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THE EURASIAN ECONOMIC COMMISSION

THE BOARD

RECOMMENDATION

July 17, 2018 **No. 11** Moscow

On the Guidelines on General Issues of Clinical Trials

In accordance with Article 30 of the Treaty on the Eurasian Economic Union dated May 29, 2014 and paragraph 3 of Article 3 of the Agreement on Common Principles and Rules of Circulation of Medicinal Products within the Eurasian Economic Union dated December 23, 2014,

with a view to harmonize the requirements for conducting clinical trials established by the legislation of the Eurasian Economic Union Member States,

the Board of the Eurasian Economic Commission **recommends** the Eurasian Economic Union Member States to apply the Guidelines on General Issues of Clinical Trials as laid down in the annex when conducting clinical trials of medicinal products for their marketing authorization in accordance with the Rules of Marketing Authorization and Assessment of Medicinal Products for Medical Use approved by Decision No. 78 of the Eurasian Economic Commission's Council dated November 3, 2016 and bringing the registration dossiers of medicinal products in conformity with the specified Rules after 6 months have elapsed from the date this Recommendation is published on the Eurasian Economic Union's official website.

Chairman of the Board
of the Eurasian Economic Commission T. Sargsyan

SEAL: *THE EURASIAN ECONOMIC COMMISSION * FOR DOCUMENTS*

ANNEX
to the Recommendation No. 11
of the Eurasian Economic Commission's
Board dated July 17, 2018

GUIDELINES
on General Issues of Clinical Trials

I. General provisions

1. The objectives of these Guidelines are:

to describe principles and approaches to conducting individual clinical trials involving the human as a subject (hereinafter referred to as clinical trials) and defining an overall development strategy for new medicinal products;

to facilitate the evaluation and acceptance of the results of clinical trials conducted in third countries' research centers by supporting common understanding of general principles and general approaches to conducting clinical trials and defining relevant terms.

2. The clinical trial principles established in these Guidelines may also be applied to other clinical trials (e.g. radiotherapy, psychotherapy, surgery, clinical trials of medical devices and alternative therapies).

II. General principles

1. Protection of clinical trial subjects

3. The principles and approaches to conducting clinical trials that affect the safety of clinical trial subjects are reflected in the Good Clinical Practice Rules of the Eurasian Economic Union approved by Decision No. 79 of the Eurasian Economic Commission's Council dated November 3, 2016 (hereinafter referred to as the Good

Clinical Practice Rules), comply with the ethical principles of the Helsinki Declaration adopted at the XVIII General Assembly of the World Medical Association in 1964 and should be observed during all clinical trials.

The concepts used herein shall have the meanings as defined in the Good Clinical Practice Rules.

4. Before any clinical trial is initiated, the person responsible for assigning clinical trials shall submit the results of non-clinical or previously conducted clinical trials confirming the safety of the planned clinical trial to the authorized authority of the Eurasian Economic Union Member State. The purpose and timeframes of animal pharmacology and toxicology trials needed to initiate the clinical trial of a given duration are set forth in the guidelines on non-clinical safety studies for conducting clinical trials and marketing authorization of medicinal products approved by the Eurasian Economic Commission (hereinafter – the Commission). The role of such trials with respect to biological products is described in Chapter 5.3 of the Rules for Conducting Trials of Biological Medicines of the Eurasian Economic Union approved by Decision No. 89 of the Eurasian Economic Commission's Council dated November 3, 2016.

5. When developing a medicinal product, results of emerging animal toxicological and clinical trials should be considered and evaluated in terms of safety for the clinical trial subjects. Based on the results obtained, planned and (if necessary) current clinical trials should be appropriately modified in a timely manner to ensure the safety of clinical trial subjects. Investigator, sponsor and institutional review board (independent ethics committee) share responsibility for the protection of clinical trial subjects. The responsibilities of these parties are reflected in the Good Clinical Practice Rules.

2. Scientific approach to design and analysis

6. Optimal development of medicinal products rests upon obtaining information (experimental evidence) on the fundamental issues raised regarding the efficacy and safety of medicinal products. The primary objective of any trial should be clearly and explicitly stated. For this objective to be achieved, clinical trials should be designed, conducted and analyzed according to scientific principles, and trial findings should be appropriately reported.

7. Clinical trials are classified either by their conducting priority during clinical development of a medicinal product, or, as shown in Table 1, by their objectives (the below examples are not exhaustive).

