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GUIDE FOR CONDUCTING CLINICAL STUDIES IN PEDIATRIC POPULATIONS

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1 - INTRODUCTION AND GENERAL PRINCIPLES

To provide adequate protection in special situations to vulnerable populations arouses special interest, because they are weaker and have a greater risk during the studies, especially with new medicines or pharmaceutical products.

Among populations and vulnerable groups are children, subject to the risk being seen as "therapeutic orphans" for being subjected to treatments that have been evaluated only in adults, without their safety and efficacy having been yet assessed in this age group, and because in some childhood diseases there are not enough pharmaceutical laboratories and production centers that provide safe and effective medicines for said diseases. For this reason, it is not convenient and it is unfair to exclude children from participating in clinical studies that must be conducted within the strictest scientific and ethical parameters.

Consideration should be given the relevant information about the appropriate use of the product in children of various ages and the appropriate pediatric formulation of these products. Advances in technology and formulations in the design of studies in children facilitate the development of products for pediatric use. Usually, the Program for Development of a product should include an evaluation of the pediatric population when studied for a disease or condition in adults and its use in children can be anticipated. A very important goal should be obtaining information from children but should always be done without jeopardizing the welfare of the pediatric patient participating in the clinical study. This responsibility should be shared by laboratories, regulatory authorities, medical professionals and society as a whole.

1.1 OBJECTIVES

The guide’s objective is to establish guidelines for clinical research for pharmaceutical products in children, and to allow the development of these studies in the Americas Region in a rigorous, scientific and safe manner. It will offer a group of critical aspects in the development and evaluation of a drug for pediatric use, safety, efficacy and handling of ethics in clinical trials in children.

2. SCOPE OF THE GUIDE

Specific aspects of clinical trials that include:

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

2.1.1 Pediatric formulations

2.2 Moments during the product development for conducting the studies.

2.3 Types of study: Pharmacokinetics-Pharmacodynamics, efficacy and safety

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2.6 Acceptance of the complete information from the studies conducted on children in the country of origin by the country where registration is sought for marketing .

2.7 The needs and requirements for clinical trials in children in the country where the product will be registered in case of insufficient data from the country of origin.

This guide is not exhaustive, it must be complemented with other guides from local and regional authorities and recommendations of pediatric societies.

2.1 When to start the Development Program of a medical pharmaceutical product for use in children

Information must be generated from the appropriate use of pharmaceuticals in the pediatric population unless it is clearly inappropriate for this population. The justification of the approach and timing of commencement of the Clinical Program must be consulted with the Regulatory Authorities in early stages and then systematically and periodically throughout the process. The Development Program in children should not be delayed waiting for the full results of use in adults or availability in the market, or move ahead without sufficient scientific and ethical justification.

Factors influencing the decision to launch the Development Program in Children and the nature of these studies are:

- The prevalence of the disease or condition to be treated in the pediatric population.
- The seriousness or severity of the condition to be treated.
- The availability and ease of alternative treatments for pediatric condition in question, taking into account the effectiveness, safety and adverse events profile of current treatment.
- The novelty of the product or whether it belongs to a compound with well-known properties.
- If the indication of the product is unique to the child population.
- The need to develop specific evaluation variables for the child population.
- The ranges of ages of pediatric patients likely to be treated with the medical pharmaceutical product.
- Unique safety aspects of the pharmaceutical product for the child population.
- Need development potential of the formulation for pediatric use.

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

The preliminary information related to product safety is produced mainly from information obtained from adults. Pre-clinical information must be available of repeated dose toxicity, genotoxicity and reproductive studies. Studies should be undertaken in young animals if necessary, which must be analyzed case by case depending on the toxicity of the product.

2.1.1 Pediatric Formulations

New formulations more suitable for infant use must be obtained, 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 it has brought fatal consequences, such as death by kidney failure in 107 children in 1938 due to the excipient diethylene of sulfanilamide.

