance data are important to determine possible effects for example on the osteomioarticular system, cognitive, sexual, and immune system maturation.

2.3.4 Studies and Post-Marketing Information

Normally there are few pediatric studies and limited pediatric data at the time of product approval and sanitary registration. Therefore, pharmacovigilance (post-marketing surveillance) can be very important to determine the effects of a new medical pharmaceutical product, especially on the process of growth and development of the child in its various stages. Similarly, long-term follow-up studies can provide important information on safety and efficacy in different age groups.

2.4 Classification according to the Age of The Pediatric Patients

The classification of pediatric patients according to age group provides a basis for approaching study design and stratification to better achieve homogeneity of these groups. The decision on how to stratify and the difference between strata should be based on biological and pharmacological variables of the groups. Therefore, a flexible approach is needed to ensure that studies reflect current knowledge of pediatric pharmacology. The identification of what ages to study should be specific for the medicinal product and should be justified. From the foregoing, it is important to specify age groups in which there is a noticeable difference from the pharmacological point of view, specially in the “clearance” and other pharmacological variables. If the route of clearance of a medicinal product is well established in the different groups and the ontogeny of this route is well understood, the so-called “break points” where the clearance changes substantially from one age group to another may be used to designate the age categories.
But sometimes it may be more appropriate to collect data in broad ranges of ages and examine the effect of age as a continuous covariant. For the evaluation of efficacy, various endpoints can be selected for study in different age groups, and these age groups may not always coincide with the classification proposed below.
If the study population is divided into too many groups, this may unnecessarily increase the sample size required. In long-term studies, patients may also move from one range or group to another; so the design and the statistical analysis planning must prospectively take into account these changes in number within each category.

The following classification is one possible categorization, however, the categories can have overlap in terms of development (physical, cognitive and psychosocial). The ages are defined in completed days, months, and years:

2.4.1 Pre-term newborn
2.4.2 Term-born infant (0 – 27 days)
2.4.3 Sucklings and toddlers (28 days to 23 months)
2.4.4 Children (2 to 11 years)
2.4.5 Adolescents (12 to 16-18 years)

2.4.1 Pre-term Newborn

The study of medicinal products in pre-term newborns is a special challenge because of the unique pathophysiology and therapeutic response in this population. The complexity and ethical considerations of studies in this child population forces to a careful protocol development by experts not only in neonatology, but also in pharmacology. For this population, the results from adults and children can rarely be inferred.

The category of pre-term newborns is not entirely uniform, since a newborn of 25 weeks and 500 grams is very different from a newborn of 30 weeks and 1500 grams. Another distinction must be made between newborns with low birth weight and those who have retarded growth and development which may impact on the maturity of organs such as kidneys and liver and thereby with drug clearance. Therefore, the following should be considered:

a) Gestational age and time of birth;

b) Maturity of the liver and kidneys for clearance of medicines;

c) The limits of protein, especially bilirubin, as well as albumin and 1-glycoprotein because of the union or not with the medications to study and its repercussion in the blood concentration of these and its possible adverse reactions.

d) Transfer of the product into the Central Nervous System;

e) Unique diseases of the newborn (Distress Syndrome of the Newborn; persistent ductus arteriosus, primary pulmonary hypertension);

f) Conditions that are more common in pre-term newborns (necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of the premature baby);

g) Metabolic physiological process in variable maturation of organs that conduct to regimes of variable dosage and chronic exposure.

h) Transdermal absorption of medicines and other chemicals products.

The study design should take into account:

1) Weight and age;

2) Small volume of blood (a 500 gram newborn has approximately 40 ml of blood);

3) Small numbers of patients in any clinical center and the possible differences between centers in relation to the management of patients;

4) Difficulties in the evaluation of variable response.

2.4.2 Term-born Infants (0 to 27 days)

Although term-born infants are more mature than pre-term born, many of the physiologic and pharmacologic principles apply to this population. The volumes of distribution of products may be different compared to older children because of the fat and water content and the high relation of body surface to weight. The brain-blood barrier is not mature enough and there can be some associated toxicity due to a greater passage of medicinal products and endogenous substances (e.g., bilirubin) to the central nervous system. Absorption of oral medicines could be less predictable than in older pediatric patients. The mechanisms for clearance in kidney and liver are immature and rapidly changing, so the dose must be adjusted during the first weeks of life. An increase in susceptibility to the toxic effects of medicinal products may arise due to limited clearance in these patients (e.g., gray baby syndrome by chloramphenicol). On the other hand, term-born infants may be less susceptible to certain types of adverse effects (nephrotoxicity by aminoglycosides) than older age patients.

2.4.3 Sucklings and Infants (28 days to 23 months)

This is a period of rapid maturation of the central nervous system, immune system and body growth. Absorption by the oral pathway is more reliable. The pathways of hepatic and renal clearance mature very quickly and by one year and two years of life, the clearance of many medicines may exceed the values in adults on a mg per kg basis. The developmental pattern of maturation of clearance depends on the specific clearance pathway. Variability of maturation between individuals is very common and can be substantial.