Classification of clinical trials by their objectives

Trial Type	Trial Objective	Examples
Study of the medicinal product's pharmacological properties	Tolerance assessment	Dose tolerance studies
	Definition (description) of pharmacokinetics and pharmacodynamics	Single and multiple dose pharmacokinetic and (or) pharmacodynamics studies
	Study of drug metabolism and interactions	Drug-drug interaction studies
	Activity estimation	
Therapeutic exploratory study	Exploration of use for the targeted indication	Earliest trials of relatively short duration in well-defined small patient populations, using surrogate or pharmacological endpoints or clinical indicators
	Estimation of dosage for subsequent studies	
	Obtaining baseline data for design selection, endpoints and confirmatory study design	Dose-response exploratory studies
Therapeutic confirmatory study	Confirmation (demonstration) of efficacy	Adequate and well controlled studies to establish efficacy
	Establishment of safety profile	Randomized parallel dose-response studies
	Obtaining necessary data for assessing the benefit/risk ratio to support marketing authorization	Clinical safety studies
	Establishment of dose-response relationship	Studies of morbidity (mortality)

Trial Type	Trial Objective	Examples
		Large "simple" studies Comparative studies
Therapeutic use studies	Obtaining additional data for the refinement of the benefit/risk ratio for the population in general, its separate groups and (or) the environment Identification of less common adverse reactions Optimization of dosage regimen	Comparative efficacy studies Studies of morbidity and mortality Studies of additional endpoints Large "simple" studies Pharmacoeconomic studies

The fundamental principle of serially conducted trials of a medicinal product is that the results of prior trials should influence the planning of later trials. Emerging data often require to modify the medicinal product development strategy (for example, results of a therapeutic confirmatory study may require additional human clinical pharmacology studies).

8. Subject to the requirements of the Good Clinical Practice Rules and guidelines for the assessment of ethnic factors affecting the acceptability of clinical data approved by the Commission, the availability of clinical data obtained in third countries' research centers enables to obviate the need to newly obtain such data in the Eurasian Economic Union.

III. Principles and Approaches to Planning Clinical Trials and Individual Components of Clinical Trials

1. Issues of planning clinical trials and individual components of clinical trials as part of medicinal product development

Non-clinical trials

9. Important aspects in determining the scope and timeframes of non-clinical trials for the subsequent conduct of clinical trials are:

a) duration and planned course dose in individual patients;

b) characteristics or origin of the medicinal product (e.g. long half-life, biotechnology products);

c) disease or condition targeted for treatment;

d) use of the medicinal product in special patient populations (e.g. women of childbearing potential);

e) route of administration.

10. Information on non-clinical (toxicological, pharmacological and pharmacokinetic) studies to support the conduct of clinical trials is provided in the guidelines on non-clinical safety studies for conducting clinical trials and marketing authorization of medicinal products and Chapter 5.3 of the Rules for Conducting Trials of Biological Medicines of the Eurasian Economic Union.

Safety studies

11. For the first studies in humans, the dose that is administered should be determined by detailed examination of the prerequisite non-clinical pharmacological, pharmacokinetic and toxicological evaluations in accordance with the guidelines on non-clinical safety studies for the conduct of clinical trials and marketing authorization of medicinal products. Early non-clinical studies should provide sufficient information to support selection of the initial human dose and safe duration of exposure, and to provide information about physiological and toxicological effects of a new medicinal product.

Pharmacological and pharmacokinetic studies

12. The starting point, the direction of development and the clinical study of a medicinal product are determined by a non-clinical pharmacological and pharmacokinetic profile, which includes the following information:

a) pharmacological basis of principal effects (mechanism of action);

b) dose-response and concentration-response relationships and duration of action;

c) study of the potential clinical routes of administration;

d) organized general pharmacology data including pharmacological effects on major organ systems and physiological responses;

e) studies of absorption, distribution, metabolism and excretion.

Quality and quantity of investigated medicinal products

13. Medicinal products used in clinical trials should be well characterized, including information on bioavailability (if applicable). The formulation of a medicinal product should be appropriate for the stage of its clinical development. The quantity of a medicinal product should be adequate to allow testing in a series of studies that examine a range of doses. During medicinal product development, different formulations of a medicinal product may be studied.

