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the Eurasian Economic Commission
of , 20

GUIDELINES
on Preclinical Safety Studies in Order to Conduct Clinical Studies and Registration of Medicinal Products

I. General Provisions

1. The purpose of these Guidelines is to introduce international standards for the implementation and speeding-up of the harmonisation of the preclinical safety studies required for clinical studies of a certain nature and duration, as well as for registration of medicinal products in the Eurasian Economic Union.

2. These Guidelines have the following objectives:

Safe and ethical development and introduction of new medicinal products;

Timely conduction of clinical studies;

Decreased usage of laboratory animals in accordance with the 3R principles (replacement, refinement, reduction);

Decreased use of other resources within the development of medicinal products.

It is necessary to take into account the possibility of using new alternative *in vitro* safety evaluation methods, which can replace the existing standard methods subject to their proper validation and approval by the expert organisations of the member states of the Eurasian Economic Union (hereinafter referred to, respectively, as the Member States, the Union).

3. The instructions in these Guidelines are prepared to harmonise preclinical safety studies aimed at justification of the clinical development at various phases.

4. These Guidelines reflect the agreements on the type and duration of preclinical safety studies and the timing of conduction thereof as the justification for clinical studies and registration of medicinal products.

5. Preclinical safety evaluation for registration of medicinal products provides for conducting the pharmacological studies, studies of general toxic characteristics, toxicokinetic and preclinical pharmacokinetic studies, reproductive toxicity studies, genotoxicity studies, as

well as the assessment of carcinogenic potential for medicinal products of special concern or medicinal products intended for long-term usage.

6. The necessity of other preclinical studies to assess phototoxicity, immunotoxicity, toxicity to immature animals and the predisposition to development of the medicinal product dependence shall be determined on an individual basis. These Guidelines reflect the relationship between the necessity in preclinical safety studies and the clinical studies in humans.

7. These Guidelines cover the situations which routinely occur within the development of medicinal products, they shall be considered as general instructions for the medicinal products development. Planning and design of preclinical safety studies and clinical studies in humans shall be based on an approach being satisfactory from the scientific and ethical points of view.

8. The corresponding safety studies of the biotechnological medicinal products shall be conducted in accordance with the Rules for the Biological Medicines Study of the Eurasian Economic Union, as approved by Decision of the Council of the Eurasian Economic Commission No. 89 of November 03, 2016.
In case of studying of such medicinal products, these Guidelines provide instructions only for the timing of the preclinical studies, depending on the phase of the clinical development thereof.

9. Medicinal products developed for the treatment of life-threatening and serious diseases (for example, advanced cancer, resistant HIV infection, conditions related to congenital enzymatic impairment) and lacking the effective therapy also require an individual approach both to the toxicological evaluation and clinical development in order to optimise and speed-up their development. In these cases, as well as for medicinal products based on innovative therapeutic methods (for example, small interfering RNA (siRNA) and adjuvant vaccines) certain studies can be reduced, postponed, omitted or added. It is necessary to follow the instructions of the Union or the Member States on the specific groups of medicinal products, if any.

10. Preclinical safety studies of medicines shall be conducted taking into account the requirements of Clauses 34 and 35 of the Rules for Registration and Examination of Medicines for Application in Humans, as approved by Decision of the Council of the Eurasian Economic Commission No. 78 of November 03, 2016 (hereinafter referred to as the “Rules”).

11. Preclinical safety studies conducted out of the territory of the Union shall comply with these Guidelines and other regulations forming the law of the Union in the sphere of circulation of medicines.

12. The applicants are entitled to seek advice on the issues that are not covered hereby in accordance with Clause 26 of the Rules.

13. Development of a medicinal product is a gradual process that involves the evaluation of the data on the medicinal product effectiveness and safety, both in animals and in humans. The objectives of the preclinical safety evaluation, in general, are as follows:

establishment of characteristics of toxic effects on the target organs;

dose dependence;

exposure dependence;

potential reversibility (as appropriate).

14. This information is used to determine the initial safe dose and the dose range in human studies, as well as to determine the parameters for clinical monitoring of the potential adverse effects.

15. Preclinical safety studies, although limited at the beginning of their clinical development, shall be sufficient to describe the potential adverse effects that may occur in a justified clinical study.

16. Clinical studies in humans are conducted to study the effectiveness and safety of a medicinal product, starting from a relatively low system exposure in a small number of persons. These are followed by clinical studies in which the medicinal product exposure increases, usually as the result of the duration of use and (or) the size of the patient population.

17. Clinical studies shall be extended following the results of the previously conducted clinical studies confirming the sufficient safety, as well as on the basis of additional preclinical safety data that become available as the clinical development advances.

18. Serious adverse clinical and preclinical effects may impact the continuation of the clinical development. In order to determine the feasibility of conduction and the design of additional preclinical and (or) clinical studies, these data shall be considered within the overall clinical development plan.

19. Clinical studies are conducted in phases which may have different titles. These Guidelines use the concepts contained in the Guidelines on General Clinical Studies Issues, as approved by the Eurasian Economic Commission (hereinafter referred to as the “Commission”). As there is a trend to unite the phases of clinical development, this document specifies a number of requirements to preclinical studies in some cases not by phases, but by the nature of clinical studies, as well as by the characteristics of the subjects involved.

II. Selection of maximum doses in the general toxic characteristics studies

20. In general, the potential clinically significant effects in toxicology studies can be characterised by administering doses up to the MTD range. The MTD shall not be established for each study.

21. Other suitable dose limits include doses providing high multiple exposures, exposure impregnation or the use of MFD. These limiting doses provide for not using the doses on animals that do not represent additional value for clinical safety forecast (Figure 1). These instructions are consistent with the Guidelines on the design of reproductive toxicity and carcinogenicity studies for which the limiting dose and / or exposures were determined.[3,4]