In general these formulations should be in accordance with internationally harmonized standards in excipients as in 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, product safety and the safety and efficacy of the available treatments. If the development of a new formulation is required, it must be performed early in the product development.

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 must be obtained from adults. This information could 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 it could pose too much risk for adults. Examples include the surfactant in the respiratory distress syndrome of the newborn and metabolic 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 this condition would mean a start as soon as possible of the studies in pediatric population, which must be initiated once safety is studied and evidence is found 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 latter stages of studies in adults or in some cases, once the product is registered and its marketing is launched, providing substantial experience in adults.

Laboratories should have a Clinical Development Program for Child population, which usually should not be initiated before the end of phase II or III in adults. Taking into account that many Phase II studies fail to reach valid conclusions, children should not be subjected to a product that could not have benefit. The risk-benefit analysis on each product development program must be weighted to make the decision when to start.

2.3 Types of studies

When a medical pharmaceutical product is studied in a region's pediatric patients, the extrapolation of the results of this study to other regions should take into account the intrinsic (for example, Pharmacogenetics) and extrinsic factors (for example, diet) that might impact the extrapolation of the data.

When attempting to use a medical pharmaceutical product in the pediatric population in 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 data from children effectiveness in adults. In this case, pharmacokinetic studies in different age ranges defined for pediatric patients to receive medical pharmaceutical product, coupled with the safety studies, could provide adequate information for the use of the product, thus allowing the selection of pediatric doses that would yield optimal therapeutic levels of the product in blood. If it is decided that approach, the pharmacokinetic data from adults must be available for the design of pediatric studies.

When it is intended to use a medical product pharmacist in younger pediatric patients at the same indication that the studied and approved in older pediatric patients, the process of the disease is similar and it is likely that treatment outcomes are comparable, The extrapolation of efficacy data obtained in older pediatric patients may be possible if the maturation processes of

those main organs involved in the process of metabolism, and excretion of medicines has already been achieved in these patients. If this maturation has not been obtain yet, pharmacokinetic studies in this type of younger pediatric patients intended to receive the product, jointly with the safety studies, could provide adequate information for the use of the product in them.

An approach based on the pharmacokinetics may be insufficient: 1) for pharmaceutical products in which it is known or expected that blood levels do not match the efficiency, 2) if there is a possibility that the concentration-response relationship may differ between pediatric and adult populations. In these 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 the therapy in the pediatric patient is similar to that obtained in adults, although 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 efficiency and define the doses and concentrations necessary to achieve the pharmacodynamic effect on children. Such studies could provide a high confidence to assume that reaching a given exposure of the drug in pediatric patients the desired therapeutic response will be produced. Then, a PK / PD approach combined with the 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 is the case of medical pharmaceutical products for topical use, the extrapolation of the effectiveness of a patient population to another may be based on studies of pharmacodynamics 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 of the product and thus able to assess its safety . When seeking for 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 necessary to conduct clinical studies of efficacy in child population.

2.3.1 Pharmacokinetics

Generally pharmacokinetic studies should be done for the purpose of giving support to the development of the formulation and determine the pharmacokinetic parameters in different age groups and thus 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, which aims to use the medicine, final pharmacokinetic studies should be made in pediatric populations, which are usually performed in patients with the disease. The former can lead to higher inter-subject variability in studies with healthy volunteers, but the data reflect better the clinical use. For products that show linear pharmacokinetics in adults, single dose pharmacokinetic studies in the pediatric population may be sufficient to provide information on the selection of dosage. Conversely, if the kinetics is not linear in the absorption, distribution and/or elimination or is there any difference in the duration of effect between single dose and repeated doses in adults, it is necessary conduct steady state studies in the pediatric population.

The selection of the 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 of them of great use in designing studies in children. 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/m2 body surface area, clinical experience suggests that it is common errors of calculation by measuring the height or the length of the body surface area, particularly in infants and other young children. For some medications (for example, medicines with a narrow therapeutic index, such as in oncology), the use of a guide dosing-surface area would be required, although this is not enough 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 draw in pediatric studies should be minimized and justified in the protocols.