14. Links between different formulations of a medicinal product established by bioequivalence studies or other means are necessary for interpreting the results of clinical trials conducted throughout the entire medicinal product development program.

Phases of clinical development of the medicinal product

15. Clinical development of the medicinal product is often described as a four-phase process (development phases from I to IV). The development phase does not always represent a sufficient ground to classify clinical trials because the same trial type may appear in several phases. Therefore, the classification based on trial objectives as described in subsection 2 of Section II of these Guidelines is recommended. The concept of "phase" shall be considered as a characteristic of the medicinal product development process, and not as a set of requirements to it. In addition, phases do not imply a fixed trial priority, since for some medicinal products

a development plan in the form of a fixed trial priority is not appropriate or non-mandatory. For example, although human pharmacology studies are typically conducted during Phase I, many such studies are also conducted at each of the other three phases, while the researcher, however, may label them as Phase I studies. The figure below demonstrates the relationship between objective-based and phase-based classifications of the medicinal product trial process.

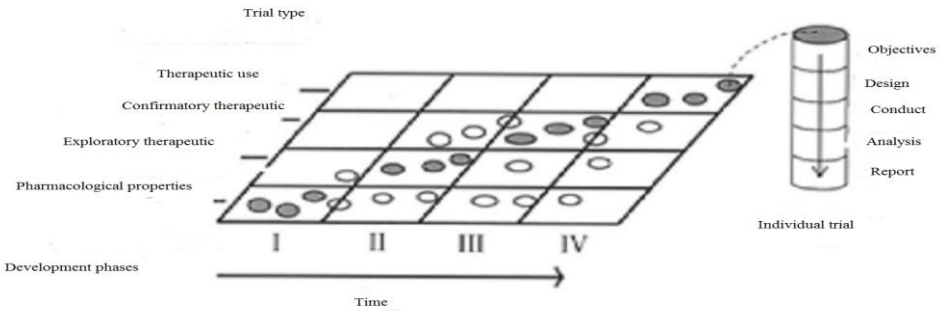

Fig. Correlation between development phases and trial types. *

* The matrix graph illustrates the relationship between development phases and trial types by their objectives that may be conducted during each clinical development of a new medicinal product. The shaded circles show the trial types most usually conducted in a certain development phase, while the open circles show the trial types that are less usual for a specified development phase. Each circle represents an individual trial. To illustrate the structure of an individual trial, one circle is joined by a dotted line to a column that depicts the stage priority for the individual trial. The circles distribution on the graph shows that the trial type is not fully consistent with the development phase.

16. Medicinal product development should be a logical, phased process, in which the results of previous clinical trials with a small number of participants are used to support and plan larger, well-elaborated trials. To develop a new medicinal product in an efficient way, it is necessary to identify its characteristics at the early development stages and to draft a further study plan based on the established profile.

17. The results of initial trials provide first information on short-term safety and tolerance, as well as pharmacodynamic and pharmacokinetic properties needed to

choose a suitable dosage range and a dosing regimen for initial exploratory therapeutic studies. Later confirmatory studies are generally larger and longer and include a more diverse patient population. Dose-response information should be obtained at all development stages, from early tolerance studies and studies of short-term pharmacodynamic effects to large efficacy studies. New data obtained during development may suggest the need for additional trials that are typically part of an earlier phase. For example, blood level data obtained in a late trial may suggest a need for a drug-drug interaction study, whilst adverse reactions may suggest a need for further dose finding and (or) additional non-clinical trials. Furthermore, to support a new indication approval, pharmacokinetic or therapeutic exploratory studies deemed as part of Development Phase I or II shall also be conducted.

Phase I (most typical trial type is human study of the medicinal product's pharmacological properties)

18. Phase I starts with the initial administration of an investigated new medicinal product into humans.

19. Although human studies of the medicinal product's pharmacological properties are typically Phase I studies, they may also be required at later stages of medicinal product development. Studies in this development phase usually have non-therapeutic objectives and may be conducted in healthy volunteer subjects or certain groups of patients (e.g. patients with mild hypertension). Medicinal products with significant potential toxicity (e.g. cytotoxic ones) are usually only studied in patients (i.e. without healthy subjects' participation). Studies in this phase can be open, baseline controlled, or randomized and blinded to improve the reliability of the results.