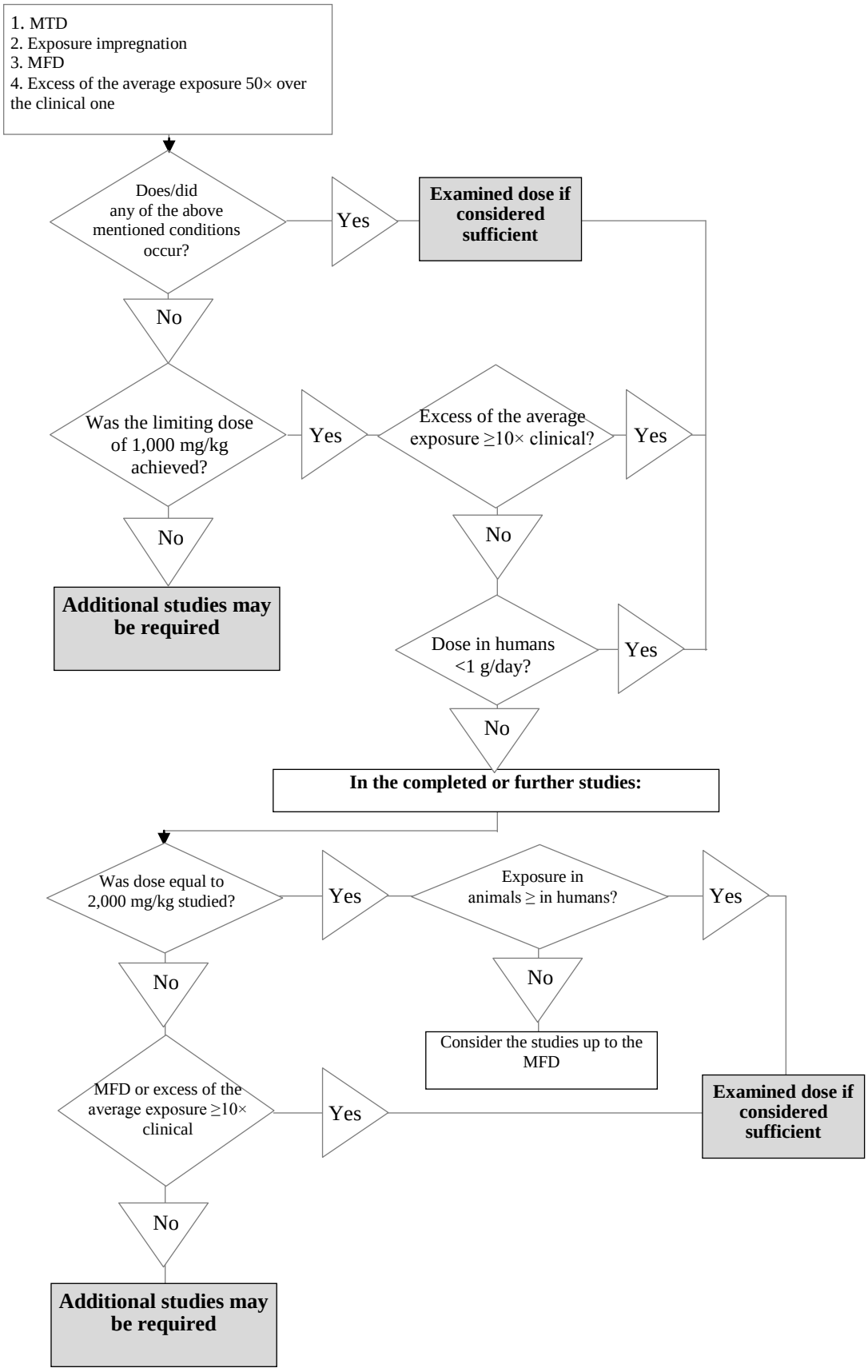
22. Limiting doses for toxicity studies for single and repeated (multiple) administration, are equal to 1,000 mg / kg / day for rodents and non-rodents, and were considered appropriate in all the cases, except for those listed below. In some cases, if the dose of 1,000 mg / kg / day does not provide 10-fold excess of the clinical exposure, and the clinical dose exceeds 1 g / day, doses in toxicological studies shall be limited to 10-fold exposure, or the dose of 2,000 mg / kg / day, or the MFD, whichever is less. In cases where the dose of 2,000 mg / kg / day is below the clinical exposure, an increase in the dose up to the MFD may be required.

23. Doses of 50-fold exposure (usually determined by the group mean AUC[1] value of the parent compound or a pharmacologically active pro-drug molecule) compared to the systemic clinical exposure, in general, are also acceptable as the maximum dose in the studies of acute toxicity and toxicity with multiple introduction in all animals.

24. In order to substantiate Phase III of the clinical studies, it is usually necessary to specify the dose-limiting toxicity on one (or more) type of animals with the limiting dose providing 50-fold excessive exposure. Otherwise, it is recommended to conduct a one-month or a longer study in one species of animals with the limiting dose of 1,000 mg / kg, the MFD or the MTD, whichever is less. Such a study may not be required if the study with a shorter duration established the dose-limiting toxicity in doses exceeding the dose of the 50-fold excessive exposure.

25. If the studies of general toxicity include genotoxicity endpoints, the appropriate maximum dose shall be selected based on the MFD, the MTD, or the limiting dose of 1,000 mg / kg / day.

Figure 1 Recommendations for the selection of the maximum doses in the general toxic studies



III. Pharmacological studies

26. Pharmacological safety studies and pharmacodynamic studies are defined in the Guidelines for study of the pharmacological safety of medicinal products for use in humans, as approved by the Commission.

27. The main battery of pharmacological safety studies provides for the assessment of the impact on the cardiovascular, central nervous and respiratory systems, which, usually, need to be carried out before the beginning of the clinical development in accordance with the principles established in the Guidelines for study of the pharmacological safety of medicinal products for use in humans, as approved by the Commission.

28. Additional and subsequent studies of pharmacological safety, if necessary, may be carried out at the later stages of the clinical development.

29. In order to reduce the use of animals, whenever possible, it is necessary to consider the possibility of evaluating certain endpoints *in vivo* within the general toxicity studies.

30. Moreover, primary pharmacodynamics studies (*in vivo* and (or) *in vitro*) are aimed at establishing the mechanism of action and (or) effects of the substance with respect to its intended therapeutic target. Such studies are usually conducted in the initial phase of pharmaceutical development and, thus, do not comply with the requirements of good laboratory practice. The results of these studies can contribute to the dose selection, both for preclinical and clinical studies.

3.1. Toxicokinetic and pharmacokinetic studies

31. Before conducting the clinical studies, it is usually necessary to assess the metabolic profile and the degree of fixation to the plasma proteins in animals and in humans *in vitro*, as well as the data on system exposure in animal types used to study toxicity in case of multiple administration (the Guidelines to study toxicokinetics: evaluation of the system exposure in toxicological studies, as approved by the Commission).

32. Before application of the medicinal product on a large number of subjects or for a long time (usually before the onset of Phase III), it is necessary to have a more detailed data on the pharmacokinetics (including information on absorption, distribution, metabolism and excretion) in the test animal types and *in vitro* biochemical data that are significant for identification of the potential medicinal product interactions. These data are used to compare the metabolites of humans and animals, as well as to determine the necessity in additional tests.

33. Preclinical establishment of metabolite characteristics in humans shall be conducted only when the said exposure exceeds 10% of the total exposure of the medicinal product and the exposure value in humans is significantly higher than the exposure registered in the toxicological studies. Such studies shall be conducted to justify Phase III of the clinical studies. In case of medicinal products with a daily dose of less than 10 mg, a larger fraction of the medicinal product may become an acceptable justification for the study. Some metabolites do not incite toxicological concerns (for example, the majority of glutathione conjugates) and do not require the conduction of any study. Preclinical establishment of the metabolite characteristics with the specified cause for concern (for example, a person-specific metabolite) shall be considered on an individual basis.

3.2. Acute toxicity studies

34. Data on the acute toxicity traditionally was obtained within the toxicity studies with a single administration in two mammalians using clinical and parenteral modes of administration. However, this information can also be received from the appropriately conducted dose escalation studies or short-term dosing range studies, which provide for specification of the MTD in animals used in the general toxicity studies.

35. In case of information about any acute toxicity from other studies, a separate study with a single administration is not required. If the administration of a medicinal product under clinical conditions is justified by the relevant toxicity studies with the multiple administration within the framework of the Rules of Good Laboratory Practice of the Eurasian Economic Union in the sphere of circulation of medicines, as approved by Decision of the Council of the Eurasian Economic Commission No. 81 of November 03, 2016, it is permitted to limit the single administration toxicity (acute toxicity) studies with this clinical mode of administration or use the data from the studies which were conducted with no adherence to the requirements of the Good Laboratory Practice. Mortality in the toxicity studies for single administration (acute toxicity) shall not be a target endpoint.

36. In specific cases (for example, in the study of microdoses), the acute toxicity studies or the single administration studies may serve as the major justification for studies in humans. In such cases, the selection of the maximum dose may differ from the one described in Section II hereof, but it shall correspond to the planned clinical dose and to the mode of administration. These studies shall be conducted in accordance with the Rules of Good Clinical Practice of the Eurasian Economic Union, as approved by Decision of the Council of the Eurasian Economic Commission No. 79 of November 03, 2016.

