

Pursuant to Article 78, paragraph 3 and Article 199 paragraph 3 of the Law on Medicines and Medical Devices ("Official Gazette of the RS", nr. 30/10)
The Minister of Health hereby adopts the

Rulebook on the Contents of the Application, and/or Documentation on the Approval of Clinical Trials for Medicines and Medical Devices, as well as the Method of Implementation for Clinical Trials of Medicines and Medical Devices

The Rulebook hereof was published in the „Official Gazette of the RS”, nr. 64/2011 of 31 August 2011

I. INTRODUCTORY PROVISIONS

1. Rulebook Contents

Article 1

The Rulebook hereof prescribes the content, and/or documentation for the approval of clinical trials for medicines and medical devices, as well as the method of implementation for clinical trials of medicines and medical devices in human medicine.

2. Terms Used in the Rulebook Hereof

Article 2

The terms used in the Rulebook hereof have, as per the Rulebook hereof, the following meaning:

1) Clinical trials of a medicine are trials conducted on humans in order to determine or confirm the clinical, pharmacological and pharmacodynamic properties of a medicine, determine all adverse reactions to the medicine being tested, to test the resorption, distribution, metabolism and excretion of the medicine, and establish its safety, and/or efficacy. Clinical trials of a medicine encompass the postmarketing intervention clinical trials of the medicine, as well as the postmarketing non-intervention clinical trials of the medicine;

2) Clinical trials of a medical device are the procedure determining or confirming the safety and efficacy of a medical device are in line with the declared application as established by the manufacturer.

3) Postmarketing intervention clinical trials of medicines are trials whereby the medicine is applied pursuant to the conditions listed in the authorization for placing the medicine on the market (conditions listed in the Summary of Product Characteristics), requiring additional diagnostic procedures, as well as monitoring procedures as established by the Protocol on Clinical Trials of the Medicine;

4) Bioequivalence studies in vivo are clinical studies on subjects (healthy volunteers or sick patients) aiming to compare the speed and degree of resorption from pharmaceutical forms of medicines expressing systemic effects and containing equimolar amounts of the active substance;

5) Postmarketing non-intervention clinical trials of medicines (pharmacoepidemiological trials) are trials whereby the medicine is applied pursuant to the conditions listed in the authorization for placing the medicine on the market, with the choice of patient not predetermined by the Protocol for Clinical Trials, instead being part of the current practice of standard treatment. However, the prescription of the medicine is clearly separate from the decision of including the patient in the trials. Additional

diagnostic procedures or monitoring procedures are not applied, while the data obtained is analysed using epidemiological methods;

6) Investigational medicinal product is the pharmaceutical form of the active substance being tested, or a placebo used for comparison with the tested substance, as well as the medicine with an authorization for placement on the market if its form or packaging is changed, and/or if it is used in a way different to the approved method of use as per the authorization for placing the medicine on the market, when the medicine is tested for application with new indications and when the medicine is used to provide new information on its approved use;

7) Guidelines of Good Clinical Practice – GCP (hereinafter: Good Clinical Practice) are a system of guidelines for quality assurance in planning and implementation of clinical trials in order to obtain valid clinical conclusions with the adequate protection of trials participants;

8) Subjects are persons taking part in the clinical trials of the medicine regardless of whether they use the medicine being clinically tested or participate in the testing in order to control the application of the medicine, i.e. if they are taking the medicine that the one being clinically tested is being compared to;

9) Informed subject consent is a written statement, dated and signed, on participation in a certain clinical trial of a medicine, provided by a person capable of providing consent or, if the person is unable to provide consent, provided by their legal representative, pursuant to the law, provided willingly and having all information on the nature, importance, consequences and health risks of the trials (hereinafter: willing informed consent);

10) Subject safety is the physical and mental integrity, i.e. safety of the subject participating in the clinical trials of the medicine;

11) Subject identification code is the unique designation assigned to all subjects by the investigator, used instead of their name, in order to provide identity protection for subjects when reporting adverse reactions to the medicine, i.e. when providing other data regarding the clinical trials of the medicine;

12) Investigator in clinical trials is a doctor of medicine or doctor of dentistry directly involved and responsible for the treatment and care for patients or participants in the trials and responsible for the implementation of clinical trials; if the clinical trials of medicines are conducted by a investigation team, the investigator responsible for the implementation of clinical trials for the medicine is the principal investigator;

13) Investigator's brochure is the document containing preclinical and clinical data on the medicine being tested, of importance for the testing of the medicine;

14) Ethics committee is the professional body formed at the healthcare institution pursuant to the law regulating healthcare protection;

15) Decision of the ethics committee is a decision made by the ethics committee approving the clinical trials of the medicine on site, within the limits established by the ethics committee and the Guidelines for Good Clinical Practice, pursuant to the law and the Rulebook hereof;

16) Protocol of clinical trials for medicines and medical devices (hereinafter: Protocol) is a document describing the goals, design, methodology, statistical considerations and organization of clinical trials. The term protocol encompasses the Protocol, versions of the Protocol and amendments to the Protocol;

17) Sponsor of the clinical trials is a natural or legal person taking on the responsibility for initiating, implementing, and/or financing the clinical trials;

18) Report on the completed clinical trials of the medicine is a document on the full testing of the therapy, prophylactic or diagnostic efficacy of the medicine being tested, listing the unified clinical and statistically significant data, findings and analysis of the obtained test results (report on the process, results and conclusions of the trials, pursuant to the Guidelines of Good Clinical Practice);

19) The tri-monthly report during the clinical trials of the medicine encompasses the report on the number of subjects involved per site, the occurrence of adverse reactions, as well as other data of importance for the implementation of clinical trials;

20) Comparator (Product) is the investigational medicine or a medicine on the market representing active control or placebo used for comparison with the investigational medicine;

21) Clinical trials control is the procedure whereby the Agency controls whether a certain clinical trial is being conducted pursuant to the Protocol, i.e. Guidelines for Good Clinical Practice, at the site, at the sponsor's location, at another legal or natural person the proposing party authorized by contract, partly or in full as regards the clinical trials of the medicine, or if needed in other relevant locations;

22) Source documentation represents the original documents, data and files (e.g. history of illness, clinical and administrative documents, laboratory findings, memos, subject journals or case report forms, records on medicines issued, automatic records, copies or transcripts validated following authenticity control, negatives of photographs, microfilms or magnetic records, roentgen recordings, records kept at the pharmacy, laboratory, or medical-technical services involved in the clinical trials of the medicines);

23) Source data represents all original medical data from the source documentation and validated copies of original clinical and laboratory findings or other results of activities implemented during clinical trials of the medicine required for the assessment of the test results, found in the source documentation (as originals or validated copies);

24) Quality assurance for the clinical trials of medicines is a set of planned and systematic activities established to secure the implementation of clinical trials, as well as the entry, storage and analysis of data pursuant to the Guidelines of Good Clinical Practice, the Law and the Rulebook hereof;

25) Site of clinical trials is the healthcare institution or multiple healthcare institutions wherein the subject is being treated, used for the implementation of clinical trials;

26) The monitor is a person specially enabled to monitor the implementation of clinical trials for a medicine for the sponsor, and provide that the flow, documentation and reports of clinical trials of a medicine are in line with the Protocol, standard operating procedures, Guidelines of Good Clinical Practice and regulations in effect;

27) Standard Operating Procedures – SOP are detailed written instructions for achieving uniformity of all procedures in the conduct of clinical trials of a medicine;

28) Monitoring report is a written report delivered by the monitor to the proposing party for the clinical trials of the medicine after all visits to the site, as well as reports on all other data regarding the clinical trials of the medicine, pursuant to the standard operating procedures of the proposing party for the clinical trials of the medicine;

29) Auditors are specially trained persons independently assessing, on behalf of the sponsor, the level of compliance of all activities related to the clinical trials of the medicine with the Protocol, standard operating procedures of the sponsor, Guidelines of Good Clinical Practice, the Law and the Rulebook hereof;

30) Essential documentation is documents enabling, individually and as a whole, the assessment of the implementation of clinical trials and the quality of the data obtained;

31) Case report forms are the printed or electronic documents for all subjects, intended for recording all data required by the Protocol, for reporting to the proposing party;

32) Multicentre clinical trials are clinical trials of a medicine performed pursuant to a unified Protocol in multiple sites and with multiple investigators, regardless of whether the sites are in one or several countries;

33) The contract research organization is the legal person to whom the sponsor of clinical trials contractually transferred part or all of their obligations regarding the clinical trials of the medicine, and responsible for sponsor affairs during the procedures of approval and implementation of clinical trials of the medicine within the territory of the Republic of Serbia;

34) Blind clinical trials of a medicine are a procedure providing for one or several parties to the trials having no insight into the affiliation of subjects with therapy groups. Single-blind clinical studies mean that the subject(s) have no insight into their affiliation with a therapy group, while a double-blind clinical study means that insight into the

affiliation with therapy groups is, as a rule, held by neither the subject, the investigator, the monitor, or the data analyst;

35) Randomization is the procedure of assigning subjects into the therapy or control group, using random selection for inclusion in order to reduce investigator bias;

36) Non-commercial clinical trials of the medicine (academic clinical trials of the medicine) are implemented by scientific investigation institutions, without participation by the pharmaceutical industry. These trials are conducted on medicines with authorizations.

