APPROVED

by Decision No. of the Board of
the Eurasian Economic Commission
of , 20

GUIDELINES
for the Selection of a dosage regiment for medicinal products

I. Data on Dose-Effect Relationship
for Justification of Medicinal Product Registration

1.1 Setting the dose-effect relationship parameters

1. It is obligatory to know the relationship between the dose, the concentration of a medicinal product in blood and the clinical effect (effectiveness and adverse reactions) to ensure safe and effective use of a medicinal product for individual patients. This information allows determining the appropriate initial dose, the best way to adjust the dose for an individual patient, as well as to specify the dose, which — in case it is exceeded — will not lead to additional advantages or will result in unacceptable adverse reactions. Data on the dose-concentration, concentration-effect and / or dose-effect relationships are used to prepare recommendations for dosing and usage in the medicinal product label. In addition, understanding of the dose-effect relationship can provide a rational approach to the global development of a medicinal product, enabling the authorised authorities to render decisions on registration on the basis of a common database.

2. The analysis of registration of medicinal products for the previous years shows that they were often registered in doses which were later acknowledged as excessive (i.e. in doses exceeding the plateau of the dose-effect curve for the desired effect), being in some cases the cause of adverse effects (e.g. hypokalemia and other metabolic disorders due to use of thiazide-like diuretics by patients with hypertension). The cases of registration of medicinal products in such doses decreased when the pharmaceutical companies started trying to determine the lowest dose having an obvious positive effect, or the maximum dose, the excess of which does not lead to additional benefit, but up to now there were no recommendations of the member states of the Eurasian Economic Union (hereinafter referred to as the "Member States") at the national level to plan studies aimed at precise ranging for such doses. Moreover, according to the latest scientific data, the concepts of the minimum effective dose and the maximum useful dose do not fully cover individual differences and, thus, do not provide for the comparison of the desired and adverse effects at different doses. The desired and adverse effects occur with any dose in a different ratio, at that it is not always possible to identify the optimal dose for all the patients.

1.2 Use of the Information on the Dose-Effect Relationship when Choosing Doses

3. When choosing the starting dose, the knowledge of the shape and location of the population (group) average dose-effect curve for the desired and adverse effects is of utmost value. At a dose choice, the above mentioned information and decision on the relative importance of the desired pharmacological (therapeutic) and adverse effects shall be considered as guidelines. For example, if the dose ranges of desired and adverse effects of a medicinal product are sufficiently broad or if a fast progressing disease

requires immediate effective therapy, it is recommended to prescribe relatively high initial doses (located on the plateau of the dose-effect curve or close to it). At the same time, if the ranges of dose of desired and adverse effects of a medicinal product differ insignificantly, the use of a high initial dose is not recommended. In such cases, the best way is to use the lowest dose that results in the clinically significant effect in some patients, followed by a gradual increase in the dose till a well tolerated dose is reached. The choice of the initial dose can also be influenced by the potential inter-individual variability of pharmacodynamic effects at a certain concentration of a medicinal product in blood or the expected inter-individual pharmacokinetic differences, which can result from non-linear kinetics, metabolic polymorphism, or a high probability of pharmacokinetic medical interactions. In such cases, prescription of a lower initial dose protects patients in whom the concentration of a medicinal product in blood reaches high levels. It is highly probable that, due to different understandings of the benefit-risk relationship, different doctors and even different authorised authorities of the Member States will choose (using the same data as the basis) different initial doses, methods of the selection thereof and maximum recommended doses to be put on the label of a medicinal product. Reliable data on the dose-effect relationship help to avoid such situations and take similar decisions about the choice of the dose schedule of a medicinal product.

4. In case of the dose adjustment in a patient based on the results of the response to the initial dose, the forms of the individual dose-effect curves are the most valuable data, ans such curves, as a rule, are not identical with the population (group) average dose-effect curve. Thus, designs of studies that allow the determination of individual dose-effect curves can provide valuable

data in the selection of a dose, but experience of using such designs as well as of analysis of such studies results is limited.

5. When using the dose-effect relationship data, one shall identify (to the extent possible) the factors resulting in the differences in pharmacokinetics of medicinal products between different persons, including demographic factors (e.g. age, sex, race), concomitant diseases (e.g. renal impairment or hepatic decompensation), diet, concomitant therapy or individual characteristics (e.g. body weight, physique, use of other medicinal products, metabolic differences).