37. Information about the acute toxicity of a medicinal product can be used to foresee the consequences of an overdose in humans, so they shall be available to justify Phase III studies. When examining the indications in populations of patients facing the high risk of overdose (e.g. depression, pain, and dementia), an earlier evaluation of acute toxicity might be required within the outpatient clinical studies.

3.3. Multiple administration toxicity studies

38. The recommended duration of the toxicity study in case of multiple administration, in general, depends on the duration, indications for use and the direction of the planned clinical study. The duration of toxicological studies in animals conducted in two species of mammals (one of which is other than rodents) shall usually be equal or exceed the duration of the clinical studies up to the maximum recommended duration of the toxicity studies with multiple administration (Table 1). The limiting doses (exposures) suitable for toxicity studies with multiple administration are described in Section II hereof.

5.1. Clinical development studies

39. Studies of toxicity in case of multiple administration in two species of animals (one of which is other than rodents) with a minimum duration of two weeks (Table 1) are usually sufficient to support all clinical studies of the development up to two weeks.

40. Longer clinical studies shall be justified by the toxicity studies with multiple administration of at least the same duration. 6-month studies in rodents and 9-month studies in non-rodents usually provide the grounds for dosing in clinical studies exceeding 6 months (exceptions are provided in footnotes to Table 1).

Table 1

Recommended duration of studies
in case of multiple administration required for justification of
the clinical studies

Maximum duration of the clinical study	Recommended duration of toxicity studies in case of multiple administration required for justification of the clinical studies	
	rodents	non-rodents
Up to 2 weeks	2 weeks [1]	2 weeks [1]
2 weeks to 6 months	The same as in clinical studies [2]	The same as in clinical studies [2]
> 6 months	6 months [2,3]	9 months [2, 3, 4]

[1] A possible alternative to 2-week studies to justify clinical study with a single administration is an extended toxicity study with a single administration (footnote 3 to Table 3). Clinical studies of at least 14 days can be justified by studies of toxicity of the same duration.

[2] In some cases, clinical studies of more than 3 months can be started with the results of a 3-month study in rodents and a 3-month study in non-rodents, if the complete results of the clinical study of the chronic toxicity in rodents and non-rodents in accordance with local regulatory procedures for conducting clinical studies will be provided before the dose period is exceeded. In case of serious or life threatening indications or on an individual basis, studies can be prolonged subject to the results of the completed chronic toxicity studies in rodents and the results of *in vivo* studies and necropsy data of the study in non-rodents. Comprehensive pathohistological data in non-rodents shall be obtained within the next 3 months.

[3] In some cases, the main population is children, whereas the available pre-clinical animal studies (toxicological or pharmacological) indicate potential ontogenetic risk to target organs. In these cases, the long-term toxicity studies in immature animals may be required in certain circumstances.

[4] In some cases, the main population is children, whereas the available pre-clinical animal studies (toxicological or pharmacological) indicate potential ontogenetic risk to target organs. At the same time, if the longer-term studies are conducted, an additional 6-month study shall not be required. Below please find the examples of the situations when 6-months studies in non-rodents are also sufficient:

if immunogenicity or intolerance distort longer-term studies;

in case of a multiple short-term exposure, even if the duration of the clinical study exceeds 6 months, for example, in a situation of occasional treatment of migraine, erectile dysfunction or herpes catarrhalis;

a medicinal product intended for a long-term use to reduce the risk of recurrence of cancer;

a medicinal product intended for use on indications with a short life expectancy foreseen.

5.2 Registration

41. Due to the size of population at risk and a relatively less controlled clinical practice conditions, in contrast to the clinical studies, the longer preclinical studies can be valuable. The duration of toxicity studies with multiple administrations required to justify the therapy of different duration is given in Table 2. At the same time, in case of a small number of health conditions with a recommended duration of application from two weeks to three months, when a vast clinical experience confirms a more extensive and longer use in excess of the recommended use (e.g. anxiety, seasonal allergic rhinitis, pain), the duration of the study is more consistent with cases when the recommended duration of administration is over three months.

Table 2

Recommended duration of multiple administration studies required to justify registration

Duration of use for the indication	Rodents	Non-rodents
Up to 2 weeks	1 month	1 month

> 2 weeks to 1 months	3 months	3 months
1 weeks to 3 months	6 months	6 months
> 3 months	6 months [3]	9 months [3,4]

Note. The text of the footnotes is given in Table 1.

6. Determination of the first dose in humans

42. Determination of the first dose in humans is an important step to ensure the safety of persons participating in studies first conducted in humans.

43. When determining the recommended starting dose for humans, all relevant preclinical data, including the pharmacological dose-response relationship, pharmacological (toxicological) profile, pharmacokinetics shall be considered.

44. In general, the most important information is provided by NOAEL, which is established in preclinical safety studies in suitable animals. The planned clinical starting dose can also depend on various factors, including pharmacodynamics, certain characteristics of the molecule, as well as the design of the clinical studies.

45. Search clinical studies in humans can be started with a different amount of preclinical studies than the one required for the clinical studies, and therefore the determination of the clinical starting (and maximum) dose may differ. The recommended criteria of the starting doses selection in various clinical studies are given in Table 3.

7. Search clinical studies

46. It was established that in some cases early access to the data received in humans can improve the understanding of the human physiology (pharmacology), the characteristics of a medicinal product and the compliance of therapeutic targets with the specific disease. These can be reached by optimised early search approaches.

47. For the purposes of these Guidelines, search clinical studies shall be conducted at the beginning of Phase I, which involve limited exposure in humans and do not involve an evaluation of therapeutic effectiveness and clinical tolerance. These are conducted to study various parameters, such as pharmacodynamics, pharmacokinetics and other biomarkers, which can include receptor binding and suppression, which are established by means of the positron emission tomography (hereinafter referred to as the “PET”), or other diagnostic parameters. Both patients from the target population, and healthy persons can be subjects of these studies.

48. The amount and kind of justifying preclinical data required in these situations will depend on the amount of exposure in humans in terms of both the maximum clinical dose and the dose duration. Five different examples of clinical search approaches are presented below, the same are shown in details in Table 3, together with the preclinical study programs that are recommended for these approaches.

49. However, it is also possible to use alternative approaches that are not described in these Guidelines, including the strategy for the development of biotechnological medicinal products. These alternative approaches are recommended to be discussed and agreed with the appropriate authorised authorities. Following any of the approaches described herein can reduce the overall use of animals during the development of medicinal products. Table 3 provides the recommended starting doses and maximum doses for five approaches. In all the cases, in order to justify the dose selection for humans one shall establish the characteristics of pharmacodynamics and pharmacology using *in vivo* and (or) *in vitro* models specified in Table 3 and Section III hereof.

7.1. Microdose studies

50. Two different microdose study approaches are shown below and provided in details in Table 3.

51. The first approach provides for the application of a total dose up to 100 μg, which can be administered to any subject in the form of a single dose or divided into several doses. It can facilitate the PET study of binding with the target receptor or distribution in tissues. Another objective can be research of the pharmacokinetics using an isotope-labeled substance or without it.