2.4.4 Children (2 to 11 years)

In this age group most pathways of clearance of medicines (liver and kidney) are mature with clearance rates that sometime exceed that of adults. Changes in the clearance of a drug may depend on the maturation of the specific metabolic pathway. The specific strategy to assess any effect on the growth and development of children should be defined in the protocol. Children have key moments or development milestones that could be affected by medicines active on the central nervous system. Entry into school and increased cognitive and motor skills can affect a child's ability to participate in certain types of clinical trials. The growth of the skeleton, weight gain, school attendance and school performance are factors useful in measuring the effect of a drug in children. The recruitment of patients should ensure representation across all age ranges in this category, and it is important to ensure sufficient numbers of younger patients. Stratification by age within this category is often unnecessary though it may be appropriate to stratify based on the pharmacokinetics or efficacy endpoint considerations.

The onset of puberty is highly variable and occurs at younger ages in girls, sometimes at the age of 9. Puberty can affect the activity of certain enzymes that metabolize the drug, and dosage required for some medicines on the basis of mg per kg in weight can change

dramatically (e.g., theophylline and those medicines which are stored in fatty tissue which tends to increase in girls at this stage). In some cases, it may be advisable to assess the effect of the drug at puberty, studying pre- and postpubertal pediatric patients. In other cases it may be appropriate to record the Tanner stage of puberty development and obtain biological markers of the same and examine the data to detect any potential influence of the pubertal changes.

2.4.5 Adolescents (12 to 16-18 years) (depends on the region or country)

This is a period of sexual maturation in which a medicine can interfere with the action of hormones and avoid normal development. In some studies, pregnancy testing and review of sexual activity and the use of contraception might be appropriate.

This is also a period of rapid growth and neurocognitive development. Medicines or the underlying disease itself can accelerate or delay the onset of puberty, and this may influence or have a profound effect on the pattern of development and therefore stature. The evolution of cognitive aspects and emotional changes might potentially influence the results of clinical studies. Many diseases are influenced by the hormonal changes around puberty (for example, the increase in insulin resistance in diabetes mellitus, the relapse of seizures at menarche, changes in the frequency and severity of migraine and exacerbation of asthma). Such hormonal changes can also affect the results of clinical studies.

Within this age group, adolescents assume more responsibility for health care and medication. For this reason, they are often confronted with problems with adherence to treatment, especially when treatment can affect appearance (for example, the use of steroids). Therefore compliance with treatment must be systematically checked, and it should also be taken into account that adolescents can ingest or use substances such as alcohol and tobacco as well as non-prescribed medications, which can influence the speed of biotransformation in the microsomal liver system.

The upper age limit in this category varies between regions or countries. Teenagers can be included in studies of older adults but can present problems in some aspects of treatment compliance. Given that teenagers offer challenges that are unique, it might be appropriate to consider studying adolescents in centers with knowledge and preparation in the care of this special population.

2.5 Ethical issues in Pediatric Studies

The pediatric population represents a vulnerable subgroup. Therefore, measures are required to protect the rights of participants and to keep away from any possible risk. The purpose of this part is to provide a general framework to ensure that pediatric studies are conducted under all the ethical requirements.

To benefit the participants as well as future pediatric patients, a clinical study must be designed with utmost rigor for the purpose of ensuring the quality and interpretation of data obtained. In addition, except in very special conditions, participants in clinical studies should be able to clinically benefit from their participation.

2.5.1 Independent Ethics Committee / Institutional Review Committee (IEC / IRC)

The functions and responsibilities of the Ethics Committees are described in the GCP Document of the Americas from the Working Group on Good Clinical Practice (WG/GCP) of the Pan American Network for Drug Regulatory Harmonization. The role of the Ethics Committee is critical to the protection of study participants, especially in vulnerable populations.

In the case of protocols in which children will be enrolled, if there were no members with knowledge concerning the subject, the consultation is recommendable to experts that have knowledge in the peculiarities in the pediatric studies, as well as the clinical point of view and clinical and physcosocial.

2.5.2 Recruitment

The recruitment of study participants should occur in a manner free from improper inducement for either parents or guardians or the children themselves. The cost, reimbursement or maintenance costs should be covered in the context of the clinical trial, and any compensation must be reviewed by the Ethics Committee. The inclusion of patients should be representative of the pediatric population of the region and of the disease being studied unless there is a valid reason to restrict enrollment.

2.5.3 Consent and Agreement

As a general rule, a pediatric subject is not legally competent to give consent. For this reason, pediatric study participants rely on parents or legal guardians to assume the responsibility for their participation in the study.