20. Studies conducted at Phase I typically solve one or a combination of the following tasks:

a) estimation of initial safety and tolerance. Usually, the initial and subsequent administration of an investigated new medicinal product into humans is aimed at determining the tolerance to the dose range expected to be needed for later clinical trials and to determine the nature of adverse reactions that can be expected. These studies typically include both single and multiple dose administration;

b) assessment of pharmacokinetics. Study of absorption, distribution, metabolism, and excretion of the medicinal product continues throughout the development process. However, their preliminary characterization is an important objective of Phase I. Pharmacokinetics is assessed in separate studies or as a part of efficacy, safety and tolerance studies. Pharmacokinetic studies are particularly important to assess the clearance of the medicinal product, assessment of possible accumulation of the parent medicinal product or its metabolites and potential drug-drug interactions. In order to obtain certain data, some pharmacokinetic studies are commonly conducted in the later phases. For many orally administered medicinal products, especially modified release products, the study of food effects on bioavailability is important. Pharmacokinetic study in special patient populations (e.g. patients with renal or hepatic failure, the elderly, children, women and ethnic subgroups) should be considered. Drug-drug interaction studies are needed for most medicinal products. These studies are generally conducted in later phases, but the results of studies in animals and in vitro studies of metabolism and potential interactions may lead to initiating such studies earlier.

c) assessment of pharmacodynamics. Depending on the medicinal product and the endpoint studied, pharmacodynamic studies and concentration-response studies (pharmacokinetic studies, pharmacodynamic studies) may be conducted in healthy volunteer subjects or in patients with the target disease. If there is appropriate criteria, pharmacodynamic data obtained from such patients can provide early estimates of activity and potential efficacy and may guide the dosage and dose regimen in later studies;

d) early measurement of drug activity. When planning this type of clinical study, preliminary studies of activity and potential therapeutic benefit may be considered in Phase I as a secondary objective. Such studies are generally conducted in later phases but may be appropriate when drug activity is easily measurable with a short duration of drug exposure in patients at this early stage.

Phase II (most typical trial type is therapeutic exploratory study)

21. Initiation of study, the main objective of which is to explore the therapeutic efficacy of the medicinal product in patients is usually considered the start of development Phase II.

22. Design of initial therapeutic exploratory studies may vary including concurrent controls and comparisons with baseline values. Subsequent trials are randomized and concurrently controlled to evaluate the efficacy of the medicinal product and its safety for a particular therapeutic indication. Studies in Phase II are typically conducted in a group of patients who are selected by rigid criteria, aimed to form a relatively homogeneous population that is closely monitored.

23. An important objective for this phase is to determine the dose and dose regimen for Phase III trials. Early studies in this phase often feature dose escalation designs to give an early estimate of dose-response relationship. Later studies may confirm the dose-response relationship for the indication in question by using recognized parallel dose-response designs (these studies could also be deferred to Phase III). Confirmatory dose-response relationship studies may be conducted in Phase II or left for Phase III. Doses used in Phase II are usually less than the highest doses studied during Phase I.

24. Additional objectives of clinical trials conducted in Phase II may include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target patient populations (e.g. mild or severe disease) for further

study in Phase II or III. It may be reached by exploratory analyses, examining subsets of data and by including in trials multiple endpoints.

Phase III (most typical trial type is therapeutic confirmatory study)

25. Initiation of study, the main objective of which is to demonstrate, or confirm therapeutic benefit is usually considered the start of development Phase III.

26. Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II indicating that a medicinal product is effective and safe for use in the intended indication and recipient population. The objective of these studies is to obtain sufficient data for marketing authorization. Studies in Phase III further explore the dose-response relationship, the possibility of medicinal product use in various patient populations, in different stages of disease, or in combination with other medicinal products.

27. Medicinal products intended to be administered for long periods are studied in the framework of long-term studies, which are ordinarily conducted in Phase III, although they may be started in Phase II. General requirements for the clinical safety of chronically administered medicinal products and medicinal products used in the elderly are provided in the recommendations on the size of exposure in the population necessary to assess the clinical safety of medicinal products intended for long-term treatment of non-life-threatening conditions according to the appendix and in the guidelines for conducting clinical trials in special groups (elderly patients) approved by the Commission. Phase III studies finalize the collection of information needed to make appropriate recommendations for use of the medicinal product (official information on the medicinal product).

Phase IV (variety of trials - therapeutic use)

28. Phase IV begins after marketing authorization of the medicinal product. It is intended neither to demonstrate efficacy and safety, nor to select doses.