1.3 Use of the data on Concentration-Effect Relationship

6. In case that safe and effective use of a medicinal product is possible only subject to its concentration in blood follow-up, the significance of the information on the concentration-effect relationship is obvious. In other cases determination of the concentration-effect relationship is not required, but such data are important to specify the clinical consequences:

а) related to pharmacokinetic differences, for instance related to concomitant diseases (e.g. kidney failure) or medicinal product interactions; or

б) aimed at assessing the effect of the modified pharmacokinetics due to new medicinal product form (e.g. extended release pharmaceutical formulations) or new dose schedules without any additional clinical data provision, if permitted by the authorised authority.

7. Prospective randomised studies of the concentration-effect relationship are of key importance in determination of the therapeutic window requiring concentration monitoring, as well as they are significant in case of high pharmacokinetic variability among patients. In the latter

situation, the determination of the concentration-effect relationship is possible within the prospective study with fewer persons involved than it is required in determining the dose-effect relationship in a standard dose-effect study.

8. It should be noted that the collection of information on the dose-effect relationship does not result in the obligatory monitoring of the therapeutic medicinal product concentration in blood for its correct application. The concentration-effect relationship can be transformed into the dose-effect relationship. If the relationship between concentration and the observed phenomena (for example, the desired or adverse effects) is established, the dose selection can be made in line with the patient's response without further need to monitor the medicinal product concentration in the patient's blood. The information on the concentration-effect relationship also provide for the selection of doses (based on the range of concentrations to be reached after usage), which are likely to result in satisfactory response.

1.4 Problems with Design of Studies on Dose Selection by Titration

9. The design of a study, which is used to confirm effectiveness, is based on selection of a dose that allows reaching a certain endpoint of effectiveness or safety of application. In general, such designs aimed at dose selection in the absence of a thorough analysis provide insufficient information to establish the dose-effect relationship.

10. Many studies demonstrate a trend to spontaneous improvement over time, which is not always recognised due to an increased response to high doses or accumulated medicinal product. All these facts allow persons to choose the highest doses used in the study as the recommended one if these are well tolerated. According to the analysis of the data on the earlier

registration of a medicinal product, this approach often resulted in the selection of a dose that exceeded the actually required dose, leading to an increased incidence of adverse effects (e.g. high doses of diuretics used in hypertension).

11. In some cases, especially when fast effects are needed, the approach based on selection of the highest tolerated dose is acceptable, and usually it requires a minimum number of patients. For example, zidovudine was first registered for treatment of patients with AIDS following the results of studies of its use in high doses; later, it was shown that lower doses were equally effective and better tolerated. Considering the urgent need to introduce the first effective therapy against HIV, the lack of data on the dose-effect relationship was acceptable (subject to the subsequent collection of additional post-registration data), but in less urgent situations such studies are mandatory.

1.5 Interaction of the Dose-Effect Relationship and Time

12. The choice of an individual dose of a medicinal product is interrelated with the frequency of such medicinal product use. If compared to the half-life of a medicinal product, the dose interval is longer in general, then such an interval should be selected based on pharmacodynamic considerations. For example, it is acceptable to compare a long dose interval with the same dose in a divided schedule, keeping the eye on, if appropriate, the maintenance of the desired pharmacological effect throughout the entire interval, as well as the adverse effects that may occur at maximum concentrations in blood. The dose-effect relationship within a dose interval at the maximum concentration and with decreasing concentration may differ and depend on the chosen dose interval.

13. Studies of the dose-effect relationships shall also consider the time matter. The duration of a specific dose study shall be sufficient to fully demonstrate the effects of a medicinal product, regardless of the fact whether the delayed effects resulted from pharmacokinetic or pharmacodynamic factors. The dose-effect relationship can be influenced by the time of use (in the morning or in the evening). The dose-effect relationship at the beginning of treatment may not coincide with the dose-effect relationship of the subsequent supporting therapy. The effect may also depend on the cumulative dose (rather than on a daily dose), the duration of use (e.g. tachyphylaxis, acquired tolerance, hysteresis) or depend on the time of use in relation to the meal time.

II. Receipt of the information on the dose-effect relationship

2.1 Evaluation of the dose-effect relationship as an integral part of a medicinal product development program

14. The evaluation of the dose-effect relationship is an integral part of a medicinal product development program. It is mandatory to evaluate the effectiveness and safety in studies aimed at assessment of the said relationship. If obtaining the data on the dose-effect relationship is included in the development process, it is usually performed without any time loss and with minimal additional effort compared to the development program without obtaining such data.