II. CLINICAL TRIALS OF MEDICINES

Article 3

The proposal of clinical trials, implementation of clinical trials and reporting on clinical trials of medicines are performed pursuant to the Guidelines of Good Clinical Practice (GCP).

Clinical trials of medicines on children are likewise implemented pursuant to the Guidelines of Clinical Testing of Medicines on Children, printed with the Rulebook hereof and comprising its integral part.

Clinical trials of medicines also encompass the postmarketing intervention, or non-intervention clinical trials of medicines, non-commercial clinical trials of medicines (academic clinical trials of medicines) and clinical trials of bioavailability, and/or bioequivalence.

The provisions of the Rulebook hereof do not apply to postmarketing non-intervention clinical trials of medicines, unless the Rulebook hereof prescribes otherwise.

1. Application for the Approval of Clinical Trials of Medicines

Article 4

The application for the approval of clinical trials for medicines shall be submitted to the Agency, using the application form for the approval of clinical trials.

The application as per paragraph 1 of the Article hereof is provided on Form 1, printed with the Rulebook hereof and comprising its integral element.

The submitter of the application for the approval of clinical trials of medicines and medical devices is the sponsor of the clinical trials (hereinafter: sponsor) with their headquarters in the Republic of Serbia, and/or the contract research organization authorized for the work by the sponsor.

2. Application Form for the Approval of Clinical Trials

Article 5

The sponsor shall, prior to the start of clinical trials of medicines, submit to the Agency an application using Form 1 as per Article 4, paragraph 2 of the Rulebook hereof with the documentation for the approval of clinical trials.

3. Documentation for the Approval of Clinical Trials

Article 6

The documentation for the approval of clinical trials of medicines shall contain:

- 1) Covering letter by the sponsor;
- 2) Protocol;
- 3) Protocol Synopsis in the Serbian language;
- 4) Information on adverse reactions to the medicine, unless part of the Investigator's Brochure;
- 5) Investigator's Brochure;
- 6) Investigational Medicinal Product Dossier (IMPD), i.e. the documentation from the investigational medicinal product dossier in another format if the sponsor does not have the required documentation prepared in the IMPD format;
- 7) Summary of Product Characteristics with authorization;
- 8) Case Report Form (CRF);

9) Decision of the ethics committee of the healthcare institution that will implement the clinical trials, and/or ethics committees if they are multicentre clinical trials;

10) Written consent by the general manager of the healthcare institution, and/or healthcare institutions wherein the clinical trials of the medicine will take place;

11) Documentation on the investigational medicine, Good Manufacturer Practice certificate of a European Union country or another country with the same or similar requirements regarding Good Manufacturer Practices, and/or a certificate on the application of Good Manufacturer Practice issued by the competent ministry pursuant to the law, and/or a report by the inspection for medicines of the competent ministry on compliance with the conditions for the manufacture of medicines for clinical trials, no older than six months, an analysis certificate, labelling for the medicine in the Serbian language and the original language, both for the medicine being tested, as well as the comparative medicine;

12) Certificate confirming that the material of animal or human origin being used in the production of the medicine does not pose a risk of transmission of spongiform encephalopathy – TSE certificate, if required;

13) Additional requirements for medicines with specific characteristics (genetically modified organisms, radiopharmaceuticals);

14) Certificate of Good Manufacturing Practice for the location of the production of the active biological substance of a European Union country or another country with the same requirements regarding Good Manufacturer Practice, and/or a statement by a person qualified for releasing a series of medicines for clinical trials confirming the active biological substance was manufactured pursuant to Good Manufacturing Practices for active substances, and/or a report by the inspection of the competent ministry on the compliance of the manufacturing of the active biological substance with the Guidelines of Good Manufacturing Practice for active substances no older than six months,

15) Written statement by the principal investigator of being familiar with the properties of medicines in clinical trials and the goal of the clinical trials, as well as on conducting the trials pursuant to the regulations in effect and the principles of Good Clinical Practice;

16) Evidence of the importer of the medicine for clinical trials holding an authorization for the wholesale of medicines issued by the competent ministry;

17) Brief resume and references for the principal investigator;

18) Evidence of the sponsor insuring persons undergoing clinical trials in case of health damage to subjects for the period of the implementation of clinical trials;

19) Form for subject information and written consent signed by the subjects, in the Serbian language;

20) Validated copy of the contract on the transfer of authorization to the contract research organization;

21) Other subject information (patient journal, instructions, etc. in the Serbian language);

22) List of countries where the medicine obtained authorization;

23) List of countries where clinical trials for the same medicine were approved, and/or approvals of ethics committees and authorized bodies;

24) List of places where the same clinical trials of medicines are being conducted, if the trials are multicentre trials;

25) Additional information related to the protection of subject health, at the request of the Agency;

26) Evidence of having paid the prescribed tariffs to the Agency for issuing authorizations for the clinical trials of the medicine.

4. Method for the Submission of Documentation for the Approval of Clinical Trials

Article 7

The documentation for the approval of clinical trials as per Article 6 of the Rulebook hereof shall be submitted to the Agency in writing, in the script and language in official use in the Republic of Serbia.

The documentation as per paragraph 1 of the Article hereof may also be submitted electronically (10 disks), with the sponsor delivering the documentation in writing along with the electronic documentation.

If the sponsor is submitting the documentation on the medicine as a photocopy, they shall confirm in writing the veracity of the photocopy to the original documentation to the Agency.

The documentation for the approval of clinical trials as per Article 6, paragraph 1, items 2), 4), 5), 6), 8), 11), 12), 13) and 14) may also be submitted in the English language.

5. Content of the Covering Letter

Article 8

The covering letter as per Article 6, paragraph 1, item 1 of the Rulebook hereof contains the:

- 1) Logo, name and address of the sponsor;
- 2) Case, or brief contents of the application for the approval of clinical trials;
- 3) Name of the clinical trials;
- 4) Name of the investigational medicine;
- 5) Pharmaceutical form and potency of the medicine;
- 6) Manufacturer name;
- 7) List of documentation;
- 8) Date and signature of the person responsible for the clinical trials of the medicine.

6. Contents of the Protocol for the Clinical Trials

Article 9

The Protocol as per Article 6, paragraph 1, item 2) of the Rulebook hereof contains:

- 1) General information;
- 2) Basic information;
- 3) Goals and purpose of the clinical trial of the medicine;
- 4) Plan of clinical trials for the medicine;
- 5) Choice of subjects
- 6) Data on subject treatment;
- 7) Efficacy assessment;
- 8) Safety assessment;
- 9) Statistical Data;
- 10) Data on direct access to source data or documents;
- 11) Data on quality control and assurance;
- 12) Ethical aspects of the clinical trials for the medicine;
- 13) Data on data management and documentation storage;
- 14) Data on financing the clinical trials for the medicine and subject insurance;
- 15) Method of publishing results on the clinical trials of the medicine;
- 16) Other documents.

The contents of the Protocol are provided in Annex 1, printed with the Rulebook hereof and comprising its integral element.

7. Investigator's Brochure

Article 10

The Investigator's Brochure as per Article 6, paragraph 1, item 5) of the Rulebook hereof contains:

- 1) Title page;
- 2) Non-Disclosure Agreement;
- 3) Contents;
- 4) Synopsis;
- 5) Introduction;
- 6) Physical, chemical and pharmaceutical characteristics of the pharmaceutical form of the medicine;

- 7) Data on the pre-clinical testing of the medicine;
- 8) Data on the effects of the tested medicine on humans;
- 9) Conclusions.

The contents of the Investigator's Brochure are provided in Annex 2, printed with the Rulebook hereof and comprising its integral element.

In addition to the data as per paragraph 1 of the article hereof, the Investigator's Brochure also contains data on the quality, safety and efficiency of the medicine, as well as an assessment of the risk to benefit ratio of the tested medicine.