29. In Phase IV all studies (other than routine surveillance) conducted after marketing authorization of the medicinal product and related to the approved indications are possible. These studies are not necessary for marketing authorization but are required for optimizing the medicinal product's use. The studies may be of any type but should have sound scientific objectives. Commonly these studies include additional drug-drug interaction, dose-response or safety studies and studies aimed to support use under the approved indication (e.g. mortality and morbidity studies, epidemiological studies).

Development of the approved medicinal product for a new use

30. After its initial approval, the medicinal product development may continue with studies of new or modified indications, new dosage regimens, new routes of administration or new patient populations. If a new dose, formulation or combination of active substances is studied, additional human pharmacology studies may be required, necessitating drawing of a new development plan.

31. The need for some studies may be obviated by the availability of data from the original development plan or from therapeutic use.

Special Considerations

32. A number of special circumstances and various patient populations require consideration on their own when they are part of the medicinal product development plan.

Studies of medicinal product metabolites

33. Major active metabolites should be identified and their pharmacokinetic should be studied in detail. Timing of the metabolic assessment studies within the

medicinal product development plan depends on the characteristics of the individual medicinal product.

Drug-drug interactions

34. If a potential for drug-drug interaction is suggested based on the metabolic profile, the results of non-clinical studies or information on similar medicinal products, studies on drug-drug interaction during clinical development of a medicinal product are highly recommended.

35. For medicinal products that are frequently prescribed together it is necessary to conduct drug-drug interaction studies as part of non-clinical and (if appropriate) human studies. This is of particular importance for medicinal products that are known to affect the absorption and metabolism of other medicinal products (guidelines for conducting clinical trials in special groups (elderly patients)), and in respect of medicinal products whose metabolism or excretion can be affected by other medicinal products' effects.

Special populations

36. Due to the special circumstances that need to be taken into account during medicinal product development, or because of the expected need to modify the dose or dosage regimen compared to the dose or dosage regimen for the general population when determining the risk/benefit ratio, some groups of patients may require additional studies. Pharmacokinetic studies in patients with renal and hepatic dysfunction are an important step in assessing the impact of impaired medicinal product metabolism or excretion. Issues of conducting clinical trials in elderly patients are addressed in the guidelines for conducting clinical trials in special groups (elderly patients); and those in patients of different ethnic groups are addressed in the guidelines for the assessment of ethnic factors affecting the acceptability of clinical data.

37. The need for non-clinical safety studies to support human clinical trials in special patient populations is addressed in the guidelines on non-clinical safety studies for conducting clinical trials and marketing authorization of medicinal products.

38. In accordance with the Good Clinical Practice Rules, particular attention shall be paid to the ethical considerations related to informed consent from vulnerable groups of trial subjects and the relevant procedures:

a) trials in pregnant women. Pregnant women should be excluded from clinical trials where the medicinal product is not intended for use in pregnancy. If a patient becomes pregnant during administration of the medicinal product, treatment should be discontinued (if this can be done safely). Follow-up evaluation of the pregnancy, fetus, and child is necessary. If the medicinal product is intended for use during pregnancy, the need for follow-up evaluation of pregnancy, fetus and child remains;

b) trials in nursing women. Excretion of the medicinal product or its metabolites into human milk should be examined (where possible). When nursing mothers are enrolled in a clinical trial, their babies should be monitored for the effects of the medicinal product;

c) trials in children. The extent of the trials needed depends on the current knowledge of the medicinal product and the possibility of extrapolation of data obtained from adults and children of other age groups. Some medicinal products may be used in children from the early stages of medicinal product development (guidelines on non-clinical safety studies for the conduct of clinical trials and marketing authorization of medicinal products).

39. For a medicinal product expected to be used in children, evaluation should be made in the appropriate age group. When clinical development includes studies in children, it is appropriate to begin with older children before extending it to younger children including babies.

2. Principles for conducting clinical trials as part of medicinal product development

40. The below principles should be followed in planning the objectives, design, conduct and reporting of a clinical trial as well as in analyzing such report. Before the trial is initiated, each part of it should be described in a protocol as specified in the Good Clinical Practice Rules.

Objectives

41. The trial's objective should be clearly stated. The trial's objectives may include exploratory or confirmatory characterization of safety and (or) efficacy and (or) assessment of pharmacokinetic parameters and pharmacological, physiological, and biochemical properties of medicinal products.