2.2 Studies in case of life-threatening diseases

15. There were various diagnostic and therapeutic approaches developed within specific clinical areas, which influence the types of standard studies.

16. In case of availability of an effective treatment, it is unacceptable to conduct placebo-controlled studies with parallel dose-effect design and studies with placebo-controlled dose selection (high-performance designs used in case of angina pectoris, depression, hypertension, etc.) for studying of such conditions as life-threatening infections or potentially treatable tumors. If the clinical areas mentioned above allow significant toxicity, relatively high doses are prescribed to quickly achieve the maximum desired effect. Such approach can lead to selection of doses that will deprive some patients of potential desired effects due to toxicity resulting in the cancellation of the therapy as recommended doses. On the other hand, it may be unacceptable to prescribe low, potentially sub-effective doses or select a dose to achieve the desired effect because the primary treatment ineffectiveness may occur in such cases and the possibility of the treatment will be irretrievably lost.

17. For all life-threatening diseases medicinal product developers need to balance the advantages and disadvantages of various schedules and decide on the best way to select the dose, the dose interval and the dose-increase scheme. Even if a patient has life-threatening diseases, the highest tolerated dose or the dose with the maximum effect on the surrogate marker of the disease will not always be optimal.

18. In case of evaluation of a single dose, data on the concentration of a medicinal product in blood, which almost always are subject to significant individual variability due to pharmacokinetic differences, may to some extent retrospectively characterise the concentration-effect relationship.

19. Examination of a single dose is typical for large interventional studies (for example, a study in patients with myocardial infarction), as they require a large sample. When planning an interventional study, it is necessary to evaluate the potential benefits of multiple dose studies. In some cases, it is

possible to decrease the amount of information collected from each patient in order to simplify the study activities, thus providing for a study of a large population of patients who were administered different doses without a significant increase in costs.

2.3 Regulation issues of incomplete data on the dose-effect relationship

20. It should be taken into account that even thorough planning of studies of the dose schedule of medicinal products cannot be always implemented in practice. There are situations when, during the assessment of results in a well-planned study, it turns out that the used medicinal product doses were too high or so insignificantly different that these were equal (but still superior to placebo). In this case, there is a possibility that the minimal evaluated dose still exceeds the dose needed for a medicinal product to show its maximum effect. However, an acceptable ratio between the detected desirable and adverse effects for one of evaluated doses can make the registration acceptable.

21. The decision to register, despite the lack of studies on the appropriate range of doses, can be taken only if a medicinal product is of particular importance for the treatment of the disease. In other cases, with the study results available and partially demonstrating the proper dose range, further selection of doses can be conducted within the post-registration period.

22. A similar approach is used when planning of programs for study of the dose-effect relationship. The registration of a medicinal product on the basis of studies related to a single dose or a certain range of doses (without getting proper information on the dose-effect relationship) may be accepted only if the benefits of using such a new medicinal product for the treatment or prevention of a serious disease are obvious.

2.4. Analysis of the database as to the dose-effect relationship

23. In studies aimed at getting the data on the dose-effect relationship, the entire database shall be carefully searched through for such information. At that, it is necessary to take into account the limitations imposed by certain study designs. For example, in many studies, the dose is titrated to increase for the safety of use of a medicinal product. As the majority of adverse effects related to a medicinal product occur early and can be terminated when the treatment is ongoing, an erroneous conclusion that the increased frequency of adverse effects occurs at lower doses can be made. Similarly, in studies, where the dose selection is performed till the desired response in patients, the patients that are insensitive to the medicinal product will likely receive higher doses; this will lead to development of a clear but erroneous dose-effect curve of an inverted U-shape. Despite the above risks of a wrong conclusion, it is necessary to analyse all the available clinical data for the dose-dependent effects of covariates, using the multivariate analysis method or any other suitable method, even if the analyses result mainly in hypotheses and not in unambiguous conclusions. For instance, the influence of the inverse relationship of the body weight or the creatinine clearance may reflect the dose-effect relationship pattern. If the pharmacokinetic screening was conducted (receipt of a small number of measurements of the equal concentration in blood in the majority of patients within the study phases II-III), or other approaches were used to determine the concentration of a medicinal product, it is possible to determine the dependence of the desired and adverse effects on the concentration of a medicinal product in blood. This dependence can serve a true confirmation of the dependence of the response on the concentration of a medicinal product in the blood or require further examination.