The documentation as per paragraph 3 of the article hereof relates to the medicine being clinically tested, as well as the comparative medicine.

8. Application of Postmarketing Non-Intervention Clinical Trials of Medicines

Article 11

The postmarketing non-intervention clinical trials of an authorized medicine shall be reported to the Agency by the sponsor prior to the start of trials for the medicine, if the trials are conducted as per the approved Specification of Product Characteristics.

The Report as per paragraph 1 of the article hereof contains:

- 1) Covering letter by the sponsor as per Article 6, paragraph 1, item 1) of the Rulebook hereof;
- 2) Completed Form 1 as per Article 4, paragraph 2 of the Rulebook hereof, of the request related to the application for clinical trials;
- 3) Opinion of the ethics committee of the healthcare institution wherein the clinical trials are to be held, i.e. ethics committees if it is to be a multicentre clinical trial for the medicine;
- 4) Evidence of having paid the prescribed tariffs.

The Agency shall issue a receipt on the application for postmarketing non-intervention clinical trials of the medicine as per paragraph 1 of the article hereof at the latest 30 days as of the date of application submission.

9. Application for Amendments to the Postmarketing Non-Intervention Clinical Trials

Article 12

Should the sponsor submit an application for new sites for postmarketing non-intervention clinical trials, the Agency shall issue a confirmation on the amendments to the application for postmarketing non-intervention clinical trials.

10. Amendments to the Implementation of Clinical Trials for Medicines

Article 13

The sponsor shall monitor the scientific-technical development of the profession, pharmacovigilance results and other key data, and thus report to the Agency on administrative and substantial amendments to the implementation of the clinical trials of a medicine that might significantly impact the safety, and/or the physical and psychological integrity of the subject, the scientific value of the clinical trials, the further implementation of clinical trials, as well as the quality and safety of the medicine being tested (hereinafter: substantial amendments).

Administrative amendments as per paragraph 1 of the article hereof may also relate to other prescribed documentation for the procedure of issuing approval for clinical trials.

The Agency shall issue a confirmation for administrative amendments as per paragraph 1 of the Article hereof on the date of submitting the application.

11. Substantial Amendments

Article 14

Substantial amendments also relate to the:

- 1) Protocol;
- 2) Organization of clinical trials;
- 3) Quality of the medicine being tested;
- 4) Pharmacological-toxicological data;
- 5) Clinical data;
- 6) Other prescribed documentation for the procedure of issuing approval for clinical trials of the medicine pursuant to Agency assessment.

a) Substantial Amendments to the Protocol

Article 15

Substantial amendments to the Protocol relate to: the goals of clinical trials, design of clinical trials, wilful informed consent of the subjects, procedure of subject selection, efficiency parameters, system for sampling the subjects, changes to the procedure for monitoring the subjects, number of subjects, age of subjects, criteria for including and excluding subjects from the medicine trials, safety monitoring, duration of taking the medicine being tested, changes to the dosage of the medicine being tested, changes to the comparative medicine, analysis of statistical data.

b) Substantial Amendments to the Organization of the Implementation of Clinical Trials

Article 16

Substantial amendments to the organization of the implementation of clinical trials are changes to the principal investigator, site (new sites), sponsor or the authorized representative, changes in duties transferred to the contract research organization, as well as changes to the end of clinical trials.

v) Substantial Amendments to the Data on the Quality of the Medicine Being Tested

Article 17

Substantial amendments to the data on the quality of the medicine being tested are: changes to the code or name of the medicine being tested, internal packaging of the medicine, manufacturer of the active substance, production process for the active substance, active substance specification, manufacturing of the medicine, medicine specification, specification of excipients where they may impact the final medicine, expiry date of the medicine including expiry date after the first opening and reconstitution, large changes to the formulation, conditions of medicine storage, procedure of testing the active substance, procedure of testing non-pharmacopoeic excipients.

g) Substantial Amendments to the Pre-Clinical Pharmacological – Toxicological Data

Article 18

Substantial amendments to pre-clinical pharmacological - toxicological data relates to: results of new pharmacological tests, new interpretations of existing pharmacological tests, results of new toxicological tests, new interpretation of the existing toxicological test, and results of new medicine interaction studies.

d) Substantial Amendments to the Clinical Data

Article 19

Substantial amendments to the clinical data relate to: data on the safety of clinical trials or data on the safety obtained based on experiences from clinical trials with the medicine being tested, results of new clinical pharmacological tests, new interpretation of existing clinical pharmacological tests, results of new clinical trials, new interpretation of existing clinical data, new data obtained based on clinical trials with the medicine being tested and new interpretation of existing data based on clinical experiences with the medicine being tested on humans.

12. Contents of the Request for the Approval of Substantial Amendments

Article 20

The request for the approval of substantial amendments as per Article 14 of the Rulebook hereof contains:

- 1) Covering letter;
- 2) Completed form for substantial amendments;
- 3) Documentation related to the substantial amendments;
- 4) Decision of the ethics committee of the healthcare institution wherein the clinical trials are to take place, or ethics committees if they are multicentre clinical trials for the medicine;
- 5) Evidence of payment for the prescribed tariffs.

The request for the approval of substantial amendments is provided on Form 3 printed with the Rulebook hereof, comprising its integral element.

a) Contents of the Covering Letter

Article 21

The covering letter as per Article 20, paragraph 1, item 1) of the Rulebook hereof contains the:

- 1) Logo, name and address of the sponsor;
- 2) Brief notification on the substantial amendments;
- 3) Name of the clinical trials of the medicine;
- 4) Name of the investigational medicine;
- 5) Pharmaceutical form, potency and packaging of the medicine;
- 6) Name of the medicine manufacturer;
- 7) List of documentation;
- 8) Date and signature of the person responsible for the clinical trials of the medicine.

13. Decision of the Ethics Committee when the Substantial Amendment is Related to the Quality of the Investigative Medicine

Article 22

The decision of the ethics committee or ethics committees as per Article 20, paragraph 1, item 4) of the Rulebook hereof is not required if the substantial amendments are related to the quality of the investigational medicine, and/or changes to the bearer of the authorization for the implementation of clinical trials for the medicine.

14. Documentation Delivered when Substantial Amendments Relate to the New Site, and/or the Replacement of the Principal Investigator

Article 23

If the substantial amendment relates to the new site, and/or the replacement of the principal investigator, the sponsor, in addition to the documentation as per Article 20, paragraph 1 of the Rulebook hereof, shall also deliver: the insurance policy, the resume of the principal investigator, consent of the healthcare institution – new site, statement by

the principal investigator of being familiar with the characteristics of the investigational medicine and the goal of the clinical trials, as well as whether the trials will be conducted pursuant to regulations in effect and the principles of Good Clinical Practice.

15. Adequate Application of the Provisions on the Rulebook Hereof

Article 24

The provisions of Articles 13-23 of the Rulebook hereof, related to amendments to the Protocol, and/or the authorization for the implementation of clinical trials, shall be adequately applied to the postmarketing intervention clinical trials of medicines, non-commercial clinical trials of medicines (academic clinical trials of medicines), as well as the issuing of authorizations for bioavailability, and/or bioequivalence.

16. Obligations in the Implementation of Clinical Trials of Medicines

Article 25

The obligations in the implementation of clinical trials of medicines relate to the obligations of the sponsor, the principal investigator, the obligations of the healthcare institution wherein the clinical trials are being implemented, and the obligations of the ethics committee.

