METHODOLOGICAL ASPECTS OF DEVELOPMENT MEDICINES FOR CHILDREN

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To date only a small number of medicines exist in specifically designed for children dosage forms. That is why the acute question is to continue scientific research in the field of children's medicines, which should be based on a common methodological approach to pharmaceutical development of medicines meeting the requirements for specific dosage forms. The aim of this work is to study the methodological aspects of development medicines for children with existing requirements for pharmaceutical medicines development for use in pediatric practice in the European Union. During the analysis of existing regulations, it was found that when choosing a design of children's medicines, primarily, it is necessary to pay attention to: the characterization of the active substances, methods of using medicines and dosage forms, dosing frequency, characteristics of excipients, the choice of containers and weighing devices. Composition of medicines intended for use in pediatric patients, including the concentration of active ingredients should be verified both theoretically and experimentally, and should be attributed the role of each adjuvant. Also it should be noted that the diversity and specificity of physical, metabolic and psycho-physiological processes are responsible for the inability to consider children as a homogeneous group in a certain age group and emphasize the need for the development of medicines for specific pediatric age groups.
**Introduction.** According to WHO statistics, more than 9 million children of age under 5 years die each year from diseases that can be treated with safe and effective medicines. However, the lack of medicines for children, especially in developing countries and the use of existing medicines in violation of instructions of application leads to an increase in infant mortality [2, 6].

To date, only a small amount of medicines is in a specially designed for children dosage forms, but often even they are not available. For example, each year in the world of almost 3 million children die from diarrhea and pneumonia. It is known that, there is a treatment for diarrhea in the form of oral rehydration salts and zinc, but studies show that these medicines are often absent in pharmacies and clinics of countries where these diseases are the most common [8, 9].

In the absence of special children's medicines, health professionals and parents often share adult dosage forms by crushing tablets or partial dissolution of capsule contents in water. The process of making these "medicines" is rather difficult for parents and those who take care of the child, and taking them can have serious consequences. As a result of such dosage is incorrect medicine administration for the child in the lack or in the excessive amounts that leads to the development of a number of adverse reactions [1, 10, 11, 12].

That is why the acute question is to continue scientific research in the field of children's medicines, which should be based on a common methodological approach to pharmaceutical development of medicines meeting the requirements for specific dosage forms. Diversity and specificity of physical, metabolic and psycho-physiological processes are responsible for the inability to consider children as a homogeneous group in a certain age group and emphasize the need for the development of medicines for specific pediatric age groups.
The aim of this work is to study the methodological aspects of development medicines for children with existing requirements for pharmaceutical medicines development for use in pediatric practice in the European Union [3, 4, 7].

Results. It is known that medicines are composed not only of biologically active substances - the main carrier of the therapeutic effect, and with combinations of chemicals both organic and inorganic (preservatives, stabilizers, fillers, emulsifiers, etc.). The specified combination should provide not only the stability of medicines quality in the manufacture and storage, but also the necessary conditions for the release and absorption of the active substance, which will permit to develop effective and safe medicine. Composition of medicines intended for use in pediatric patients, including the concentration of active ingredients should be verified both theoretically and experimentally, and should be attributed the role of each adjuvant [5, 13, 14].

When choosing a design of children's medicines, primarily, it is necessary to pay attention to: the characterization of the active substances, methods of using medicines and dosage forms, dosing frequency, characteristics of excipients, and the choice of containers and weighing devices.

In the development process of children's medicines can be used various chemical modifications of active substances according to developed dosage form. Thus, the production of liquid medicines usually requires the use of readily soluble substances; however the compliance of children may be increasing due to the choice of a less soluble form, such as the base instead of salt. Moreover, the safety of medicines in children can be achieved by excluding from their composition inorganic anti-ions and organic salts [3, 5].

Various routes of administration and / or dosage forms may be required for the same active substance in order to ensure the desired effect in the treatment of children of different age groups. Choice of routes of administration and dosage form should also include aspects and compliance of patients, for example, the amount of pills, taste etc. Ad-
vantages and disadvantages of routes of administration and dosage form should also be considered, taking into account other aspects of the medicine. For example, the choice of a liquid dosage form usually is accompanied by a choice of metering device and preservative, if it is impossible to suggest other ways of ensuring microbiological purity of the medicine [7, 13].

In developing of oral medicines should primarily focus on the size of solid dosage forms as the main factor that determines the ability of a child to swallow them and on the appearance, which must be different from the confectionery candies, and also on the volume of solvent to dissolve the soluble tablets which should be determined according to the age group of children.

If in a certain age group of children is still a need for shredding of solid dosage forms such as tablets, it should be considered the impact of crushing on the taste of the medicine, compliance of patients, bioavailability of medicinal substances. In necessity of disclosure of hard capsules before applying their contents should comply with the same requirements as powders, pellets or granules. necessity of disclosure of soft capsules - with the requirements for liquid oral dosage forms. When using capsules unchanged, it is necessary to justify their size for each age group of children based on their health.