III. Designs of studies to evaluate the dose-effect relationship

3.1 General Provisions

24. The selection of the study design and the population for examination of the dose-effect relationship is determined by the development phase, the indications and the disease severity in the target group of patients. For example, the lack of necessary therapy in case of life-threatening or serious pathological conditions with irreversible results may, for ethical reasons, prevent research at doses below the maximum tolerable ones. Usually, the homogeneous population provides for the achievement of the study objectives, if each dose is given to a small group of patients. On the other hand, large and diverse populations make it possible to identify potentially important covariate effects.

25. Valuable data on the dose-effect relationship can usually be obtained in studies specifically aimed at comparing several doses. In some cases the information can be retrieved from comparison of the results of two or more controlled studies in which different doses were studied (if the compared groups were similar), but even in this case many differences between the studies do not allow using this approach.

26. In some cases, it is also possible to receive retrospective data on the concentration-effect relationship from the data on concentrations provided by the studies where a single dose was examined. Despite the fact that the results of these analyses are potentially distorted by the severity of the disease or other patient factors, the information may be useful and used in future studies. The dose-effect studies at the early stages of clinical development can reduce the number of unsuccessful phase III studies, thus providing for the development speed up and resources saving.

27. The use of pharmacokinetic data makes it possible to select doses that provide the necessary range of dose-effect relationship and reduce, or eliminate the overlap of different concentrations specified in the dose-effect relationship studies. It is recommended to use a greater dose range for medicinal products with high pharmacokinetic variability. In contrast, it is permitted to customise for pharmacokinetic covariates (for example, the body weight adjustment, the lean body weight or the kidney function), or to conduct a concentration control study for groups receiving different doses.

28. Practically thinking, reliable data on the dose-effect relationship are easier to obtain if the effect is measured by a continuous or categorical variable, is relatively quickly defined after the beginning of the therapy and quickly disappears after its cancellation (e.g. the blood pressure, analgesia, bronchodilation). In this case, it is possible to use different study designs, whereas valuable information can be obtained from the results of relatively small and simple studies.

29. The placebo-controlled study designs with individual dose selection are typical for many medicinal product studies at the early stage of their development. Properly conducted and analysed studies (quantitative analysis modelling and conducting a population and an individual dose-effect relationship assessment) may be the basis for more specific parallel studies of the dose-effect relationship with a fixed dose or provide for a conclusion on the dose-effect relationship without additional research activities.

30. On the contrary, if the endpoint of a study or the adverse effect is delayed, stable or irreversible (e.g. prevention of a stroke, myocardial infarction or bronchial asthma, treatment of arthritis with the late-onset therapeutic effect, cancer survival, depression treatment), selection and simultaneous assessment of the effect, in general, are impossible, thus, a parallel study of the dose-effect relationship is usually required.

31. The study of the dose-effect relationship in parallel groups also provides for appropriate detection of an effective dose despite an inverted U-shaped (in the form of an umbrella or bell) dose-effect curve, when higher doses are less effective than the lower ones. For example, such an effect is possible in case of evaluation of the mixed antagonist - agonist groups.

32. In order to ensure comparability of the compared groups, as well as to minimise potential systematic errors on the part of the patient, the researcher and the analyst of the study aimed at assessing the dose-effect relationship or the concentration-effect relationship and, thus, are subject to adequate control with randomisation and blindness (except for the cases when blindness is not needed or impossible). A sufficient number of persons shall be included in the compared groups.

33. In order to find clinically significant differences, one shall study a wide range of doses, which is achieved in reality and is safe for the patient. It is particularly important if there are no pharmacological or acceptable surrogate endpoints that serve as the basis for selection of initial doses.

3.2. Specific study designs

34. There is a series of study designs to evaluate the dose-effect relationship. The same approaches can be used to determine the concentration-effect relationship. The described approaches demonstrated their suitability for getting reliable information on the dose-effect relationship, despite the fact that the list of approaches hereunder is not exhaustive. Some of the designs listed in these Guidelines are methodologically better considered than others, but all of them can be taken into account when planning of the research work. All these designs can be used in a study with the established clinical or surrogate endpoints.