17. Sponsor

Article 26

The sponsor shall conduct the following activities in completing their obligations during clinical trials of medicines:

1) Prepare documentation required for obtaining an authorization for clinical trials of medicines or medical devices, and/or prepare documentation for the application of postmarketing non-intervention clinical trials of medicines, as well as documentation submitted with the request for the approval of substantial amendments;

2) Designate the principal investigator to sign the statement of compliance with the proposed Protocol and sign the contract for conducting the clinical trials of the medicine with the principal investigator, pursuant to the Law and the Rulebook hereof;

3) Establish the site for the clinical trials of the medicine wherein the clinical trials of the medicine will be conducted pursuant to the contract with the healthcare institution on the use of space, equipment and human resources for the implementation of clinical trials of the medicine;

4) Prior to the start of clinical trials of the medicine insure persons undergoing clinical trials pursuant to the law, in case of damage to the health of subjects caused by the clinical trials of the medicine;

5) Provide sufficient preclinical and clinical data on the investigational medicine, placed at the disposal of the principal investigator in the relevant form;

6) Notify the principal investigator, Agency and the ethics committee of the healthcare institution on all new important data related to the investigational medicine;

7) Provide for the updating of the Investigator's Brochure at least once per year;

8) Provide data on the quality of the investigational medicine, as well as data on previous preclinical and clinical trials of the medicine, and deliver the medicine to the principal investigator after obtaining the authorization for clinical trials;

9) Store records documenting the transport, reception, issuing, return and destruction of the investigational medicine;

10) Secure the system for the reception of the investigational medicine and document the reception (e.g. for the return of a medicine with defects, reception of medicines upon the completion of clinical trials, reception of the medicine following its expiry);

11) Provide a system for the recall of unused test medicines and the documentation of such recall;

12) Undertake measures to secure medicine quality relative to medicine stability during the implementation of clinical trials of the medicine;

13) Have sufficient quantities of the investigational medicine for subsequent confirmation of specifications if required and keep documentation on the analysis and characteristics of production series samples;

14) Establish the conditions for the storage of the investigational medicine, as well as the procedures for dissolving the medicine and the infusion agents, if planned, and notify all parties on the above (monitors, investigators, pharmacists, etc.);

15) Provide for the coding system of the investigational medicine in blind studies contains mechanisms enabling the quick identification of the medicine in emergencies, but preventing the improper termination of the testing;

16) Report to the Agency and the ethics committee on all serious adverse reactions to the investigational medicine, and serious adverse reactions in clinical trials, pursuant to the bylaw regulating the method for reporting, collecting and monitoring adverse reactions to the medicine;

17) Provide the subject with full healthcare protection for the treatment of a disease or state arising as a consequence of clinical trials of the medicine;

18) Is responsible for the introduction and assurance of quality, and quality control system pursuant to the standard operating procedures, in order to provide for the implementation of trials, obtaining of data, documentation and reporting to be pursuant to regulations on clinical trials, the Protocol and Good Clinical Practice;

19) Provide a monitor and auditor in clinical trials of medicines;

20) Report to the Agency and principal investigator on substantial amendments in a timely manner and pursuant to the law regulating medicines and medical devices, and the Rulebook hereof;

21) Keep essential documentation related to clinical trials;

22) Destroy the unused amounts of investigational medicine.

18. Contract Research Organization

Article 27

The sponsor may, during the procedure of approval and implementation of clinical trials of a medicine or medical device, transfer part or all of their obligations regarding the clinical trials of the medicine to the contract research organization based in the Republic of Serbia.

Sponsors based outside the Republic of Serbia may conduct their obligations as regards the approval and implementation of clinical trials through their proxy, or representative based in the Republic of Serbia, pursuant to the law regulating companies and the law regulating foreign trade operations.

The contract research organization is responsible for the transferred obligations or part of the obligations regarding the clinical trials of the medicine, with the transfer of all or part of the obligations to the contract organization not relieving the sponsor of the clinical trials of ultimate responsibility for the implementation of the clinical trials.

The legal person, and/or proxy or representative as per paragraphs 1 and 2 of the article hereof, shall submit evidence of entry into the relevant registry, pursuant to the law regulating the registration of legal entities, to the Agency.

19. Person Responsible for Documentation and Pharmacovigilance

Article 28

The sponsor shall have a person responsible for the documentation of the procedure on obtaining an authorization for the implementation of clinical trials and pharmacovigilance in the Republic of Serbia, with a signed full-time open-ended employment contract.

The person as per paragraph 1 of the article hereof shall have a diploma of completed medical, dentistry or pharmaceutical faculty and additional education in the field of clinical trials and pharmacovigilance.

The sponsor shall notify the agency of the person responsible as per paragraph 1 of the article hereof.

20. Principal Investigator and Investigation Team

Article 29

The principal investigator is responsible for the implementation of clinical trials pursuant to the law, regulations adopted based on the law, the Protocol and Guidelines for Good Clinical Practice.

a) Principal Investigator

Article 30

The principal investigator is a person with at least a completed medical or dentistry faculty, completed specialization in the field wherein the investigational medicine is primarily used, and employed full time on an open-ended basis at the healthcare institution.

The principal investigator shall have evidence on obtaining additional knowledge in the field of clinical trials of medicines (certificate, and/or confirmation of participation on certified, and/or accredited education in the field of clinical trials), as well as evidence of having previously participated in the implementation of clinical trials.

b) Obligations of the Principal Investigator prior to the Start of Clinical Trials

Article 31

Prior to the start of clinical trials, the principal investigator shall:

- 1) Deliver a resume and documentation proving their expertise and capacity as principal investigator to the sponsor, pursuant to Article 30, paragraph 1 of the Rulebook hereof;
- 2) Sign a statement on being familiar with the characteristics of the investigational medicine, as well as the goal of clinical trials to be undertaken as per the supplied Protocol, pursuant to regulations;
- 3) Sign the relevant contract on conducting clinical testing of the medicine with the sponsor of the clinical trials, pursuant to the law and the Rulebook hereof;
- 4) Deliver to the sponsor and keep a list of investigation team members with assigned important roles in the clinical trials.

c) Principal Investigator and Members of the Investigation Team

Article 32

The principal investigator shall introduce the investigation team members to the Protocol, preclinical and clinical data on the medicine and test lists during the procedure of proposing the investigation team, and regularly notify them of important amendments to the Protocol and problems in the implementation of the clinical trials of the medicine.

The members of the investigation team shall notify the principal investigator on adverse reaction to the investigational medicine or adverse events and measures required to protect the health of the subjects.

d) Tasks of the Principal Investigator and the Investigation Team

Article 33

The principal investigator and the investigation team shall perform the following activities during clinical trials of the medicine:

- 1) Establish the sufficient number of subjects, pursuant to the criteria envisaged by the Protocol for including subjects and exclusion from clinical trials;

2) Provide oral and written explanation to subjects, in terms they understand, of the data on the investigational medicine, the goal and plan for the clinical trials, hazards and benefits to the subjects, method for subject selection, approximate number of subjects and other potential methods of treatment, as well as the advantages and disadvantages of such treatment;

3) Obtain written willing informed consent by subjects for participation in the clinical trials of the medicine;

4) Provide the subject with the relevant healthcare protection for the duration of clinical trials, and after the completion of clinical trials if the treatment continues, or if the disease or state are the consequence of the clinical trials of the medicine;

5) Provide for accuracy, completeness, clarity and up-to-date data regarding clinical trials of the medicine, as well as for the confidentiality of data available to the supervisor of the proposing party and the Agency;

6) Provide for the data listed in the case report form to comply with the source documentation;

7) Safeguard the confidentiality of subject codes, and/or observe the process for test randomization, if any, and provide for the code to be revealed only in cases allowed by Protocol, while in case of blind trials, the principal investigator shall urgently document and explain all early decryptions of the investigational medicine to the sponsor;

8) Keep essential documentation related to the clinical trials.

e) Obligations of the Principal Investigator Regarding the Investigative Medicine

Article 34

The principal investigator shall, during the clinical trials of the medicine:

1) Establish the start and end date for clinical trials of the medicine in agreement with the sponsor, as well as notify the sponsor on the termination of clinical trials for the medicine;

2) Provide for the relevant safekeeping of the list of received investigational medicines, record the issuing and use of investigational medicine samples for all subjects, and return to the sponsor unused amounts of the investigational medicine. The records shall contain the date, amounts, charges and/or serial numbers, expiry dates (unless expired) and unique identification codes assigned to the investigational medicine and the subjects;

3) Keep records documenting the subjects were given doses listed in the Protocol and identical to the number of doses of the investigational medicine as received from the sponsor;

4) Provide for the investigational medicines to be kept as stated by the sponsor and pursuant to regulations;

5) In case of immediate danger for subjects, notify the sponsor on the termination of clinical trials of the medicine;

6) Prepare a Report on the Completed Clinical Trials of the Medicine.

The principal investigator shall, if required, propose amendments to the Protocol, and if the proposed amendments are approved, provide for all subjects to be introduced to the approved amendments to the Protocol and continue treatment pursuant to the amendments to the Protocol.

f) Composition of the Investigation Team

Article 35

The principal investigator shall determine the composition of the investigation team for the site.

The composition of the investigation team as per paragraph 1 of the article hereof shall be made up of: doctors of medicine, doctors of dentistry, graduate pharmacists, as well as other experts with relevant education, depending on the type of clinical trials of the medicine.

21. Contract with the Sponsor of the Clinical Trials for the Medicine

Article 36

The principal investigator, members of the investigation team, as well as persons listed under Article 35, paragraph 2 of the Rulebook hereof, shall sign work contracts with the sponsor pursuant to the law regulating labour, containing the amount of reimbursement for conducting work in clinical trials of the medicine.