52. The second microdose approach provides ≤5 administrations to a maximum of 100 μg per administration (up to a total of 500 μg per subject). This approach can be used to solve problems similar to the approach described above, but for ligands being less active with the PET. In some cases, it is reasonable to conduct a clinical study of microdoses with intravenous administration of a medicinal product intended for an oral administration, for which a number of toxicological studies with oral administration were conducted. In this case, the intravenous microdose can be justified by the available oral toxicity studies described in Table 1 and Table 3 (Approach 3) if sufficient exposure is reached. In this case, the local intravenous tolerance is not recommended to be studied, as the dose administered is too small (maximum 100 μg). Local tolerance shall be assessed when using the new intravenous media.

7.2. Studies with a single administration of sub-therapeutic doses or doses within the intended therapeutic range

53. The third approach involves a single administration clinical study, which usually starts with the administration of sub-therapeutic doses with a possible increase to the pharmacological or prospective therapeutic range (Table 3). The maximum allowable dose shall be based on the preclinical data. Further, on the basis of the emerging clinical data from the study, the dose can be reduced. For example, this approach can:

a) determine the pharmacokinetic parameters of the radiologically unlabeled medicinal product under the condition of its administration in the predicted pharmacodynamically active dose or within the close range of doses;

б) assess the participation of the target or pharmacology after administration of a single dose. This approach is not intended to justify the determination of the maximum tolerable clinical dose (exceptions are shown in footnote [1] to Table 1).

7.2. Studies with multiple administration

54. Table 3 shows two different preclinical approaches (4 and 5) to conduction of the clinical studies with multiple administrations. These approaches justify application of dose up to 14 days in order to study pharmacokinetics and pharmacodynamics in humans within the therapeutic range, but are not intended to justify the determination of the maximum tolerable clinical dose.

55. Approach 4 provides for 2-week toxicity studies with multiple administrations in rodents and in non-rodents, in which the selection of doses is based on the exposure multiple to the expected AUC in case of the maximum clinical dose.

56. Approach 5 provides for 2-week toxicity studies with multiple administrations in rodents and in non-rodents to confirm that NOAEL, as established for rodents, is also not a toxic dose for non-rodents. If toxic effects are observed in rodents and in non-rodents during the NOAEL exposure, the clinical use of a medicinal product shall be postponed until additional preclinical studies are finalised in animals of this species (usually a standard toxicology study).

Table 3

Recommended pre-clinical studies
to justify the conduction of the search clinical studies

Clinical		Preclinical		
Administered dose	Initial and maximum dose	Pharmacology	General toxic characteristics study[1]	Genotoxicity[2]/ other
Approach 1: Total dose of≤ 100 μg (without limitations of the interdose interval) and Total amount of ≤1/100 NOAEL and ≤1/100 of the pharmacologically active dose (in mg/kg for intravenous administration and in mg/m^2 for oral administration).	The maximum and starting dose can be equal but shall not exceed the total cumulative dose of 100 μg.	It is necessary to conduct profiling of the binding to the targets (receptors) *in vitro*. In order to justify the selection of dose for humans, it is necessary to have the results of an appropriate establishment of the characteristics of the primary pharmacology (mechanism of action and (or) effects) on the pharmacologically significant model.	A broader toxicity study with a single administration [3,4] in one species of animals, usually rodents, with a planned route of administration with data on toxicokinetics or with intravenous administration. A maximum dose equal to 1,000-fold clinical dose in mg / kg for intravenous administration and in mg / m^2 for oral administration can be used.	Conduction of the genotoxicity studies is not required, but the clinical study file is to include all the studies and assessment of the structural and functional dependency. It is necessary to present the relevant pharmacokinetic data and dosimetric indicators of highly radioactive substances (for example, substances for the PET imaging).
Approach 2: A total cumulative dose of ≤500 μg, with maximum 5 administrations and a washing period between administrations (6 or more valid or supposed half-live periods) AND Each dose of ≤100 μg	The maximum and starting dose can be equal but shall not exceed 100 μg.	It is necessary to conduct profiling of the binding to the targets (receptors) *in vitro*. In order to justify the selection of dose for humans, it is necessary to have the results of an appropriate establishment of the characteristics of the primary pharmacology (mechanism of action and (or) effects) on	7-day toxicity study with a single administration in one species of animals, usually rodents, with a planned route of administration with data on toxicokinetics or with intravenous administration. It is necessary to include the data on hematology, clinical chemical content,	Conduction of the genotoxicity studies is not required, but the clinical study file is to include all the studies and assessment of the structural and functional dependency. It is necessary to present the relevant pharmacokinetic data and dosimetric indicators of highly

Clinical		Preclinical		
Administered dose	Initial and maximum dose	Pharmacology	General toxic characteristics study[1]	Genotoxicity[2]/ other
AND Each dose of≤1/100 NOAEL and ≤1/100 of pharmacologically active dose.		the pharmacologically significant model.	autopsy and histopathology. A maximum dose equal to 1,000-fold clinical dose in mg / kg for intravenous administration and in mg / m^2 for oral administration can be used.	radioactive substances (for example, substances for the PET imaging).
Approach 3: Studies with a single administration of sub-therapeutic doses or doses within the intended therapeutic range	The starting dose shall be determined based on the character of the toxic data specified for the most sensitive animal species, as well as the estimated pharmacologically active dose. Other issues related to the selection of the initial dose in humans are covered by local guidelines. The maximum dose may be the dose that provides for the achievement of ½ NOAEL exposure in the most sensitive animals if all the significant toxicity in animals is monitored and is reversible in humans.	It is necessary to conduct profiling of the binding to the targets (receptors) *in vitro*. In order to justify the selection of dose for humans, it is necessary to have the results of an appropriate establishment of the characteristics of the primary pharmacology (mechanism of action and (or) effects) on the pharmacologically significant model. The main battery of pharmacological safety	A broader toxicity study for a single administration in rodents and non-rodents[3] in the clinical mode of administration, together with the data on toxicokinetics, hematology, clinical chemical characteristics, autopsy and histopathology. In this case, the maximum dose shall be MTD, MFD or the limiting dose.	The Ames test (or an alternative method if the Ames test is not possible, for example, in case of an antibacterial medicinal product).
Approach 4: Dose application up to 14 days in the therapeutic range, but not for the	In case the toxicity is found in two types of animals, the clinical starting dose shall be defined on the basis of	It is necessary to conduct profiling of the binding to the targets (receptors) *in vitro*. In order to justify the	2-week toxicity studies with the multiple administration in rodents and non-rodents, with the	The Ames test (or an alternative method if the Ames test is not possible, for example, in case of an

Clinical		Preclinical		
Administered dose	Initial and maximum dose	Pharmacology	General toxic characteristics study[1]	Genotoxicity[2]/ other
purpose of assessment of the clinical MTD.	local guidelines. If no animal species is found to be toxic (i.e. NOAEL were the highest doses studied, which were not otherwise limited, for example, were not the MFD) or toxicity was detected in only one animal type, the clinical starting dose shall be the dose providing the forecast clinical value of AUC (based either on interspecific pharmacokinetic modelling, or on the conversion in mg / m^2), which approximately equals to 1/50 AUC for NOAEL in animals with less exposure. Other issues related to initial dosing in humans, for instance, the forecast pharmacodynamic activity, are described in local guidelines. In case of no toxicity found in the two animal species, the maximum clinical dose shall not exceed 1/10 of the smaller exposure (AUC)	selection of dose for humans, it is necessary to have the results of an appropriate establishment of the characteristics of the primary pharmacology (mechanism of action and (or) effects) on the pharmacologically significant model. The main battery of pharmacological safety in doses equal to the doses used in toxicological studies.	evaluation of the standard parameters and dose selection in animals based on the multiple exposure from the expected clinical AUC at the maximum dose.	antibacterial medicinal product) and the test (*in vitro* or *in vivo*), which can find damage to chromosomes in mammals.