Design

42. The appropriate trial design should be chosen to provide the desired information (for example, parallel group, cross-over, factorial, dose escalation or dose-response relationship) in accordance with the guidelines for the estimation of medicinal products' dosage, guidelines on the principles for using biostatistics in clinical trials, guidelines on the principles for selecting control group in clinical trials, approved by the Commission, and the Good Clinical Practice Rules.

43. Appropriate comparators should be used and adequate numbers of subjects included to achieve the study objectives. Primary and secondary endpoints and plans for their analyses should be clearly stated in accordance with the guidelines on the principles for using biostatistics in clinical trials. The methods of monitoring adverse reactions by changes in clinical signs and symptoms and laboratory studies should be described (Annex No. 1 to the Good Clinical Practice Rules). The protocol should specify procedures for the follow-up of patients who stop treatment prematurely.

Selection of trial subjects

44. The development stage and the indication to be studied should be taken into account in selecting the subject population (e.g. normal healthy subjects, cancer patients or other special populations) in the early phase of medicinal product development as should results of non-clinical and prior clinical trials. It is allowed to establish strict selection criteria in order to reduce the heterogeneity of groups of patients or healthy volunteers in early trials, but as development proceeds, the populations tested should be broadened to reflect the target population.

45. Depending on development stage and level of concern for safety of the medicinal product, it may be necessary to conduct trials in closely monitored conditions, i.e. in inpatient facility.

46. As a general principle, trial subjects should not participate concurrently in more than one clinical trial but there can be justified exceptions. Subjects should not be enrolled repetitively in clinical trials without time off treatment adequate to protect safety and exclude carry-over effects.

47. Women of childbearing potential should be using highly effective contraception to participate in clinical trials (guidelines on non-clinical safety studies for the conduct of clinical trials and marketing authorization of medicinal products).

48. For male subjects participating in clinical trials, potential hazards of medicinal product exposure to their sexual partners or resulting progeny should be considered. When indicated (e.g. trials of medicinal products that are potentially mutagenic or toxic to the reproductive system), an appropriate contraception provision should be included.

Selection of control group

49. Trials should include an adequate control group. Comparisons should be made with placebo, no treatment, and active controls or of different doses of the investigated medicinal product. The choice of method of comparison also depends on the objective of the trial (guidelines on the principles for using biostatistics in clinical

trials, guidelines on the principles for selecting control group in clinical trials). Historical (external) controls can be justified in some cases but particular care should be used to minimize the likelihood of erroneous inference.

Number of subjects

50. The size of a trial depends on the disease to be investigated, the trial objective and its endpoints. Statistical assessments of sample size should be based on the expected magnitude of the treatment effect, the variability of the data, the specified (small) probability of error (guidelines on the principles for using biostatistics in clinical trials) as well as information desired, patient groups or secondary endpoints.

51. In some circumstances, a larger data may be needed to assess the safety of a medicinal product. Minimal requirements for the safety assessment of medicinal products to obtain registration data for a new indication are provided in the recommendations on the size of exposure in the population necessary to assess the clinical safety of medicinal products intended for long-term treatment of non-life-threatening conditions according to the appendix to these Guidelines and in the guidelines for conducting clinical trials in special groups (elderly patients). These numbers should not be considered as absolute and data may be insufficient in some cases (e.g. where long-term use in healthy individuals is expected).

Response variables

52. Response variables should be defined prospectively, giving descriptions of methods of observation and quantification. Objective methods of observation should be used (when appropriate) in accordance with the guidelines on the principles for using biostatistics in clinical trials.

53. Trial endpoints are the response variables that are chosen to assess the medicinal product’s effects that are related to pharmacokinetic parameters,

pharmacodynamic properties, efficacy and safety. A primary endpoint reflects clinically relevant effects and is typically selected based on the principal objective of the study. Secondary endpoints assess other effects of the medicinal product that may be unrelated to the primary endpoint. Endpoints and the plan for their analysis should be specified in the clinical trial protocol.

54. A surrogate endpoint is an endpoint that is intended to relate to a clinically important outcome, but it does not measure a clinical benefit on its own. Surrogate endpoints may be used as primary endpoints when sufficiently justified (when such endpoint is highly likely or well known as an indicator of clinical outcome).

55. The methods used to make the measurements of the endpoints, both subjective and objective, should be validated and meet appropriate standards for accuracy, precision, reproducibility, reliability, and responsiveness (sensitivity to change over time).