22. Site of the Clinical Trials for the Medicine

Article 37

The clinical trials of the medicine, as well as postmarketing intervention clinical trials of medicines and postmarketing non-intervention clinical trials of medicines are conducted at the healthcare institution holding an authorization for undertaking the healthcare activities, issued by the ministry competent for healthcare affairs, pursuant to regulations regulating healthcare.

The clinical testing as per paragraph 1 of the article hereof may be conducted in one or several sites proposed by the sponsor.

23. Sponsor Contract with the Healthcare Institution

Article 38

The sponsor of the clinical trials of the medicine shall complete the contract with the healthcare institution on the implementation of the clinical trials of the medicine.

The contract as per paragraph 1 of the article hereof determines the: conditions and method for the implementation of a given clinical trials for the medicine, the amount and method of payment of reimbursements paid by the sponsor to the centre for using the centre capacities for the implementation of clinical trials, the number of healthcare workers and other persons participating in the implementation of clinical trials of the medicine, employed at the healthcare institution, as well as other issues of importance for the regulation of their mutual relationship.

The healthcare institution as per paragraph 1 of the article hereof shall provide the working conditions for the investigators and the principal investigator, as well as the unimpeded work of monitors, auditors and authorized persons from the Agency for the control if the implementation of clinical trials is pursuant to the law, the Rulebook hereof and the guidelines of Good Clinical Practice.

24. Ethics Committee of the Healthcare Institution Wherein the Clinical Trials of the Medicine Take Place

Article 39

The ethics committee is formed at the healthcare institution pursuant to the law regulating healthcare protection.

25. Ethics Committee Decisions

Article 40

The ethics committee makes decisions based on sponsor documentation, as related to obtaining an authorization for the implementation of clinical trials, and/or amendments to the Protocol or authorization, delivered to the Agency as well.

The ethics committee shall notify the sponsor and Agency on the decision on the implementation of clinical trials within 15 days, in writing.

26. Notification of the Ethics Committee on the Implementation of Postmarketing Non-Intervention Clinical Trials for Medicines

Article 41

The sponsor, and/or the principal investigator, shall report to the Ethics Committee on the site of the implementation of postmarketing non-intervention clinical trials of the medicine on subjects realizing healthcare protection in the healthcare institution wherein the principal investigator is employed.

27. Multicentre Clinical Trials of Medicines

Article 42

For multicentre clinical trials of medicines undertaken within the territory of the Republic of Serbia across multiple healthcare institutions, the ethics committee of the healthcare institution wherein the clinical trials of the medicine take place shall make the decision as per Article 6, paragraph 1, item 9 of the Rulebook hereof.

28. Ethics Committee of Serbia

Article 43

The work of Ethics Committees in healthcare institutions in the implementation of clinical trials of medicines is coordinated by the Ethics Committee of Serbia, founded pursuant to the law regulating healthcare protection.

The Ethics Committee of Serbia, pursuant to the law regulating healthcare protection, shall monitor the implementation of clinical trials of medicines in healthcare institutions within the territory of the Republic of Serbia, decide, and provide opinions on disputable issues of importance for the implementation of clinical trials of medicines in healthcare institutions in the Republic of Serbia.

The Agency shall notify the Ethics Committee of Serbia on the implementation of clinical trials of medicines with issued authorizations for the implementation of clinical trials.

The Agency may, prior to issuing an authorization for the implementation of clinical trials of medicines, request the opinion of the Ethics Committee of Serbia on the submitted application for the implementation of clinical trials of the medicine, and/or all issues that may arise during the implementation of clinical trials of medicines.

29. Reporting on the Implementation of Clinical Trials of Medicines

Article 44

The sponsor shall issue tri-monthly reports to the Agency and ethics committee on the implementation of the clinical trials of the medicine, as well as on the early completion or termination of the clinical trials, within 15 days of the date of completion or early termination of the implementation of clinical trials of the medicine.

The sponsor shall notify the Agency and the ethics committee on the completion of the implementation of clinical trials of the medicine within 90 days of the completion of the clinical trials of the medicine.

The termination, and/or early completion, or the regular completion notice for the clinical trials, is provided on Form 4, printed with the Rulebook hereof and comprising its integral element.

30. Final Report on the Results of Clinical Trials of the Medicine

Article 45

The sponsor shall prepare a final report on the results of clinical trials of a medicine, delivered to the Agency within a year of the date of completing clinical trials of the medicine.

The report as per paragraph 1 of the article hereof shall contain positive and negative results of clinical trials of a medicine, for the objective assessment of clinical trials of the medicine, and/or health benefit and risk assessment for the investigational medicine, as well as the safety and efficacy of the medicine.

The contents of the report on the completed clinical trials are provided in Annex 3, printed with the Rulebook hereof, and comprising its integral element.

The sponsor shall prepare the final report on the results of postmarketing non-intervention clinical trials of medicines.

31. Import of Investigative Medicines

Article 46

Investigational medicines are imported based on Agency authorization.

The Agency issues authorizations for medicine import as per paragraph 1 of the article hereof, based on a request from a legal person holding an authorization for the wholesale of medicines.

The Agency approval for the implementation of clinical trials, the form of the statement of the principal investigator of the healthcare institution – site for the clinical trials and the analysis certificate of the medicine being imported for clinical trials are submitted with the application for the import of the investigational medicine.

The statement as per paragraph 3 of the article hereof is printed along with the Rulebook hereof and comprises its integral element.

III. CLINICAL TRIALS OF MEDICAL DEVICES

Article 47

The sponsor, prior to the start of clinical trials for a medical device, shall submit to the Agency an application for the approval of clinical trials for a medical device with documentation, for class IIa, IIb and III medical devices.

The application as per paragraph 1 of the article hereof is provided on Form 2, printed along with the Rulebook hereof and comprising its integral element.

1. Contents of Documentation for the Approval of Clinical Trials for Medical Devices

Article 48

The documentation for the approval of clinical trials for a medical device shall contain:

- 1) Covering letter by the sponsor;
- 2) Protocol for the clinical trials for the medical device;
- 3) Protocol Synopsis in the Serbian language;
- 4) Information on adverse reactions to the medical device (unless part of the Investigator's Brochure);
- 5) Investigator's Brochure;
- 6) Positive decision of the relevant ethics committee, and/or ethics committees if they are multicentre clinical trials of the medical device;
- 7) Written consent by the general manager of the healthcare institution, and/or healthcare institutions wherein the clinical trials of the medical device will take place;
- 8) Documentation on the investigational medical devices, EN ISO certificate 13485 of the quality management system, the risk analysis certificate, biocompatibility tests, the final product analysis certificate, labelling for the medical device in the Serbian language and the original language, both for the medical device being tested, as well as the comparative medical device; as well as the relevant device certificate (certificate on compliance with the directives of the European Union related to electromagnetic compatibility and electric safety);
- 9) Data on the medical device: name, type, model, designation, size;
- 10) Documentation related to the source materials;
- 11) Documentation related to the procedure of manufacturing the medical device;
- 12) Documentation related to the final product related to its purpose and risk;
- 13) Proposal for the labelling of the medical device and usage instructions;
- 14) Written statement by the principal investigator on being familiar with the characteristics of the investigational medical device and the goals of clinical trials, as well as of conducting the trials pursuant to regulations and the principles of Good Clinical Practice;
- 15) Authorization for the wholesale of medical devices issued to the importer by the competent ministry;
- 16) Brief resume and references for the principal investigator;

- 17) Evidence of the sponsor ensuring persons undergoing clinical trials in case of health damage to subjects for the period of the implementation of clinical trials;
- 18) Form for subject information and written consent signed by the subjects, in the Serbian language;
- 19) Validated copy of the contract on the transfer of authorization to the contract research organization;
- 20) Other subject information (patient journal, instructions, etc. in the Serbian language);
- 21) List of countries wherein the medical device obtained authorization;
- 22) List of countries where clinical trials for the same medical device were approved, and/or approvals of ethics committees and authorized bodies;
- 23) List of sites where the same clinical trials of medical devices are being conducted, if the trials are multicentre trials;
- 24) Additional information related to the protection of subject health, at the request of the Agency;
- 25) Evidence of having paid the prescribed tariffs to the Agency for issuing authorizations for the clinical trials of the medical device.

2. Relevant Application of the Provisions of the Rulebook Hereof to Medical Devices

Article 49

The provisions of articles 7 – 46 of the Rulebook hereof shall be adequately applied to medical devices.

FINAL PROVISIONS

Article 50

On the date of coming into effect of the Rulebook hereof, the Rulebook on the Conditions and Methods of Clinical Trials of Medicines, Procedure and Content of Documentation for the Approval of Clinical Trials for Medicines shall be deemed expired („Official Gazette of the RS“, nr. 19/07 and 44/09).