Clinical		Preclinical		
Administered dose	Initial and maximum dose	Pharmacology	General toxic characteristics study[1]	Genotoxicity[2]/ other
	achieved in any of the animals at the highest dose tested. If the toxicity was found only in one animal type, the maximum clinical dose shall not exceed NOAEL of the animal type in which toxicity was found, or ½ of the highest tested dose in the animals which did not show toxicity, whichever is less. If both species demonstrated toxicity, the maximum clinical dose shall be based on the standard approaches to the risk assessment, and in this case it is acceptable to study the clinical MTD.			
Approach 5: Dose application up to 14 days, which is not exceeding the dose duration in non-rodents; the therapeutic range, but not for the purpose of assessment of the clinical MTD.	The forecast exposure at the starting dose shall not exceed 1/50 NOAEL in the most sensitive type of animals in mg / m^2. Other issues related to selection of the initial dose in humans are covered by local guidelines.	It is necessary to conduct profiling of the binding to the targets (receptors) *in vitro*. In order to justify the selection of dose for humans, it is necessary to have the results of an appropriate establishment of the characteristics of the primary	Standard 2-week toxicity test with the multiple administration in rodents (subject to justification that rodents are the relevant animal species). The maximum dose shall be MTD, MFD, or the limiting dose. The confirming study	The Ames test (or an alternative method if the Ames test is not possible, for example, in case of an antibacterial medicinal product) and the test (*in vitro* or *in vivo*), which can find damage to chromosomes in mammals.

Clinical		Preclinical		
Administered dose	Initial and maximum dose	Pharmacology	General toxic characteristics study[1]	Genotoxicity[2]/ other
	The maximum exposure in humans shall not exceed the AUC at NOAEL in non-rodents or ½ of the AUC at NOAEL in rodents, whichever is less[5].	pharmacology (mechanism of action and (or) effects) on the pharmacologically significant model. The main battery of pharmacological safety in doses equal to the doses used in toxicological studies.	in non-rodents (n = 3) with the dose equal to the expected NOAEL exposure in rodents for minimum 3 days and at least for the planned duration of the clinical study. Or the study with the dose escalation in non-rodents of minimum 3 days and at least for the planned duration of the clinical study with the expected NOAEL exposure in rodents.	In case of *in vivo* evaluation, it is allowed to be conducted within the toxicological study in rodents.

[1] Studies of the general toxic characteristics shall be conducted in accordance with the requirements of the Good Laboratory Practice.
[2] The design and dose selection relevant for genotoxicity studies.
[3] In the framework of a prolonged toxicity study in case of a single administration, it is usually necessary to evaluate data on hematology, biochemistry, necropsy and histopathology (only for control and the maximum dose, if no pathological phenomena due to medicinal product are found at the maximum dose) after a single administration and further study in 2 weeks to assess the delayed toxicity and (or) recovery. The standard design for a study in rodents involves the use of 10 animals of each sex per group, which are evaluated the day following the administration, and 5 animals of each sex for doses assessed on the 14th day after administration. The standard design for a study in non-rodents involves the use of 3 animals of each sex per group, evaluated on day 2, and 2 animals of each sex for doses assessed on the 14th day after administration.
[4] In the microdose approach, it is allowed to assess the reversibility (delayed toxicity) on the 14th day after a single administration. The dose used shall not necessarily be the maximum dose, but it shall 100-fold exceed the clinical dose.
[5] In the absence of adverse effects during the clinical studies, a further increase in AUC is allowed if the effects identified within the toxicology studies can be monitored, are reversible and have a low severity in humans.

8. Local tolerance studies

59. Local tolerance with the planned mode of administration shall preferably be studied in studies of the general toxical characteristics; individual studies are usually not required.

60. It is sufficient to conduct a local tolerance study with a single administration on a single animal type to justify the limited administration with non-therapeutic modes (e.g. single intravenous administration to determine the relative bioavailability of the medicinal product for ingestion). If the expected systemic exposure (AUC and C_{max}) is overlapped by the available toxicological data in the non-therapeutic mode of administration, endpoints of local tolerance studies may be limited to clinical symptoms and macroscopic and microscopic examination of the site of administration. The substance intended for studying local tolerance may comply with the clinical substance, but shall be similar to it.

61. In case of an intravenous microdose study, if the said microdose is justified by toxicological data when administered orally, an evaluation of the local tolerance of the active substance is not required. In case of a new media, it is necessary to assess its local tolerance.

62. In case of parenteral medicinal products, local tolerance shall be assessed, if necessary, at unintentional administration sites prior to the exposure of a large number of patients (e.g. Phase III of the clinical studies). It is recommended to perform a single paravenous administration for medicinal products with an intravenous mode of administration. Other parenteral modes of administration shall be assessed on an individual basis.

9. Genotoxicity studies

63. In order to justify all clinical studies with a single administration, it is usually sufficient to conduct studies of the gene mutations. In order to justify the clinical studies with the multiple administration, an additional evaluation is required to detect chromosomal damage in the mammals.
A full battery of genotoxicity studies shall be completed before the start of Phase II studies.

64. If the results are positive, it is necessary to conduct an evaluation, and if necessary, additional studies in order to determine whether it is possible to continue the administration in humans.

65. Genotoxicity studies recommended to support approaches to clinical studies are discussed in Section 7.

10. Carcinogenicity studies

66. Conditions requiring investigation of the carcinogenic potential of a medicinal product were established in the Guidelines for the evaluation and control of DNA-reactive (mutagenic) impurities in medicines and the establishment of the limits of potential carcinogenicity risk, as approved by the Commission. If carcinogenicity studies for a medicinal product are required for clinical indication, these shall be carried out to justify the registration of the medicinal product use for this indication. The results of the studies shall be presented before conducting the clinical studies only in case of good reasons for fear of the carcinogenic risk. Longer clinical studies itself shall not be an important reason of a possible carcinogenic risk.

67. Studies of the carcinogenic potential of medicinal products developed for the treatment of serious illness in adults or children, if necessary, may be conducted after the registration of a medicinal product.

11. Reproductive and ontogenetic toxicity studies

68. Reproductive and ontogenetic toxicity studies shall be conducted taking into account the population, which will be exposed.

11.1. Males

69. As the evaluation of the reproductive system of males is conducted within the toxicity studies with repeated administration, it is allowed to include men in studies of Phases I and II before conducting the fertility study in males[2].

70. Fertility studies in males shall be completed before large or long-term clinical studies (for example, Phase III studies).

11.2. Women without childbearing potential

71. If the corresponding toxicity studies were performed with multiple administration (which involves the evaluation of reproductive organs of females), then it is allowed to include in clinical studies the women without childbearing potential (i.e. surgically sterilised or postmenopausal women) without any reproductive toxicity studies. Postmenopause is defined as the absence of menstruation for 12 months in the absence of other medical reasons.

11.3. Women with childbearing potential

72. In case of women with childbearing potential, there is a high risk of unintended exposure of the embryo or the fetus until information is received about potential benefits and potential risks.

73. In case women with fertility potential are included in the clinical studies, it is necessary to describe and minimise the risk of unintended exposure of the embryo or the fetus. The first approach to achieve this goal is to conduct the reproductive toxicity studies to assess the medicinal product's risk and take appropriate precautions in women with childbearing potential in the clinical studies. The second approach is to limit the risk by taking measures to prevent the pregnancy during the clinical studies. Such measures include as follows:

pregnancy tests (for example, by definition of free β-subunit of human chorionic gonadotropin);

use of highly reliable methods of contraception;

inclusion in the study only after confirming the menstruation.