3.2.1. Dose-effect parallel design

35. Randomisation in several groups using fixed doses (a randomised parallel study of the dose-effect relationship) is a simple and widely used method. A fixed dose is the final or supporting dose in this design. A fixed dose can be given to patients immediately or by stepwise selection (according to the forced selection scheme), if this approach seems safer. In both cases, the final dose shall be used within a sufficient period in order to compare the dose-effect relationship.

36. Although it is recommended to include a placebo group in the dose-effect relationship in line with the method used, it is not required in all the cases: a positive value of the dose-response curve slope is a confirmation of the effect of a medicinal product even in the absence of the placebo group. In general, in order to measure the absolute value of the medicinal product effect, there is a need in a group using placebo (hereinafter referred to as the "placebo group") or using a different control with a very low effect on the endpoint under study. As the difference found between the assessed groups and the placebo group clearly indicates the effectiveness, the inclusion of a placebo group may provide for the study analysis in which all used doses were too high and did not reveal the slope of the dose-effect curve (if all such high doses proved to be superior to placebo).

37. The ability to find a statistically significant difference in the paired comparisons between doses is not necessary if, using all the data available on all doses, a statistically significant trend (ascending slope) is demonstrated. Nevertheless, it is necessary to confirm that the smallest assessed and recommended for use dose(s) is/are of a statistically and clinically significant effect.

38. Following the results of the parallel dose-effect study, a group average (population mean) of individual dose-effect relationship is deducted, but not a distribution or shape of individual dose-effect curves.

39. It is often found at the end of the parallel dose-effect study that all doses were either too high (situated on the dose-effect curve plateau) or insufficient. In this case, during the approval of the research program there is a need to plan an intermediate analysis (or use one of the multi-phase study designs) that can identify such a problem and allows selecting the appropriate range of doses.

40. As in the case of standard placebo-controlled studies, it is advisable to include one or more doses of active control into this type of study. The inclusion of both placebo groups and active control groups provides for evaluation of the analytical sensitivity, recognition of an ineffective medicinal product and an "ineffective" (lacking of a result) study.

41. Comparison of the dose-effect curves of the assessed medicinal product and active control is a more reliable and informative comparative study of its effectiveness (safety) than comparing single doses of two medicinal products.

42. During a factor study, the parallel study design with fixed doses is used, where the range of doses of specific medicinal products and some (or all possible) combinations thereof are studied.

43. In order to distinguish individual variants (observations) in paired comparisons, a large sample is not needed, as all data can be used to get information on the dose-effect relationship of individual components and their combinations, that is, the dose-effect relationship surface. Thus, it is possible to stick to a restrained sample.

44. Doses and combinations that can be approved within the registration are not limited to the studied ones and may include all doses and

combinations, which are intermediate to the doses and combinations studied. However, during the selection of doses, it is not possible to rely entirely on the analysis of surface of the dose-effect relationship in all cases. If the doses used in the study are below the established effective doses of a specific medicinal product, then it is, in general, necessary to confirm that such doses exceed the placebo effect in paired comparisons in case of using the doses from the lower end of the dose range. One way to confirm it in a factorial study is to insignificantly increase the number of patients in the lower dose combination group and in the placebo group compared to other groups; a separate study of lower dose combinations can also be conducted. When using the doses from the upper dose range, it may be necessary to confirm the contribution of each component of a medicinal product into its cumulative effect.

3.2.2. Dose-effect cross-over design

45. A randomised multiple cross-over study of different doses will be successful if the effect of a medicinal product is fast demonstrated and patients return to their initial state immediately after termination of the therapy, and, at that, the effects are not irreversible (recovery, death), whereas the disease is characterised by a relatively stable course. Such a design has the disadvantages as all cross-over examinations have: if there are many dropouts in the study groups, there may be analytical difficulties; in addition, there are often problems of the transfer effect (longer periods of treatment can minimise this problem), comparability of the initial parameters at the end of the first period and the period-medicinal product interaction. The duration of the study can be reduced by using approaches according to which not all patients receive each assessed dose (for example, study designs with the balanced incomplete blocks).

46. The advantage of the design is that each person receives several different doses, which provides for evaluation of the distribution of individual dose-effect curves, as well as of the average population curve, which requires less patients compared to their number in the parallel study design. Moreover, unlike in the dose selection study designs, the dose and time are not distorted, whereas the transfer effects are better controlled.

3.2.3. Forced titration

47. In the forced titration study, all patients are consistently assigned the prescribed ascending doses. The methodology and limitations of the forced titration study are similar to the randomised multiple cross-over study of the dose-effect relationship, except that doses are prescribed not randomly but orderly.