COMING INTO EFFECT

Article 51

The Rulebook hereof shall come into effect on the eighth day of the date of publishing in the „Official Gazette of the Republic of Serbia“,
Nr. 110-00-00009/2011-03
In Belgrade, 9 May 2011

Minister,
prof. dr **Zoran Stanković**, s.r.

ICH GUIDELINE: E 11 (phase 5) CLINICAL TRIALS OF MEDICINES ON CHILDREN

1. INTRODUCTION

1.1. Guideline Goals

The choice of registered medicines for the treatment of children is currently limited. The goal of the Guideline hereof is to stimulate and ease the development of medicines intended for the treatment of children at the international level.

The Guideline hereof provides a brief overview of key issues regarding the development of medicines for children and the basic approaches to the approval of the use of medicines in the treatment of children based on safe, efficient and ethically justified trials implemented on the paediatric population.

1.2. Basis

The Guidelines of the “International Commission for Harmonization” (ICH Guidelines) containing information of importance regarding clinical trials of medicines on children are:

E2: Clinical Safety Data Management;
E3: Structure and Content of Clinical Study Reports;
E4: Dose-Response Information to Support Drug Registration;
E5: Ethnic Factors in the Acceptability of Foreign Clinical Data;
E6: Good Clinical Practice: Unified Guidelines;
E8: General Considerations for Clinical Trials;
E9: Statistical Principles for Clinical Trials;
E10: Choice of Control Group and Related Issues in Clinical Trials;
M3: Nonclinical Safety Studies for the Conduct of Human Clinical Trials;
Q1: Stability Testing;
Q2: Validation of Analytical Procedures;
Q3: Impurities.

1.3. Guideline Subject

The guideline hereof encompasses the following issues regarding the clinical trials of medicines on children:

- 1) Considerations related to the initiation of a program of clinical trials of a medicine on children;
- 2) Planning the start of the clinical testing of the medicine on children during the medicine development phase;
- 3) Types of trials (pharmacokinetic, pharmacokinetic – pharmacodynamic (PK/PD), efficiency testing and safety tests);
- 4) Age groups of the paediatric population;
- 5) Ethical justification of the implementation of clinical trials on children.

The Guideline hereof does not provide a detailed overview of all the above issues: these issues are elaborated in more detail in the ICH guidelines and documents by competent bodies and paediatric associations of individual countries.

1.4. General Principles

Children should only be given medicines that had their use in the treatment of children adequately tested. The safe and efficient pharmacotherapy for children requires timely knowledge on the proper use of the medicine in the child populations of various ages, and frequently requires the development of adequate paediatric formulations. The improvement of formulations of substances, as well as the design of clinical trials for the medicines on children facilitates the development of medicines for paediatric use. Regarding medicines for the treatment of diseases and states of adults that are expected to be used for the treatment of children, their development programs usually encompass the child population as well. Obtaining additional knowledge on the efficacy of the medicine in the treatment of children is certainly an important goal. However, the goal should be achieved without jeopardizing the welfare of children participating in clinical trials. This responsibility is shared between the pharmaceutical companies, competent bodies, healthcare workers and society as a whole.

2. GUIDELINES

2.1. Issues to be Considered when Initiating a Program for the Development of Medicines for the Treatment of Children

Data on the adequate application of the medicine to children needs to be gathered, except for medicines wholly inadequate for use on children.

Section 2.3 contains an analysis of the planning for the start of clinical trials on children as opposed to trials on adult patients, with potential impact by medical needs and the requirements of healthcare systems of certain countries. At the very start of the development of a medicine, and thereafter periodically throughout the development of the medicine, the moment when clinical trials become justified and the initiation of the process should be clearly established with the regulatory bodies. The program of paediatric development of a medicine cannot delay the completion of medicine trials on adults, or the availability of the medicine to adult patients.

The decision on the paediatric development of the medicine, as well as the program itself, encompasses numerous factors, including:

- Prevalence of the disease or state to be treated in children;
- Severity of the disease or state to be treated in children;
- Existence and adequacy of medicines for the treatment of the disease or state in children, including their efficacy, as well as their safety profile (including all specific deliberations on the paediatric safety) of the therapy;
- The fact of the medicine being new or part of a group of medicines with known properties;
- The fact of whether the paediatric indications for the application of the medicine are specific;
- The need to establish specific paediatric parameters for monitoring the medicine efficacy;
- Range of child age groups the medicine is intended for;
- Specific problems regarding the paediatric safety of the medicine during its development, including all noted preclinical safety problems;
- Potential needs for the development of a new paediatric formulation of the medicine.

The key factor is the existence of a severe or life-threatening disease or state wherein the application of the investigational medicine can mean important advances in treatment. In such cases, the testing of the application of the medicine on children should be initiated as soon as possible.

The deliberation of the data on the medicine safety from preclinical trials, important for the implementation of clinical trials on children, is described in the ICH Guideline: M3, section 11.

It is important to note that the most important data for the implementation of clinical trials on children are data from clinical trials of the medicine on adults. In principle, preclinical trials of the toxicity of repeat dosages of the medicine, tests of reproductive toxicity and genotoxicity should likewise be available. The need for implementing special tests for the toxicity of the medicine on juvenile animals is considered on a case-by-case basis.

2.2. Paediatric Formulations

There is a need for the creation of a special formulation of the medicine for children for more precise dosage and increased compliance (with the therapy) for children. Certain formulations, tastes and colours may be acceptable in a country or region in oral application, as opposed to other regions. Different formulations may be desirable or necessary for children of various ages, such as liquids, suspensions or chewing tablets. Likewise, various concentrations of medicines in those formulations might be necessary. The development of alternative systems for the release of the medicine should be analysed as well.

For injections, the adequate concentrations of the medicine should also be determined, enabling the correct and safe application of the dosage. Regarding medicines in bottles for single use, the adequate individual packaging of one-off doses should also be considered.

Differences in the toxicity of certain assistive substances (excipients) are possible with children of different ages, as well as between children and adults; e.g. benzyl alcohol is toxic for preterm babies. Depending on the active ingredient and assistive substances, the adequate application of medicines to newborns may require a new formulation, and/or adequate data on the dilution of the existing formulation. The international harmonization of the acceptability of assistive substances in formulations, and procedures of validation will enable the availability of adequate paediatric formulations in all parts of the world.

2.3. Planning the Trials

During the clinical phase of the development of the medicine, the planning of the paediatric trials will depend on the medicine, the type of disease to be treated, and the safety of the medicine being tested, as well as the safety and efficacy of other existing

medicines. Since the development of formulations for children may be demanding and long, the paediatric development of the medicine should be planned during the early phases of the clinical development of the medicine for adults.

2.3.1. Medicines for Treating Diseases Mostly or Exclusively Impacting Children

For diseases mostly or exclusively impacting children, the entire development program of a medicine will be implemented on children, except for the testing of medicine safety, usually implemented on adults. For certain medicines, even during the early phases of the development of the medicine, testing only makes sense on children (e.g. where testing on adults would provide no new information or would expose them to unnecessary risk). One such example is the surfactant for the respiratory distress syndrome of preterm babies, as well as medicines for the treatment of metabolic or genetic disorders specific for the child population.

2.3.2. Medicines for the Therapy of Severe and Life-Threatening Diseases Occurring in Adults and Children, with None or Limited Alternative Treatment Options

The existence of a severe or life-threatening disease where the application of the investigational medicine can mean an important step forward in treatment requires the earliest possible testing of the medicine on children. In such cases the paediatric development of the medicine should start early, immediately after initial insight into the safety and efficacy of the medicine for adults. The results of testing the medicine on children should be included in the documentation along with the application for placing the medicine on the market. In cases where this is impossible, the absence of such data should be elaborated in detail.

2.3.3. Medicines for the Treatment of Other Diseases and States

In case of medicines for the treatment of other diseases and states, regardless of the medicines being used for the treatment of children as well, the treatment may begin during the late stages of clinical development of the medicine, as well as in cases of safety problems in the use of the medicine despite sufficient postmarketing experiences in the application for adult treatment. Pharmaceutical companies shall have a clear plan of paediatric trials and justified reasons for the schedule. The testing of medicines for the treatment of other diseases and states in children shall not be prior to the second or third phase of trials. In most cases, limited data on the testing of the medicine on children is available at the time of submitting the application for placing the medicine on the market, but more information is expected after the medicine is placed on the market.