Methods to minimize and identify systemic errors (biases)

56. In accordance with the guidelines on the principles for using biostatistics in clinical trials, the protocol should specify methods of allocation of subjects to treatment groups and blinding:

a) randomization. When conducting a controlled trial, randomized allocation is the preferred means of assuring comparability of test groups and minimizing the possibility of selection bias.

b) blinding. Blinding is an important means of minimizing the risk of biased trial outcomes. A trial where the treatment assignment is not known by trial subjects because using placebo or other methods of masking the intervention, is referred to as a single blind trial. When the investigator and sponsor staff involved in the trial or clinical evaluation of the subjects or data analysis are also unaware of the treatment assignments, the trial is then deemed as double blind;

c) compliance.

57. Methods used to evaluate patient usage of the tested medicinal product should be specified in the trial protocol and instructions.

Conduct

58. The trial should be conducted according to the principles described in these Guidelines and in accordance with other relevant provisions set out in the Good Clinical Practice Rules. The compliance with the trial protocol is mandatory. If the protocol is modified, a clear description of the rationale for the modification should be provided in (amendments to the protocol). Timely adverse event reporting during a trial is required and should be documented. Recommendations on expedited reporting of safety data to appropriate officials and on the content of safety reports and on privacy policy are set out in the Good Clinical Practice Rules.

Analysis

59. The trial protocol should provide analysis plan that is appropriate for the objectives and design of the trial, taking into account the method of subject allocation, the measurement methods of response variables, hypotheses to be tested, and analytical approaches to common problems including early study withdrawal and protocol violations. A description of the statistical methods used including timing of any planned interim analyses should also be included in the protocol in accordance with the Good Clinical Practice Rules and the guidelines on the principles for using biostatistics in clinical trials.

60. The results of a clinical trial should be analyzed in accordance with the plan prospectively stated in the protocol and all deviations from the plan should be indicated in the trial report. The Good Clinical Practice Rules provide detailed guidance on planning the trial protocol, preparation of research report and general approaches to statistical data processing, and the guidelines on the principles for using

biostatistics in clinical trials provide detailed guidance on the statistical analysis plan and the processing of research data.

61. Trials are normally expected to run to their scheduled completion; however, some can be stopped early. In such cases, this possibility should be clearly described in the protocol with due statistical attention to the overall levels of statistical significance and to the need to adjust the estimates of the size of treatment effects as set out in the guidelines on the principles for using biostatistics in clinical trials.

62. Safety data should be collected for all clinical trials, appropriately tabulated with adverse reactions classified according to their seriousness and their likely causal relationship.

Clinical report

63. Clinical trial reports should be adequately documented following the requirements set out in the Good Clinical Practice Rules.

APPENDIX
to the Guidelines on General Issues
of Clinical Trials

RECOMMENDATIONS
on population exposure required to evaluate clinical safety of medicinal products intended for long-term treatment of non-life-threatening conditions

1. The objective of these recommendations is to describe an accepted system of principles for evaluating the safety of medicinal products intended for long-term treatment (continuous or repeated intermittent use for longer than 6 months) of non-life-threatening conditions. The safety evaluation during clinical development shall characterize and quantify the safety profile of a medicinal product over a reasonable duration of time consistent with the intended long-term use of the medicinal product. Hence, the duration of medicinal product exposure and its relationship to both time and magnitude of occurrence of adverse reactions are important considerations in determining the size of the database required for safety evaluation.

2. Under these recommendations, it is advisable to distinguish between clinical data on adverse drug reactions derived from trials of shorter duration of exposure and data from trials of longer duration, which frequently are non-concurrently controlled trials. Short-term event rates (cumulative 3-month incidence of about 1%) should be described in detail. Adverse reactions where the rate of occurrence changes over a longer period may need to be characterized depending on their severity and importance to assess benefit/risk ratio of the medicinal product. The safety evaluation during clinical development of the medicinal product is not expected to characterize rare adverse reactions (for example, those occurring in less than 1 in 1000 patients).

3. The design of clinical trials can significantly influence the ability to make causality judgements about the relationships between the medicinal product and adverse reactions. Placebo-controlled trials allow the adverse reaction rate in a group treated with the medicinal product to be compared directly with the background event rate in the patient population being studied. Although studies with active control will allow comparing adverse event rates of the tested medicinal product with those of the reference medicinal product, no direct assessment of the initial reaction rate in the studied population can be made. A trial that has no concurrent control group makes it even more difficult to assess the causality relationship between adverse reactions observed and the investigated medicinal product.