Pregnancy tests performed during the study and patient education shall be sufficient to ensure commitment to measures aimed at pregnancy prevention during the medicinal product exposure (which may exceed the duration of the study).

74. To strengthen these approaches, the patient’s informed consent shall be based on all available information on the reproductive toxicity, such as the overall evaluation of the potential toxicity of medicinal products with the related structures and pharmacological effects. If there is no significant information on the impact on reproduction function, it is necessary to indicate potential unidentified risks to the embryo or the fetus.

75. In some cases, it is permitted to include women with childbearing potential in the clinical studies at early phases without preclinical studies of the ontogenetic toxicity (for example, without studies of the embryo-fetal development). For example:

а) intensive risk control in short-term (e.g. 2-weeks) clinical studies;

б) predominance of the disease among women and impossibility of achieving the goal of the study without the women with the childbearing potential, as well as sufficient measures to prevent pregnancy.

76. Additional factors for studies conduction in women with childbearing potential without preclinical studies of ontogenetic toxicity are information about the mechanism of action of the substance, its characteristics, the degree of exposure of the fetus and the difficulty in conducting ontogenetic toxicity studies on a suitable animal model. For example, studies of the ontogenetic toxicity of monoclonal antibodies for which, according to the available scientific

data, a low embryo-fetal exposure during organogenesis was established, are allowed to be carried out during Phase III. Complete reports shall be submitted in the registration package.

77. Prior to conduction of the basic studies on reproductive toxicity, it is allowed to include women with childbearing potential (up to 150 persons) who will receive the studied medicinal product for a relatively short period (up to 3 months), provided that preliminary data on the reproductive toxicity of the medicinal product was received from two types of animals and implementation of measures to prevent pregnancy in the subjects of the study.

78. The admissibility of such studies is related to:

a very low incidence of pregnancy in the controlled clinical trials involving up to 150 subjects;

short duration of the study[5];

the possibility to detect the majority of ontogenetic toxic effects that could affect the inclusion of women with childbearing potential in clinical studies in the appropriately planned preliminary studies.

79. The number of women with childbearing potential and the duration of the study may be influenced by the characteristics of the population that affect the frequency of pregnancy (e.g. age, disease, etc.). Except for the situations described above, it is necessary to complete the basic preclinical studies of ontogenetic toxicity before the women with childbearing potential can be included into the study.

80. As the evaluation of the reproductive organs of females is performed in the context of toxicity studies with multiple administration, it is allowed to include women with childbearing potential in clinical studies of Phases I and II with multiple administration before conducting the fertility study in females[2]. It is necessary to conduct preclinical studies to assess fertility in females in order to include women with childbearing potential in large or long-term clinical studies (for example, Phase III studies).

81. The registration package shall contain the results of studies of prenatal and postnatal ontogenetic development.

82. Prior to the inclusion of women with childbearing potential into the studies that do not use highly effective methods of contraception, or with the unknown gestational status, a full study of reproductive toxicity in females and a standard battery of genotoxicity studies shall be conducted.

11.4. Pregnant women

83. It is necessary to conduct all reproductive toxicity studies in females and a standard battery of genotoxicity studies before inclusion of pregnant women into the clinical studies. In addition, it is necessary to assess the available data on the safety of exposure in humans.

12. Clinical studies in children

84. In case children are involved in clinical studies, the most significant information is related to safety and to be derived from the experience of the medicinal product use in adults, which shall normally be available before clinical studies in children.

85. Sufficiency and scope of data in adults are determined on an individual basis. Before starting the use in children, sufficient data on the experience of a medicinal product use in adults may be lacking (for example, only for use in case of children's indications).

87. Before starting the studies in the children's population, it is necessary to have the following:

а) the results of toxicity studies in case of multiple administration of the appropriate duration for in adult animals;

б) the main set of pharmacological safety studies;

в) the standard battery of studies on genotoxicity.

88. Reproductive toxicity studies in line with the age and sex of children under examination may also be required to get information on the direct toxic or ontogenetic risks (for example, fertility and prenatal (postnatal) development studies).

89. Studies of embryo-fetal development are not required to justify the clinical studies in men and prepubescent women.

90. Toxicological studies in immature animals are allowed only if the previous data in animal and safety data in humans, including the effects of other medicinal products of this pharmacological class, are considered insufficient to justify the studies in children. If a study is required, it is sufficient to use one type of animals, preferably rodents. In case of sufficient scientific justification studies in non-rodents are permitted. In case of short-term pharmacokinetic studies in children (e.g.1-3 doses), toxicological studies in immature animals are usually not required.

91. Depending on the indications for use, the age of children and the safety data in adult animals and humans, one shall consider the necessity of getting the studies results in immature animals before the initiation of the short-term clinical effectiveness and safety studies with multiple administration.

92. One of the most important issues is the age of the study participants compared to the duration of the clinical study (that is the proportion of the development period during which the participants are exposed within the clinical study). This evaluation provides for estimation of the necessity for studies in immature animals, as well as for establishing the timing of their conduction in relation to the clinical studies.

93. In the case of long-term clinical studies in children, the preclinical studies shall be completed before studies begin if the toxicity assessment in immature animals is required.

94. Long-term toxicity studies in immature animals shall be considered in situations, when the children population is the main population that receives a medicinal product, whereas potential ontogenetic risks (toxicological or pharmacological) for target organisms were found in animal studies. This can be a chronic study, which started in animals of the appropriate age and type, with the corresponding endpoints for the analysis of such ontogenetic risk. For example, a 12 month study on dogs (which can cover the whole period of a dog development) or a 6-month study in rats. In some cases with any animals this design can be adapted to replace the corresponding standard chronic study and a separate study in immature animals.

95. Before starting the long-term clinical studies in children, the feasibility of carcinogenic potential studies shall be defined. At the same time, in the absence of a significant cause for concern (for example, signs of genotoxicity based following the results of different studies, availability of a pro-carcinogenic risk due to the mechanism of action, or the availability of the data from the general toxic characteristics studies) a carcinogenic potential study to justify clinical studies in children is not required.

13. Immunotoxicity

96. All new medicinal products for medical use are to be assessed for immunotoxic potential by means of standard toxicology studies and additional immunotoxicity studies performed on the basis of an significance of evidence analysis, including immunemediated signals specified within the standard toxicology studies.

97. If additional immunotoxicity studies are to be performed, these shall be completed before the exposure in a large population of patients (e.g. in Phase III).

14. Photosafety testing

98. The practicality and timing of the photosafety testing in relation to exposure in humans are determined by the following:

а) photochemical characteristics of the molecule (e.g. photoabsorption and photostability);

б) information on the phototoxic potential of the chemically related compounds;

в) distribution in tissues;

г) clinical or preclinical signs demonstrating phototoxicity.

99. The initial evaluation of the phototoxic potential shall be conducted based on photochemical characteristics and the pharmacological (chemical) class. If the evaluation of all available data and the suggested plan of clinical study demonstrates the potential significant risk of phototoxicity for the humans, then the corresponding protective measures shall be provided in the outpatient clinical studies.