The Independent Ethics Committees / Institutional Review Committee (IEC/IRC) can review and determine the maximum amount of blood drawn with 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 to extract and/or the number of punctures for the extractions. For example, the use of laboratory techniques with small samples, the use of samples for analysis of routine research testing, use of special catheters that makes the extraction process less-intrusive and bloody.

2.3.2 Efficacy

The aspects about the design, selection of control group, and statistical considerations of studies in adults are generally applicable to pediatrics studies. However, there are some specific aspects for the pediatric population, where it is not possible to infer for children the efficacy results in adults. When these studies are required, it is necessary to develop, validate and employ response evaluation variables for each subgroup of age. 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 state of child development. Many diseases that appear in term-born and pre-term infants are unique or have manifestations that do not permit to extrapolate to older patients and therefore requires new methods of assessment in this population.

2.3.3 Safety

The concepts on safety documents that collect and report the description of adverse events are applicable to pediatric studies. The laboratory values must be tailored to age groups and should be used in the report of adverse events. The ingestion of the drug inadvertently, by accident, could be used to provide information safety of the potential adverse events and in some cases, contribute with elements of pharmacokinetics as well as better understand the relationship between dose and adverse events or side effects.

Some products may affect growth and physical development and/or cognitive of the child. The profile of these events will differ among different age groups for developing systems respond differently according to the maturity of the organ, and thus adverse events may appear that did not show up or were not identified in the studies of adults. Additionally, because the dynamics of the process of maturation and growth it is likely that the adverse event does not manifest in acute form but in the long term, affect the process of child development. The follow-up studies are of great importance in the medium and long term as well as pharmacovigilance data in order to determine possible effects on the body such as in the osteomioarticular, cognitive, sexual and maturation of the immune system.

2.3.4 Studies and post-marketing information

Normally the databases of pediatric studies are limited to the time of approval required in the health registry. However, the pharmacovigilance can be very important in determining the closest effects, especially in the process of growth and development of the child in its various stages. Similarly, long-term monitoring studies can provide more information on safety and efficacy in different age groups.

2.4 Classification according to the age of the pediatric patients

The classification according to age groups provides a basis for approaching the study design and stratification to achieve better homogeneity of these groups. The decision of how to stratify and the difference between these strata is related to biological and pharmacological variables of the groups. Therefore, a flexible approach is needed to ensure that the studies reflect current knowledge of pediatric pharmacology. The identification of what are the ages to study must be specific for the medicinal product and must be justified. For the foregoing, it is important to specify in what age groups there is a noticeable difference in terms of pharmacological therapy, especially in "drug clearance" and other pharmacological variables. If the route of clearance 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. 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 the efficacy various variables can

be set according to age group, but it may not always coincide with the classification proposed below. If the population is divided into many groups of the study may unnecessarily increase the sample size required. In long-term studies, patients are moved from a range or group to another, so the design and statistical analysis planning must take into account these changes in number within each category. The following classification is a possible categorization. However, it can have overlap in areas of development (physical, cognitive and psychosocial). The ages are defined in elapsed days, months and years.

2.4.1 Pre-term Newborn
2.4.2 Term-born infants
2.4.3 Sucklings and infants (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 the products in pre-term newborns is a special challenge because of the pathophysiology and therapeutic response, unique in this population. The complexity and ethical considerations of studies in this child population require a carefully protocol developed with experts, not only in neonatology, but also in pharmacology. In this population, the results from adults and children can rarely be inferred. The category of newborn babies is not entirely uniform, since a newborn of 25 weeks of 500 grams is very different from a newborn 30 weeks of 1500 grams. Another distinction must be made between newborns with low birth weight and those who have retarded growth and development by the impact on the maturity of organs such as kidneys and liver and their possible connection with the clearance of the drug. Therefore, the following should be considered:

a) Gestational age and time since birth.