4. When calculating population exposure required to assess clinical safety for medicinal products intended for long-term treatment of non-life-threatening conditions, the following factors are taken into account:

a) use of harmonized approach to estimate the extent and duration of treatment needed to provide the safety database for medicinal products intended for long-term treatment of non-life-threatening conditions (despite the fact that the approach proposed in these recommendations covers many indications and pharmacological classes, certain exceptions are allowed);

b) regulatory standards for the safety evaluation of medicinal products should be based on previous experience with the occurrence and detection of adverse drug reactions, statistical considerations of the probability of detecting specified frequencies of adverse drug reactions and practical aspects;

c) information about the occurrence of adverse drug reactions in relation to treatment duration for different medicinal product classes is incomplete, and therefore further trials to obtain this information are advisable;

d) according to the available data, most adverse drug reactions first occur, and are most frequent, within the first few months of drug treatment. The number of patients treated for 6 months at dosage levels intended for clinical use, are required to

characterize the pattern of adverse drug reactions over time. To achieve this the cohort of exposed subjects should be large enough to observe whether more frequently occurring reactions increase or decrease over time as well as to observe delayed reactions of reasonable frequency (e.g., in the range of 0.5% – 5%). Usually, involving 300 to 600 patients is enough;

e) it should be taken into account that, although they are likely to be uncommon, some adverse drug reactions may increase in frequency or severity with time or that some serious adverse drug reactions may occur only after drug treatment for more than 6 months, therefore, some patients should be treated in the course of a 12-month trial. In the absence of more information about the relationship of adverse drug reactions to treatment duration, selection of a specific number of patients to be followed for 1 year is to a large extent a judgement based on the probability of detecting a given adverse drug reaction frequency level and practical aspects.

The minimum allowable size of the safety database is data on 100 patients who have been exposed for 1 year. To obtain such information for doses intended for clinical use, data should be collected from properly planned prospective trials. When no serious adverse drug reaction is observed within a 1-year period, this number of patients can provide reasonable assurance that the true cumulative annual incidence does not exceed 3%;

f) the total number of patients treated with the investigated medicinal product, including short-term use, should be at least 1500. It is acceptable to involve 500 to 1500 patients with the relevant requirements for post-marketing surveillance; the actual number is determined by the available information on the medicinal product and the pharmacological class;

g) in some cases, the harmonized general standards for clinical safety evaluation are not applicable. It should be understood that the clinical database efficacy testing may be occasionally larger or may require longer patient observation than that required by these recommendations.

5. When applying the harmonized approach specified in subparagraph a) of paragraph 4 of these recommendations, the following exceptions are allowed when calculating the population exposure (additional examples are also possible):

a) circumstances where there is a possibility of late developing adverse drug reactions, or adverse drug reactions that increase in severity or frequency over time, would require a larger and (or) longer-term safety database. In respect of these circumstances, the information obtained in the course of the following is taken into account:

non-clinical trials of the medicinal product;

clinical use of other agents with similar chemical structures or from the same pharmacological class;

study of pharmacokinetic or pharmacodynamic properties of the medicinal product, which can cause late developing adverse drug reactions, or adverse drug reactions that increase in severity or frequency over time;

b) situations where quantification of the occurrence rate of expected low-frequency adverse drug reactions will require a greater long-term database (for example, if specific serious adverse drug reactions occur when using similar medicinal products or if a reaction occurs during early clinical trials that causes serious concern of the developer or authorized authorities);

c) risk/benefit decision-making based on a larger safety database where the benefit from the medicinal product is either

small (e.g., symptomatic improvement in less serious (insignificant) medical conditions) or

is shown only in a fraction of the treated patients (e.g., certain preventive therapies administered to healthy populations) or

is of uncertain magnitude (e.g., efficacy was determined on a surrogate endpoint);

d) there is concern that a medicinal product may add to an already significant background rate of morbidity or mortality, which may require to include a sufficient number of patients in clinical trials for obtaining adequate statistical power to detect a predetermined increase over the baseline morbidity and mortality;

e) small size of the homogeneous target population of subjects allowing for the inclusion of a smaller number of patients.