48. If the majority of patients manage to receive all doses and the study includes the placebo group, then the forced titration study provides for a series of comparisons of the entire randomised group receiving several doses with the placebo group - similar to the parallel study with the fixed doses. The main disadvantage of this design is inability to separate the effect of the dose ascending from the effect of increasing the duration of therapy or the cumulative effect of a medicinal product. Such study design will be unsatisfactory if the effect is delayed, provided that each dose is not examined for a long time. Even if the effect occurs quickly (in line with the retrospective data), this study design provides little information about adverse effects, many of which depend on time.

49. The trend for spontaneous improvement of the patient's condition without any influence of a medicinal product, which is shown quite often, is recognised with the help of the placebo group. However, this problem is quite typical for this study design, because higher doses cause an increase to a

lesser extent with time. The use of such study design can, in a gross way, provide reliable data on both the population average dose-effect relationship and the distribution of individual dose-effect relationships, provided that the cumulation (time-dependent) effect of a medicinal product is minimal, and the number of dropouts is insignificant.

50. Compared to the parallel dose-effect relationship study, this study design requires fewer patients and, in case of an increase in its duration, can be used to study a wide range of doses, thus, it can be recommended when planning the first study. With the parallel placebo group, this study design can clearly confirm the effectiveness and be particularly valuable for dose selection for the parallel dose-effect relationship study.

3.2.4. Selective dose titration (placebo-controlled dose titration to the endpoint)

51. In a study design with selective dose titration, such dose titration is conducted until well-described favourable or adverse effects determined by the dose rules in the protocol are achieved. This approach is mostly applicable if the effect appears quite quickly and is not an irreversible phenomenon (for example, blood stroke or death).

52. Primary analysis of such studies, for example, comparison of effects in subgroups of patients, dose titration in which was conducted up to different values, often gives an erroneous inverted U-shaped curve, as the dose titration to high doses is continued only in persons with weak effect of a medicinal product. At that, more complex statistical analytical approaches dealing with this issue by modelling, as well as assessment of the population and individual dose-effect relationships provide reliable data on the dose-effect relationship.

53. At present, the data on the study of the dose-effect relationship within this method are insufficient. In order to take into account spontaneous changes, assumptions of the researcher when planning an experiment, etc., a placebo group is to be included in this study design. Like other designs in which one patient receives different doses of a medicinal product compared to the parallel study with the fixed doses, this study design also requires fewer patients with the same statistical significance of the study and provides the data both on the population average and individual dose-effect relationships.

54. This design is subject to the risk of distortion of time and dose effects, it is especially difficult to determine the dose-effect relationship of adverse effects using this study design. Like the design with the forced titration, it is used to study a wide range of doses, and with a placebo group it provides for a clear confirmation of the effectiveness. This design is of value as an early study to identify the doses that will be studied subsequently in a parallel study.

IV. General guidelines on study designs

55. Data on the dose-effect relationship are advisable for almost all new chemical compounds launched at the market. These data shall be derived from the results of thoroughly considered, scientifically justified studies, at that the reliable data can be obtained through various study designs. It is necessary to provide for appropriate monitoring and follow-up and to use acceptable approaches to minimise systematic errors in studies. In addition to targeted dose-effect studies, it is necessary to examine all the database available for data on the dose-effect relationship.

56. The study sponsor is to use the information based on the results of the relevant studies and analyses of the database available in order to:

а) Set up a justified starting dose, ideally adjusted (or with absolute confidence that it is necessary to correct the starting dose) according to the patient's physical parameters, sex, age, concomitant diseases, simultaneously used medicinal products, as well as reflecting comprehensive knowledge of the pharmacokinetic and pharmacodynamic variability. Depending on the circumstances (disease, medicinal product toxicity), the starting dose may be within the range from a low dose with some beneficial effect to a dose of (almost) full effect;

б) Establish acceptable measures for dose titration (subject to effect control) and the interval of their implementation taking into account the patient's characteristics. Such measures shall be based either on the form of typical individual dose-effect curves (both for desirable and adverse effects) - subject to availability of individual data on the dose-effect relationship and, if available, on the form of the population (group) average dose-effect relationship and the time necessary to detect changes in such effects. It should be noted that at present the methodology to get the population (group) average dose-effect relationship is developed better than the methodology for determining the individual dose-effect relationship.