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

c) The limits of protein, especially bilirubin, as well as 1 - glycoprotein for their binding or not with the medicines to be studied and their impact on the blood concentration of these and their possible adverse reactions.

d) Transfer of the product into the Central Nervous System

e) Unique status of the newborn (distress syndrome of the newborn, persistent ductus arteriosus, primary pulmonary hypertension)

f) Conditions that can only occur in newborns (necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of the premature baby)

g) Metabolic processes in physiological maturation processes that lead to very quick variable doses schemes and of chronic exposure

h) Transdermal absorption of medicines and other chemicals

The study design should take into account:

1) Weight and age

2) Small volumes of blood (a newborn has 40 grams of 500 ml of blood)

3) Small numbers of patients in different clinical centers and the possible differences between centers in relation to the management of patients.

4) Difficulties in the evaluation of response variables.

2.4.2 Term-born infants (0 to 27 days)

Although the term-born infants develop a more mature than pre-term born, many of the physiological and pharmacological principles apply to this population. The volumes of distribution of the products may be different with regard to older children because of the fat and water content and the high relationship of body surface and weight. The brain-blood barrier is not mature enough and can show some toxicity due to a greater passage of endogenous substances to central nervous system (e.g. bilirubin). The absorption of oral medicines could be less predictable than in older pediatric patients. The mechanisms for clearance in kidney and liver are immature and with rapid change, so the dose must be adjusted during the first weeks of life.

An increase in susceptibility to the toxic effects may arise due to limited clearance in these patients (gray baby syndrome by chloramphenicol). Moreover, the term-born infants may be less susceptible to certain types of adverse effects (nephrotoxicity by aminoglycosides) than in 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. The absorption by the oral pathway is more reliable. The pathway of hepatic and renal clearance mature very quickly and by one year and two years of life, the clearance of many medicines on the basis of mg per kg may exceed the values of adults.

The developmental pattern of maturation of clearance depends on the specific clearance pathway. The variability of maturation between individuals is very common and can be substantial.

2.4.4 Children (2 to 11 years)

In this age group because many pathways of clearance of medicines (liver and kidney) are mature with clearance rates that sometimes exceed that of adults. The changes in the clearance of a drug may be depending 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 developmental milestones that could be affected by active medicines of the central nervous system. The entry into school and increased cognitive and motor skills can affect their ability to participate in certain types of clinical trials. The development of the skeleton, weight gain, school attention and performance of school performance factors are useful in measuring the effect of a drug in children. The recruitment of patients must ensure representation in all age ranges in this category and it is important to ensure sufficient number of younger patients. Stratification by age within this category is unnecessary though it may be appropriate to stratify based on the pharmacokinetics or aspects of the evaluation of effectiveness.

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 decrease 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 postpuberal patients. In other cases it may be appropriate to register the Tanner stages of development of puberty and obtain biological markers of the same and to examine the data to detect any potential influence on 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 prevent the normal development. In some studies the pregnancy test and review of sexual activity and the use of contraception might be appropriate.

This is a period of rapid growth and neurocognitive development. The medicines or the 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 in stature.

The evolution aspects of cognitive and emotional changes could 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). Hormonal changes can 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), and should therefore compliance of treatment must be systematically checked and it should be taken into account that adolescents can ingest or use substances such as alcohol and tobacco and any 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 some aspects of treatment compliance. Given that teenagers offer challenges that are unique, it might be appropriate to consider the study of adolescents in centers with knowledge and preparation in the care of this so special population.

2.5 Ethical issues in pediatric studies

The pediatric population represents a vulnerable subgroup. Therefore, it requires special measures to protect the rights of participants and to remove them 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 and future 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 it.

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

The functions and responsibilities of the Ethics Committees are described in the proposed procedure under the Working Group on Good Clinical Practice (WG/GCP) from 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 the protocols in which children will be incorporate, if there were no members with expertise in the subject, consulting experts who have knowledge on the peculiarities of studies in children is advisable, both from ethical as from a clinical and psychosocial points of view.