100. In order to obtain the data about the risk for humans and to determine the need for further examination a subsequent preclinical evaluation of the skin and eyes distribution of a medicinal product shall be conducted. In case of necessity, one shall perform an experimental assessment (preclinical *in vitro* or *in vivo* assessment or the clinical assessment) of the phototoxic potential before exposure in a large number of subjects (Phase III).

101. Alternatively, instead of the stepwise approach described above, an immediate evaluation of the phototoxic potential can be conducted within the preclinical or clinical studies. If the results of such a study are negative, an early assessment of the skin and eyes distribution of a medicinal product, as well as the protective clinical measures shall not be required.

102. If the results of the phototoxicity testing demonstrate the potential photocarcinogenic risk, this risk is usually sufficiently controlled in patients by means of protective measures including the warning in the informed consent, as well as in the information on the registered medicinal product[6].

15. Preclinical evaluation of the dependence development

103.In case of medicinal products exhibiting activity towards the central nervous system and independently of the indication for use, the need to assess the risk of medicinal product dependence development shall be defined. Preclinical studies shall justify the following:

а) design of a clinical evaluation of the potential for medicinal product dependence;

б) conditions for provision of a medicinal product to the population;

в) preparation of information about such medicinal product.

104.In case of planning specific studies to assess the medicinal product dependence, it is possible to use the guidelines of the Member States on preclinical risk evaluation of the risk that the medicinal product dependence would develop.

105. Preclinical data obtained in the early phases of the medicinal product development may be useful for identification of the early signs of the potential for dependence development. Usually such early signs become known before the first administration to humans. These include the pharmacokinetic (pharmacodynamic) profile for specification of the duration of action, the similarity of the chemical structure with the known medicinal products that cause dependence, the profile of binding to receptors, as well as the behavioural (clinical) symptoms in preclinical *in vivo* studies.

106. If, as a result of such early studies, the potential for the dependence development is not found, the broader preclinical studies in the dependence evaluation models may not be required.

107. If the active substance demonstrates features similar to the known profile of dependence, or it has a new mechanism of action on the central nervous system, in general, additional clinical studies are required to justify additional clinical studies (e.g. Phase III).

108. If the metabolite profile and the targets of medicinal product action in rodents coincide with the metabolite profile and the targets of a medicinal product in humans, at that the preclinical risk evaluation for the dependence development shall be conducted in rodents. Non-human primates can only be used in cases when there are clear signs that they can forecast a person's susceptibility to dependence, but the models in rodents are not applicable.

109. In order to assess the risk of dependence development, most often three types of studies are conducted:

а) preference of a medicinal product;

б) self-administration of a medicinal product;

в) cancellation assessment.

110.Studies of preference and self-administration of a medicinal product are usually conducted as independent experiments. Sometimes the cancellation assessment can be included in the recovery groups of the multiple administration toxicity study. The maximum dose, which provides for achievement of the plasma concentration being several times higher than the therapeutic concentration in humans, is considered suitable for such a preclinical evaluation of the dependence development risk.

16. Other toxicity studies

111.If previous preclinical or clinical data on a medicinal product or related medicinal products demonstrate possible problems related to the safety of a medicinal product, the

additional studies are feasible (e.g. to identify potential biomarkers, to understand the mechanism of action).

112.The Guidelines on evaluation and control of DNA-reactive (mutagenic) impurities in medicines and establishment of the risk of potential carcinogenicity, as approved by the Commission, demonstrate the approaches to the qualification of impurities and degradation products. If separate studies are required to qualify impurities and degradation products, these are usually not required before Phase III, unless there are modifications that lead to the formation of a new impurity profile (e.g. a new synthesis route, a new degradation product resulting from the interaction between the components of a medicinal product). In the latter cases, the corresponding qualification studies may be required to justify Phase II or further development studies.

17. Study of combination medicinal products for toxicity

113.This section describes the studies of co-formulated medicinal products that are packaged together or administered in the same dosage form ("the fixed-dose combination"). The listed below principles are applicable to the development of medicinal products which, according to information about them, will be used simultaneously with a specific medicinal product (even if it is not included in the fixed-dose combination), and for which combination the minimal clinical information was received.

114.The instructions from this section apply to the following combinations of substances:

а) two or more substances at the last phase of development (compounds with significant clinical experience (i.e. Phase III studies and / or registered medicinal products));

б) one or more substances at the last phase of development and one or more substances at the early phase of development (compounds with the limited clinical experience (that is Phase II studies and below));

в) several substances at the early phase of development.

115.For the majority of combinations of two substances which are at the last phase of development and have sufficient clinical experience of co-administration, in case there are no significant toxicological concerns (e.g. similar target organs for toxic impact), preclinical combination studies shall not be required to justify the clinical studies and registration. Such concerns can vary depending on the safety limits and the ability to monitor adverse effects in humans. If the study is conducted to consider the cause of significant toxicological concerns, it is usually necessary to complete it before the clinical study of the combination starts.

116.In the case of combinations containing two substances being at the last phase of development but not having sufficient clinical experience of joint application, as well as in case of no significant toxicological concerns, preclinical studies to justify the conduct of small, relatively short-term clinical studies (e.g. Phase II studies up to 3 months), are usually not required. At the same time, the preclinical studies of such combinations are mandatory to conduct long-term or large-scale clinical studies, as well as for registration of a medicinal product.

117. In case of combinations of substances at an early phase of development, with the experience of clinical application with substances at the last phase of development with no significant toxicological concerns, it is not required to conduct toxicological studies of the combination to justify the conduct of the clinical studies up to one month to test the assumption.

118. Clinical study of the combination shall not exceed the clinical experience of the use of separate components thereof. Clinical studies at the later phase and longer duration shall be justified with preclinical toxicological study of the combination.

119. Preclinical toxicological studies of the combination shall be conducted for combinations of substances at the early phase of development to justify the clinical studies.

120. If a complete preclinical development program is fulfilled for individual components and preclinical toxicological studies of the combination are required to justify the clinical combination studies, the duration of the combination study shall be equal to the duration of the clinical study, but up to 90 days.

121.The 90-day toxicological study of the combination also justifies the registration of a medicinal product. Depending on the planned clinical use, a shorter toxicological study of the combination may also justify the registration of a medicinal product.

122.The design of preclinical studies recommended for establishment of the characteristics of the combination depends on the pharmacological, toxicological and pharmacokinetic profiles of its individual components, the indications for use, the target population of the patients and the available clinical data.

123.Pre-clinical studies of the combination shall, in general, be limited to one relevant type of animals. Additional toxicity studies are allowed if unforeseen toxicity is detected.

124.If a complete pre-clinical development program is not performed for individual components, the complete preclinical toxicology program may be conducted only in relation to the combination, provided that the individual components are dedicated only for the combined application.

125.If individual components were studied in accordance with the standards in force, usually, the genotoxicity, pharmacological safety and carcinogenicity studies of the combination are not required to justify the clinical studies and registration of a medicinal product.

126.If the population of patients includes women with childbearing potential, and the results of studies of individual components indicate the embryo-fetal risk, the combination studies are not required, as the potential risk to human embryo-fetal development was previously identified.

127.The combination study is not required if the preclinical studies of the embryo-fetal development demonstrate that none of the components has an ontogenetic risk for the humans, should there be no concerns (based on the characteristics of individual components) that the combination may be dangerous to humans.

128.If individual components were studied within the embryo-fetal development studies, but embryo-fetal studies of the combination are required, the results of the latter shall be presented to justify the registration of a medicinal product.