в) Establish the dose or the desired effect (adverse effect) at which further dose titration should be stopped due to lack of benefit of increasing the dose or unacceptably increase of the frequency of adverse effects.

57. Dose titration or concentration-effect relationship studies are advisable at early stages of development, as well as at the later stages of development, to avoid unsuccessful phase III of the studies or databases that mainly consist of data on ineffective or excessively high doses. Depending on the stages of medicinal product development, the endpoints of the studies can be different. For example, in the study of a medicinal product for treatment of the heart

failure, a pharmacodynamic endpoint (for example, cardiac output, wedge pressure) can be used first, after that - an intermediate endpoint (for example, exercise tolerance, symptomatology) whereas mortality or irreversible disability can serve as a final assessment (survival rate, new myocardial infarction). It is quite expected that the dose-effect relationship for the indicated endpoints is different. The choice of endpoints to be studied for registration will depend on the situation.

58. A widely used, successful and acceptable study design (but not the only one aimed at receiving the data on the population average dose-effect relationship) is a parallel randomised dose-effect study with three or more doses, one of which can be zero (placebo) dose. Following the results of such study, and if the doses are selected correctly, one can establish a relationship between the dose of a medicinal product (or its concentration), as well as the clinically desirable or adverse effects.

59. It is necessary to study several doses (at least two), plus the placebo, however, it is recommended to study as many doses as possible. Comparison of a single dose to placebo makes it possible to test the zero hypothesis on no difference between the medicinal product and the placebo, such a study does not provide for evaluation of the dose-effect relationship. Despite the linear dependence based on the results of the study of two doses (plus the placebo), such data, in general, are not sufficiently informative. Study designs usually shall indicate establishment of the dose-effect dependence function and not individual paired comparisons as their objective. If a certain point on the curve (for example, characterising the effectiveness of a specific low dose) is of concern, it shall be studied separately.

60. Data on the dose-effect relationship can provide information on desirable and adverse effects that allow the approval of a certain dose range for which the benefit is higher than the risk. A well-controlled study of the

dose-effect relationship can also become a primary proof of the medicinal product effectiveness.

61. The authorised authorities and developers shall be open to new approaches and to the concept of the well justified and documented search analysis of data in the existing or further created databases for data on the dose-effect relationship.

62. The authorised authorities shall also take into account various statistical and pharmacometric methods, such as:

а) Bayesian and population methods;

б) Modelling, pharmacokinetic and pharmacodynamic approaches.

However, such approaches shall not cancel the requirement to provide the data on the dose-effect relationship of a prospective, randomised clinical trial with multiple doses.

63. Based on the results of *a posteriori* explanatory database analysis of the data on the dose-effect relationship, which has been conducted for other purposes, new hypotheses can be prepared for further study of the dose-effect relationship, but this analysis rarely allows conducting a comprehensive final assessment of the dose-effect relationship of a medicinal product.

64. A variety of analytical methods, including the increased use of retrospective population analysis and new study designs (e.g. the sequential design method) can contribute to establishment of the dose-effect relationship. For example, designs with the fixed doses are allowed to be re-analysed if all the doses are expressed in mg / kg or adjusted by the function of the kidney, the lean body weight, etc. Similarly, determination of the medicinal product concentration in a dose-effect study may provide for a description of the concentration-effect relationship. Correction of the medicinal product exposure can be conducted based on the reliable data on the patient's commitment to the use of a medicinal product. It is always

necessary in all these cases to take into account the distorting effects, that is the availability of factors that simultaneously distort the recalculated dose and effect, the blood concentration and the effect, or the patient's commitment to a medicinal product and the effect of this medicinal product, etc.

65. The data on the dose-effect relationship shall be analysed for differences in subgroups with a break down by demographic characteristics, such as age, sex and race. To achieve it, the knowledge about the pharmacokinetic differences between these groups, for example, due to metabolic differences, differences in body or constitution etc. are required.

66. The decision on registration shall be made on the basis of all available information about a medicinal product. Despite the necessity of data on the dose-effect relationship, depending on the type and degree of the confirmed effectiveness, minor shortcomings in the presented database are possible, if after registration these are eliminated within the post-registration studies. As regards to the effects in special populations, the data on long-term use, potential interactions between medicinal products and medicinal product-disease interactions, it is necessary to provide informative data on the dose-effect relationship, but in case of significant therapeutic benefit, urgent necessity or very low incidence of toxicity, the requirement to provide them may be postponed.