In developing of oral liquid dosage forms, including drops, it is necessary to justify their size, which is determined by the physical design and dropper characteristics, physicochemical properties and methods of drops dosing. The maximum number of drops per one time should not exceed 10 (about 0.5 ml). Accurate dosing and volume of drops should be determined on the basis of their critical dose.

In developing of oral medicines with modified release of active ingredients, special attention should be paid to the physiological characteristics of children, such as the pH of gastric juice, gastrointestinal motility, because these characteristics affect the ab-
sorption of medicines. These factors should be taken into account at the stage of testing in vitro.

When creating medicines for oral mucous use it is necessary to justify their size and shape for each age group of children. To reduce the risk of swallowing liquids for mouthwash and dental gels among young children, these medicines should be used with a cotton cloth or swab [3, 7].

Medicines for nasal application require the development of special dispensers for nasal administration which are chosen based on the size of the nostrils and nasal cavities for each age group of children.

Medicines under pressure can be used to treat children from birth with special pads and mask. Older children can use inhalers with spacers. Inhalers that contain dry powder may be used only by older children (teenagers) because the dosage in this case is in the process of self-breathing.

In developing medicines for rectal administration size and shape of suppositories should be consistent with the age and height of the child [3].

When creating medicines for cutaneous application special attention should be paid on the size and form of transdermal therapeutic patches which having to depend on the size and shape of the body of the child and should not interfere with it daily life. Patches should be developed as one dose dosage form with the cut for further dosing.

To prevent the use of potentially toxic preservatives it is necessary, especially for infants, to develop single-component or multicomponent eye and ear medications that do not need to add them.

For medicinal products for parenteral nutrition, especially for premature infants should be normalized size of solid particles, viscosity, volume, single dose and compatibility of medicine with packaging material.
Selection of *frequency mode of dosage* of any medicine should be made taking into account the characteristics of the active substance, clinical effect, which is expected (immediate or extended) and the compliance of the child.

A key element in the pharmaceutical development of medicines for use in pediatric patients is a *choice of excipients*. Although in the development of medicines for children all the basic aspects of the choice of excipients remain unchanged, such as for adults, need to pay extra attention to their safety profile (Fig. 1). In general, in choice of excipients for children's medicines should be taken into account the following aspects: technological properties of excipients, their safety profile for different age groups of children, the estimated duration of treatment, baby health, features of the disease, adaptability of excipients, the presence of allergic action.

Safety of excipients, depending on specific age groups of children and route of administration of the medicines, can vary from no side effects to the contraindications to their use. In situations when you want to use adjuvant with an estimated index of risk for the health of children in the development of a dosage form, you should clearly relate the possibility of it use and the application of other existing medicines that do not contain in their composition of excipients [7, 14].

Medicines for children should not normally contain coloring agents. Use of any dye in pediatric practice must be reasonable and justifiable in terms of the possibilities of potential allergic reactions, minimal toxicological effects in specific age groups of children, errors in dosage. In necessity of differentiation of similar medicines for preventing mistakes, it is better to change their appearance - the shape and size instead of adding dyes of different colors. Inappropriate for pediatric practices are azole dye.

If medicine contains flavorings, it is necessary to ensure the implementation of qualitative and quantitative analysis and identify potential safety problems when used [3, 4, 13].
Figure 1. Decision tree to assess the safety profile of existing excipients in the development of children's dosage forms for specific age groups.
The need of adding preservatives into children's medicines and their choices in minimal concentrations should be investigated and explained. In necessity to use more than one preservative explore their individual and combined toxicity.

When choosing tasters and their concentrations must be considered: the impact of sugars on the teeth of the child (the possibility of dental caries), dosing regimen (once a day or more), duration of medicine use (short-term use (e.g., an antibiotic) or long-time (e.g., antiepileptic agents)), compatibility with other components.

Assessment of compliance of the medicine should be an integral part of the pharmaceutical development of medicines for children. It is determined directly by patients when assessing the features of medicines, such as their size and shape, dose, frequency of dosing required, dosing device packaging and the actual method of medicine administration for child [3, 5, 7].

Containers and metering devices should be designed for use in different age groups of children. Combination container with dosing device should allow the contents of the container easily flow to the dispenser and easily leave it. Unless otherwise specified, container systems for ambulatory use by children should be discrete and portable.

The size of the container must be justified in terms of recommendations for the dosage regimen and its duration for each age group of children, random errors in dosage, casual reception the entire contents of the container, environmental waste. For liquid formulations contents of the container should be not less than 10-fold relative to the recommended single dose [7, 14].

Conclusions.

1. The current requirements for pharmaceutical development of medicines for use in the pediatric practice in the European Union are analyzed.
2. The main methodological aspects of development medicines for children, taking into account characteristics of the active substances, methods of use and dosage
forms, dosing frequency, characteristics of excipients, container and dosing devices selection are given.

3. The necessity of development of medicines for specific age groups of children due to the inability to consider them as a homogeneous group in a particular age category is shown.
References