[1] "Exposure" in these Guidelines refers, in general, to the group average AUC. In some cases, it is more reasonable to determine the excess of the exposure by group average C_{max}. (e.g. if the compound or the class of compounds can cause acute cardiovascular changes or clinical symptoms associated with the central nervous system).

[2]From the point of view of sensitivity to the detection of toxic effects on the reproductive organs of animals, the evaluation of the fertility of males and females based on the results of the standard pathohistological examination of testicles and ovaries in toxicity studies (usually, in rodents) with multiple administration for at least 2 weeks is comparable with studies on fertility.

[3] Highly reliable methods of contraception are both isolated and combination methods that ensure a low failure rate (that is less than 1% per year) in case of their permanent and appropriate usage. It is necessary to consider the information about a medicinal product under review and its potential effect on contraception in case of subjects using the method of hormonal contraception.

[4]In order to achieve this objective, it is advisable to conduct a preliminary study of embryo-fetal development with sufficient doses, providing for an evaluation of the fetal survival, body weight, external examination and examination of the internal organs, using at least six females per group, as well as the females who received such medicinal product during organogenesis. The preliminary preclinical study shall be conducted in accordance with the accepted scientific standards and subject to provision of the direct access to the persons concerned to the documents on data collection or in line with the requirements of the Good Laboratory Practice.

[5] The frequency of pregnancy in women first attempting to become pregnant is ~ 17 % per a menstrual cycle. The frequency of pregnancy in the Phase III studies conducted in women with the childbearing potential is <0.1% per a menstrual cycle. During the said studies the subjects were advised to prevent pregnancy and take measures to prevent thereof. According to the data available, the frequency of pregnancy in Phase II is lower than in Phase III, but in view of the limited number of women included in this phase of studies, the value of decrease cannot be established. Based on the above mentioned data from Phase III, the pregnancy rate in Phase II

of the study involving 150 women with the childbearing potential and lasting up to 3 months is less than 0.5 pregnancies per each medicinal product examined.

6 The study of photocarcinogenicity in non-rodents using the currently available models (e.g. hairless rodents) to justify the development of medicinal products is not feasible and, in general, is not required. If phototoxicity studies demonstrate the photocarcinogenic risk and the appropriate method of study becomes available, the study shall be completed before a medicinal product is registered, whereas its results shall be taken into account in assessment of the risk to humans.

APPENDIX NO. 1

to the Guidelines
on Preclinical Safety Studies in Order to Conduct
Clinical Studies
and Registration of Medicinal Products

INSTRUCTIONS
on preclinical documents preparation for the mixed registration dossiers *

1. Objectives of the Instructions

A series of medicinal products used in humans for a long time contain the active substance(s) for which preclinical information is (are) limited or lacking. In order to better assess the risks associated with the use of such medicinal products and to avoid unnecessary repetition of the experiments in animal, these Instructions provide the minimum requirements to preclinical studies of such medicinal products. Modules 4 and 5 of the registration dossier for such medicinal products, which is a combination of the preclinical and (or) clinical studies and reviews, with references to the published pharmacological and toxicological information, including the scientific research and clinical studies, as well as post-registration experience results of the broad clinical use in humans, are called mixed registration dossiers. The data contained in the mixed registration dossier provide for sufficient characterisation of the safety of such medicinal products.

These Instructions are applicable to the medicinal products whose active substance(s) is (are) referred to the group of chemically active substances with a clearly defined chemical structure. These Instructions do not apply to biological, biotechnological and herbal medicinal products.

3.Preclinical documents

3.1. General issues

Preclinical studies are usually not required if there is sufficient well-documented clinical experience to establish all aspects of the clinical effectiveness and safety.

Preclinical studies shall be conducted if there is a well-founded concern about non-safety of a medicinal product or the probability of developing such non-safety is suspected based on the

pharmacological class to which a medicinal product belongs to or on the basis of the clinical experience of the use of a medicinal product.

The lack of certain individual preclinical studies, especially the studies of reproductive toxicity, genotoxicity and carcinogenicity, can also develop a concern about non-safety of a medicinal product. In this regard, preclinical studies may be required to study those effects that are difficult or impossible to find clinically.

3.2. Specific types of studies

Toxicity in single and multiple administration

In general, preclinical study of medicinal products that are submitted with the mixed registration dossier does not require an examination of the following:

toxicity in a single and multiple administration;

pharmacological characteristics (including the study of the safety pharmacology and pharmacokinetics).

Reproductive and ontogenetic toxicity

Studies of the impact on fertility and overall reproductive function are usually not required (in case of no reasons for concerns related to unsafe medicinal product).

It is necessary to evaluate the potential of the reproductive toxicity in relation to the embryo-fetal and perinatal (postnatal) development. Despite the fact that the reproductive toxicity data are available for many active substances, the quality of these data is usually insufficient for a complete safety evaluation.

Studies of the embryo-fetal toxicity and perinatal (postnatal) development are not required in the following cases:

if sufficient information on exposure in pregnant and newborns was received; or

if a medicinal product is not intended for use in women with the childbearing potential; or during pregnancy and breastfeeding.

Genotoxicity

It is necessary to evaluate the genotoxic potential of the active substance(s).

There is information on genotoxicity in relation to many active substances but the quality of such information is usually insufficient to fully assess the safety thereof.

If it is impossible to conduct a comprehensive evaluation of mutagenicity and (or) chromosomal damage, additional genotoxicity studies are required.

In some cases, the genotoxic characteristics of the active substance(s) of a certain pharmacological class (e.g. cytostatic substances) may be extrapolated from other substances of the same class. In such cases genotoxicity studies are not required.

Carcinogenicity

The study of carcinogenicity is not required if there is no suspicion related to the carcinogenic potential thereof.

Carcinogenicity studies are not mandatory, even if there is a suspicion related to its carcinogenic effect.

Please find below some circumstances that need to be considered at making the decision on conduction of the carcinogenicity studies:

а) if the positive result affects the evaluation of the benefits and risks;

б) if the induction of tumors is forecast based on the data from the previous studies of substances with a similar molecular structure and (or) mechanism of action;

в) if the suspicion is based on the positive results of genotoxicity studies and if it can be eliminated with additional genotoxicity studies, mainly *in vivo;*

г) if the suspicion is based on the epidemiologically confirmed human positive data (e.g. estrogen-induced breast tumors);

д) if the cumulation of the scientific data is sufficient to eliminate the suspicion (of the carcinogenic effect);

Toxicokinetic data are required only for new studies in animals.

4. Preclinical review

The specialist responsible for preparing Module 2 of the medicinal product registration dossier is to analyse the totality of the available information on which the acceptable level of the active substance safety is based. In the case of active substances with the lacking toxicological data, the specialist is to analyse the results of the relevant pharmacological and toxicological studies provided with detailed references to the published scientific literature and (or) provide the scientific justification confirming the acceptable level of the active substance safety, taking also into account the information on its extensive clinical application. It is also necessary to take

into account the significance of deviations from the currently accepted quality standards (e.g. compliance with the GLP) for the interpretation of the studies results.

Moreover, it is necessary to include the proposed wording in Sections 4.6 “Fertility, Pregnancy and Lactation” and 5.3 “Pre-clinical safety data” of the general characteristics of a medicinal product.

APPENDIX NO. 2

to the Guidelines
on Preclinical Safety Studies in Order to
Conduct Clinical Studies and Registration of
Medicinal Products

LEGEND
for pharmacokinetic and toxicological parameters

AUC	area under the curve
C_{max}	maximal concentration in plasma
MFD	maximum feasible dose
MTD	maximum tolerated dose
NOAEL	no adverse event level