2.5.2 Recruitment

The recruitment of study participants should not be subject to pressure or be improperly induced to participate, both to parents or guardians or the children themselves.
The costs, 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 must be representative of the child population of the region and of the disease being studied unless there is a valid reason to restrict it.

2.5.3 Consent and agreement

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

A full consent must be obtained from their 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 consent, where this is appropriate. The age of consent that must be determined by the local regulations. Participants with an appropriate maturation development must sign and date the form of written informed consent, designed separately from the informed consent. In all cases, participants will be informed of their right to withdraw from the study at any time. Attention should be paid to signs of discomfort or inconveniences that show the patient is unable to express it 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 that to the discretion of the investigator and legal guardians, to expose the patient if the patient were to withdraw from the study. In these cases the consent of a parent or guardian may be sufficient to allow the 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 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 must not be obtained. The studies in disabled children or children interned in care institutions should only be incorporated 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 when included in it, although it is very important to prove its value and the positive or negative result of resulting in a final benefit for the child population. For these reasons, effort shall be made to anticipate and reduce all known risks. Investigators should be fully aware of the toxicity and relevant events found in earlier clinical and preclinical studies. To minimize the risks in child population, all those who conduct the clinical trial should be adequately trained and have experience in studies in child populations, including evaluation and management of potential adverse events.

In the study design, maximum effort should be exerted to reduce the number of participants and procedures to be employed, consistent with all this good design. Mechanisms should be created to end the study quickly if any risks or dangers appear during the same.

2.5.5 Minimizing discomfort

Repeated and invasive procedures could be painful or threatening, and they could produce fears. Discomfort should be minimized and this can be achieved if the researchers who design and conduct the studies have the experience and knowledge in the treatment of pediatric diseases. Protocols and research 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:

Staff skilled in treating child populations as well as knowledgeable of their needs according to the age group they correspond to and of the procedures that should be applied to children.
An appropriate place with the furniture, equipment, food and games appropriate for the age of the participants.
The performance of the study in a place that is familiar to the child, such as the hospital, clinic or institution where he usually gets his medical care. Approaches in the study to minimize discomfort such as local anesthesia for placement of intravenous catheters, use of catheters to prevent repeated punctures as well as collecting some blood samples specified in the protocol when samples are obtained for routine analysis.
The Ethics Committee should carefully review and consider whether the number of punctures is acceptable to the protocol and ensure foreseeing what would happen if the use a catheter all the time fails. Participants have the right to refuse use of any procedure unless refusing it involves risk to life (section 2.5.4).

2.5.6 Monitoring of the study by the Ethics Committee

The EC should establish procedures to track all the studies to which they responded with a positive decision, from the moment that it was taken until the completion of the research. The lines of communication going on between the EC and the investigator should be clearly specified. The frequency of monitoring will be in connection with the characteristics of the study drug, and the disease being studied as well as aspects related to the health registration.
The EC should also provide visits for monitoring the process at research in the gathering of the informed consent/agreement as well as verification of the deviations from protocols that might compromise the autonomy, rights and safety of study subjects, which will allow establishing conditions for the continuation or discontinuation of the studies.

2.6 Acceptance of the complete information from the studies conducted on children in the country of origin, by the country where registration is sought for marketing.

In the case of those medicines that will be registered for use in the child population and the laboratory or production center originated in another country, information is required from studies

in children in the country of origin. In no case whatsoever the necessary information from the child population or proof that it was registered in the country of origin specifically for children will be foregone.

2.7 Need to conduct clinical trials in children in the country where the medicine will be registered due to insufficient data from the country of origin

As a general principle, clinical trials in children in a country of the region should not be conducted if there are no previous studies in this population in the country of origin of the laboratory. If the medicine does not have adequate information of the child population and it were indispensable due to unavailability of treatment for children in certain diseases and that could endanger the lives of this population, clinical trials for safety and efficacy will be performed, even if there were appropriate laboratory studies from other countries.

Clinical trials will be conducted at institutions that are approved by regulatory authorities for their knowledge and experience in research in children. The laboratories or sanitary officers will be obliged to report the results even if they are negative.