Namely, after the first and second phase of trials, testing for most new chemical substances is terminated on adults due to poor efficiency or unacceptable safety of the medicine. Therefore, early inclusion of the paediatric population in testing can unnecessarily expose this population to a substance that will turn out to be useless. However, if the medicine represents an important step forward in the treatment of children, trials on children should be initiated during the early stages of the development of the medicine, even if it is not a severe disease, while the documentation with the application for placing the medicine on the market should encompass data on testing the medicine on children. The reason for the absence of such data should be elaborated in detail. Therefore, prior to the start of testing the medicine on children, the potential benefits of the treatment and potential risks to children should be well assessed, along with the need for introducing the medicine into clinical practice.

2.4. Types of Testing

The principles described in ICH guidelines: E4, E5, E6 and E10 also relate to medicine trials on children. Several problems specific to trials of medicines on children should be noted. During medicine trials on children within a region, the internal (e.g. pharmacogenetic) and external factors (e.g. nutrition) should be taken into consideration as having potential impact on the capacity for extrapolation from one region to another.

If the medicine is to be used for the treatment of children with same indications as studied and approved for adults, while the development of the disease in adults and children is the same, and the outcome of the therapy is comparable, the extrapolation of results of medicine efficacy from adults to the child population is relevant. In such cases, the pharmacokinetic studies in all age groups of sick children (children to receive the investigational medicine in clinical practice), along with safety studies, may provide adequate and sufficient information on the application of the medicine in the paediatric population, allowing for a choice of paediatric dosages providing for medicine concentrations in the blood similar to those in adults. If such an approach is used, the pharmacokinetic data obtained for the adult population must be available, in order to plan the paediatric pharmacokinetic study.

If the investigational medicine is to be applied to the younger paediatric population within the same therapy indication studies in the older paediatric population, while the development of the disease is similar and the outcome of the therapy is comparable, the extrapolation of the results of medicine efficacy from the older to the younger paediatric population is possible. In such cases, pharmacokinetic studies in the relevant age groups of sick children (to receive the investigational medicine in clinical practice), along with safety guidelines, may provide adequate and sufficient information on the application of the medicine in the younger paediatric population.

The approach based on pharmacokinetics is insufficient for medicines where their blood levels are known or expected not to correspond to their effects, and/or for those presumed to differ significantly in the ratio of the dosage applied (blood level) and the response achieved between adults and children. In such cases, clinical trials on children, or trials of the pharmacological effects of the medicine are usually expected.

In cases where similar developments or disease outcomes are expected between children and adults, but the relevant blood levels of the medicine are not known, using only the measurements of the pharmacodynamic effects of the medicine related to its clinical efficiency may be applied in order to confirm the efficacy of the medicine and establish the required dosage and concentration of the medicine for achieving pharmacodynamic effects. Such trials may confirm the assumption that the achievement of a certain exposure to the investigational medicine to children may lead to the desired therapy outcome. Such a PK/PD approach, combined with safety studies and other relevant studies, enables the avoiding of the need for the implementation of clinical trials of the medicine efficacy in the paediatric population.

In other cases, where the pharmacokinetic approach cannot be applied (e.g. with medicines for local application on the skin – topical preparations), the extrapolation of the efficacy results obtained from one group of patients to another may be based on tests including pharmacodynamic monitoring parameters, and/or other relevant assessments of the medicine efficacy (monitoring parameters). Likewise, tests for the local tolerance of the medicine may be required. Establishing the medicine blood levels, as well as establishing systemic effects may be important for the assessment of medicine safety.

In regards to new indications for the application of the medicine on children, and/or if a different flow of disease and treatment outcome is expected between adults and children, clinical trials of the efficacy on the medicine on the paediatric population need to be implemented.

2.4.1. Pharmacokinetics

Pharmacokinetic studies mostly need to be implemented in order to support the development of the medicine formulation and determine the pharmacokinetic parameters for various age groups of children, supporting the recommended dosages. Comparisons of the relative bioavailability between medicine formulations for children and oral formulations of a medicine for adults should be implemented on adults. Children should be used for the implementation of final pharmacokinetics trials, in order to determine the optimal doses for all age groups of children the medicine is intended for.

Paediatric pharmacokinetic studies are implemented on sick children. Therefore a greater variability is possible between subjects in sick children, as opposed to healthy volunteers, but the results thus obtained better reflect the future clinical application of the medicine in children.

If the medicines show linear pharmacokinetics in adults, testing of the pharmacokinetic individual doses on children may provide enough information for the choice of optimal dosage. If necessary, the choice may be confirmed by periodic sampling in clinical trials of various doses of the medicine. Any non-linearity in resorption, distribution and elimination of the medicine, along with any differences in the duration of the effect between individual doses and repeat doses of the medicine in adults will indicate the need for pharmacokinetic testing of the medicine in a steady state on children. All these approaches are enabled by knowing the pharmacokinetic parameters in adults. In planning pharmacokinetic trials on children, familiarity with the elimination pathways of the medicine (renal or metabolic) may prove to be useful, along with changes in these processes depending on the age.

The recommended doses for children for most medicines are expressed in milligrams per kilogram of body mass (mg/kg) and vary up to the maximum adult dosage. Although doses expressed in mg/m² of body surface are far more favourable, clinical experience shows frequent errors in measurements of height or length (particularly in small children and infants), as well as in calculating the body surface resulting from such measurements. Certain medicines must be dosed according to body surface (e.g. medicines with low therapy margins, such as oncological medicines), but additional measures should be taken in order to calculate the doses correctly.

2.4.1.1 Practical Considerations Enabling the Testing of Pharmacokinetics

The blood volume taken from subjects in paediatric studies shall be as small as possible. It needs to be justified by Protocol. The institutional board for clinical trials (Independent Ethics Committee) shall consider and establish the largest amount of blood (usually in millilitres per kilogram – ml/kg, i.e. as a percentage of the total volume of blood) that may be taken for testing. There are several methods of reducing the number of blood retrievals and venal punctures to a minimum.

- Application of sensitive methods for establishing the content of the medicine and its metabolites, requiring lower blood volumes in the sample;
- Involvement of laboratories with experience in processing samples of low blood volume for pharmacokinetic analyses and laboratory testing of medicine safety (blood count, clinical biochemistry);
- Simultaneous collection of samples for routine clinical tests and pharmacokinetic analysis, whenever possible;
- Application of a permanent catheter and similar, in order to reduce discomfort to a minimum, as elaborated under section 2.6.5;
- Application of population pharmacokinetics and intermittent sampling, based on the theory of optimal sampling, in order to reduce the number of samples taken from all subjects to a minimum.

Sampling techniques include:

- The approach of intermittent sampling where all subjects participate with two to four samples up to the total surface under the curve established by the population, as per a predetermined schedule;
- Analysis of the population pharmacokinetics, through the application of the most optimal sampling schedule according to the data model for adults.

2.4.2 Efficiency

The principles for the design of clinical trials, statistical processing and the choice of control groups described in ICH guidelines: E6, E9 and E10 generally apply to clinical trials of medicine efficacy on children. Some details are, however, specific only to paediatric trials. Section 2.4 deals with the extrapolation of the results of efficacy testing from adults to children, or the extrapolation of efficacy testing results from older to younger children. If medicine efficacy testing on children is required, various measurement parameters should be developed, validated and applied to separate age groups and development groups of children. Different measurement parameters are required for subjective symptoms, such as pain, in line with the age group of the paediatric patients. The response of children with chronic diseases to a medicine may vary, not only due to the duration of the disease and its chronic effects, but also due to the degree of development of the patient. Many preterm newborn and newborn diseases are specific to those groups of younger children, or have specific manifestations, preventing the extrapolation of efficacy results from older children to younger ones, and require new methods for the assessment of therapy outcomes.

2.4.3. Medicine Safety

ICH guidelines: E2 and E6, describing reporting on adverse events, also apply to trials on children. Normal laboratory values and clinical measurements adjusted to the age of the children should be used for reporting on adverse events. The unintentional exposure of children to medicines (accidentally swallowed medicines, etc.) provide opportunities for obtaining additional data on the safety and pharmacokinetics of the medicine, and better insight into the link between the adverse effect with the applied dosage.

Medicines may impact the physical and mental development, while children may differ in expressing adverse reactions. Since developing organisms may respond to applied medicines different from adult organisms, certain adverse events and interactions with other medicines noted in children do not always appear in adults. Additionally, due to the rapid growth and development, certain adverse effects need not appear acutely, occurring instead in later stages of development and maturity. In order to determine the potential effects of the medicine on skeletal growth and development, behaviour, cognitive functions, reproductive organs and the immune system, long-term studies of paediatric patients during treatment, or long-term monitoring after the end of treatment may be required.