A fully informed consent must be obtained from the legal guardians according to the laws or regional or local regulations. However, given that participants should be informed of as much detail as possible about the study in language and terms that are suitable for their understanding, it is recommended that children give their assent, when this is appropriate. The age of assent should be determined by the local regulations. Pediatric participants of sufficient maturity should sign and date an assent form, which is a separate document from the informed consent signed. In all cases, pediatric participants should be informed of their right to withdraw from the study at any time. Attention should be paid to signs of discomfort or inconveniences when the patient is unable to express such discomfort more clearly. Although the desire to withdraw from the study should be respected, there may be special circumstances in therapeutic studies in which there is danger to life and in the opinion of the investigator and legal guardians, the welfare of the patient would be jeopardized if the patient were to withdraw from the study. In these cases, the consent of a parent or guardian may be sufficient to allow continuation in the study.

Older and emancipated children with autonomy in decisions (as defined in accordance with local laws) may be able to give their full autonomous consent. Whenever it is possible to obtain information from a less vulnerable population, information from a more vulnerable population or one that is not capable of providing consent should not be obtained. Studies in disabled children or institutionalized children should only be conducted if it is strictly necessary because of their disease.

2.5.4 Minimizing Risk

Any study carries a risk or probability that the individual may suffer discomfort or injury by participating, although it remains important to establish the safety and efficacy of an investigational product in the population that will be using that product. Every effort should therefore be made to anticipate and reduce all known risks. Investigators should be fully aware of all toxicity of the medicinal product found in earlier clinical and preclinical studies. To minimize risks in the pediatric population, all those who conduct the clinical trial should be adequately trained and have experience in studying the pediatric population, including evaluation and management of potential adverse events. In the study design, maximum effort should be exerted to minimize the number of participants and procedures, consistent with good study design. Mechanisms should be created to end the study quickly if unexpected serious risks or dangers arise.

2.5.5 Minimizing Discomfort

Repeated and invasive procedures may be painful or threatening, and may produce fears. Discomfort should be minimized, and this can be achieved if the researchers who design and conduct the studies have experience and knowledge in the treatment of pediatric disease. Research and protocols should be designed specifically for children and not merely adapted from a protocol tailored for adults. The protocol must be approved by the Ethics Committee as described in the corresponding section. Practical considerations to ensure that researchers and staff who lead the study have the appropriate expertise to minimize discomfort and inconvenience include:

-- Staff who are skilled in treating pediatric populations as well as knowledgeable of their needs by age group, including skill in procedures applied to children;

-- An environment with furniture, equipment, food and games appropriate for the age of the participants;

-- Performance of the study in a place that is familiar to the child, such as the hospital, clinic or institution where he/she usually gets medical care;

-- Study methods to minimize discomfort such as local anesthesia for placement of intravenous catheters, use of catheters to prevent repeated punctures, and collecting blood samples specified in the protocol at the same time samples are obtained for routine analysis.

The Ethics Committee should carefully review and consider whether the number of venipunctures is acceptable in the protocol and ensure an understanding of what would happen if an indwelling catheter fails. Participants have the right to refuse any study procedure unless refusing it involves risk to life (section 2.5.4).

2.5.6 Monitoring of the Study by the Ethics Committee

The Ethics Committee (EC) should establish procedures to track all studies approved or given a positive decision, from the moment the study is initiated until the completion of the research. The lines of communication between the EC and the investigator should be clearly specified. The frequency of monitoring will depend on the characteristics of the study drug, the characteristics of the study, and the disease being studied, as well as any conditions related to sanitary registration. The EC should optimally conduct monitoring of research processes including the obtaining of the informed consent/agreement as well as verification of any deviations from protocol that might compromise the autonomy, rights,

and safety of study subjects, allowing to establish and verify conditions for the continuation or discontinuation of the study.

2.6 Acceptance for Complete Information from Pediatric Studies Conducted in a Country Different from the One Where Registration is Sought for Marketing

In the case where registration of a medicinal product is sought for use in the pediatric population and the laboratory or productive center is located in another country, complete information is expected from all studies conducted on children in that country of origin. In no case, the necessary information will be excluded from the pediatric population or the demonstration that it was registered in the country of origin is specially in children.

2.7 Need to Conduct Clinical Trials in Children in the Country where will be Registered Due to Insufficient Data from the Country of Origin

As a general principle, clinical trials in children should not be conducted in a country of the region if there are no previous studies among the population in the country of origin of the laboratory. If there is insufficient information from pediatric studies in the country of origin and it results indispensable for not having therapies for the younger population in certain diseases and that could endanger the life of this population, clinical trials of safety and efficacy will be executed, even in the case that proceeds of laboratories of another country.

Clinical trials should be conducted at institutions that are accepted in research in children. Laboratories or promoters should be obliged to report the results of their studies, even if they are negative.

REFERENCES

This guideline was elaborated from the following document:

-Ethical Consideration for Clinical Trials on Medicinal Products Conducted with the Pediatric Population

-Recommendations of the ad hoc group for the development of implementing Guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use