2.4.4. Postmarketing Information

When obtaining an authorization for placing a medicine on the market, information on the medicine is usually limited. Therefore it is important to monitor the application of the medicine on the paediatric population, after placing the medicine on the market. In certain cases, long-term follow-up studies need to be implemented, in order to determine the effects of certain medicines on child growth and development. Postmarketing monitoring after placing the medicine on the market, and/or long-term monitoring studies, may provide information on the safety, and/or efficacy of a medicine in certain age groups of children, and/or additional information on the application of the medicine on the entire child population.

2.5. Division of Children into Age Groups

All divisions of children by age groups are somewhat arbitrary, but the classification listed below may be used as a basis for considerations of a testing plan on children. In making the decision on the division of children into age groups in trials, developmental biology and pharmacology need to be considered. Therefore, a flexible approach is required, providing for the trials to reflect existing knowledge in the field of paediatric pharmacology. The choice of age groups of children to be included in the trials depends on the medicine being tested and must be fully justified.

If the elimination pathways of the medicine are well established and the ontogenesis of these pathways is familiar, the age group of children for pharmacokinetic testing can be chosen based on a break point age, with considerable changes in the elimination of the medicine above this point. Sometimes it is more adequate to gather data for a wider range of child ages and study the effects of growth on the pharmacokinetics of the medicine, as continued covariants. Different parameters of medicine efficacy may be defined for different age groups, and the division need not correspond to the classification below. The division of the population into multiple age groups may needlessly increase the number of children to be involved in the trials. If the trials are long-term studies, the children may cross from one age group to another, thus the test design and statistical analysis plan must envisage for the changes in the number of paediatric patients in a given age group.

One potential division into age groups is proposed here. However, there are considerable development overlaps among all groups (e.g. physical, cognitive, and psychosocial). Age is determined based on days, months or years of life.

- Preterm newborns;
- Newborns born within term (0 - 27 days);
- Children ages 28 days to 23 months (infants and small children);
- Children ages two to 11 years (preschool children: two to six years, and seven to 11 years of age);
- Adolescents (12 to 16 - 18 years, depending on the country, e.g. younger adolescents 12 to 15 years and older adolescents > 16 to 20 years).

2.5.1. Preterm Newborns

Medicine testing on preterm newborns creates special issues since the pathophysiology and responses to treatment are unique to this group. The complexity of trials on preterm babies and the related ethical issues require careful design of the Testing Protocol in cooperation with neonatologists and neonatal pharmacologists. In very rare cases is the extrapolation of efficacy results for adults (even older children) to preterm newborns possible.

Preterm newborns are not a homogeneous age group. There are great differences between a 500 g preterm baby born during the 25th week of pregnancy and a 1,500 g baby born during the 30th week. Likewise, there are differences in children with low birth weights who are immature, or have developmental delays. With these patients, it is important to consider: (1) the gestation and postnatal age (adjusted age); (2) immaturity of the renal and hepatic mechanism of elimination; (3) bonds with plasma proteins and releasing these bonds (particularly bilirubin); (4) medicine penetration in the central nervous system (CNS); (5) disease states specific to newborns (e.g. respiratory distress syndrome, ductus arteriosus, primary lung hypertension); (6) susceptibilities typical for preterm newborns (e.g. tendency to necrotizing enterocolitis, intraventricular bleeding, retinopathy of preterm newborns); (7) rapid and unequal maturation of all physiological and pharmacological processes, requiring changes to dosages during chronic exposure to the medicine, and (8) transdermal resorption of the medicine and other substances. Issues to be considered regarding the design of the trials are: (1) assigning children according to body weight and age (gestation and postnatal); (2) drawing small volumes of blood (a preterm newborn weighing 500 g has only 40 ml of blood); (3) small number

of paediatric patients in a single site and variances in care for children between individual sites, and (4) difficulties in assessing outcomes.

2.5.2. Newborns

Although newborns born within term are more mature in their development than preterm newborns, the above physiological and pharmacological principles also apply. With newborns, the volume of the division of the medicine may differ to that of older children due to the different ratio of body liquids and fats, as well as the high ratio of skin surface and body mass. The blood-brain barrier is not yet fully mature, therefore medicines and endogenous substances (e.g. bilirubin) may penetrate the CNS and express toxicity. Medicine resorption after oral application is less predictable than in older children. Mechanisms for the elimination of the medicine via liver and kidneys are not yet mature and pass through rapid changes; therefore, during the first weeks of the newborn's life, medicine dosages need to be adjusted. There are many examples of increased susceptibility of newborns to the toxic effects of medicines, stemming from the limited elimination (e.g. aplastic anaemia caused by chloramphenicol – grey baby syndrome). On the other hand, newborns born within term are less sensitive to certain adverse effects (e.g. nephrotoxicity of aminoglycosides) than older patients.

2.5.3. Infants and Small Children

The CNS of children ages 28 days to 23 months matures rapidly, the immune system develops, and the entire body grows. The resorption of the medicine following oral application is more reliable. The mechanism of medicine elimination via liver and kidneys also continues to develop. Calculating in mg/kg, numerous medicines are eliminated faster in children ages one to two years than adults. The development pathway of maturity depends on the specific details of the medicine elimination pathways. Differences in maturity among children in this age group are frequently considerable.

2.5.4. Children Ages Two to 11 Years

Most medicine elimination pathways (renal and hepatic) are mature at this age, with medicine elimination frequently greater than in adults. Changes in medicine elimination may depend on the maturation of specific metabolic pathways.

The Protocol should list the specific strategies that may be used for determining all effects of the medicine on the growth and development of children of this age. There are several turning points in the psychomotor development of children at this age, with potential negative impacts caused by medicines acting on the CNS. Starting school and increased cognitive and motor skills may impact the ability of the child to participate in certain types of trials of medicine efficacy. Factors useful for measuring medicine efficacy in children include skeletal growth, body weight increases, school attendance and success. The inclusion of these subjects in the study should provide for adequate representativeness for the entire age group, since it is important to include a sufficient number of younger patients for medicine assessment. The further division of children within this age group is seldom required, but the division may prove useful based on consideration of pharmacokinetic parameters, i.e. parameters of efficacy endpoint.

The onset of puberty is very diverse among children and occurs earlier in girls, where it is normal as early as 9 years of age. Puberty may impact the actions of enzymes dissolving medicines, therefore considerable reductions of dosages for certain medicines (e.g. theophylline) may be needed. In certain cases, it is better to separately study the impact of puberty on medicines by comparing the results prior to the onset of puberty and after the onset. In other cases, the monitoring of puberty according to Tanner's scale

may be more adequate, or monitoring the biological indicators of puberty and studying their potential impact on puberty changes.

2.5.5. Adolescents (12 to 18 Years)

Adolescence is a period of sexual maturation, and medicines may impact the activity of sexual hormones and prevent child development. In certain trials, with subjects in this age group, testing for pregnancy is justified, along with tests of sexual activity and the use of oral contraceptives.

This is also a period of rapid body growth and the continued neurocognitive development. Medicines and diseases slowing down or accelerating the onset of puberty may have a strong impact on puberty growth, and therefore the ultimate height of the patient. Gradual cognitive and emotional changes may impact the outcome of clinical trials.

Hormonal changes during puberty also impact numerous diseases (e.g. increased resistance to insulin in diabetes mellitus, frequent occurrence of epileptic seizures during the menarche period, changes in the frequency and intensity of onsets of migraine or asthma). Hormonal changes may also impact the results of clinical trials.

By entering this age group, adolescents take on the responsibility of their own health and treatment. Not adhering to the treatment regime is a specific problem, particularly if the medicines (e.g. steroids) impact appearance. Subject compliance control is very important in clinical trials. Special attention should be given to the use of non-prescription medicines, alcohol and tobacco.

The upper limit to this age group varies from country to country. Older adolescents (16 to 20 years) may be included into adult trials, although there may be difficulties with the compliance of these subjects. Due to problems specific to the adolescent period, it may be more adequate to conduct adolescent trials (regardless of being included in the Protocol for adults or a separate Protocol) in places for clinical trials with the required knowledge and experience in care for this special population.

2.6. Ethical Issues Regarding Child Testing

Children are a very sensitive group of subjects. Therefore, special protection measures should be introduced for their rights in clinical trials of medicines, and exposure to unnecessary risk should be prevented. The goal of this section is to provide an ethical framework for the implementation of trials on children.

In order to make clinical trials of medicines useful for subjects, as well as other children, they must be designed well in order to provide quality and enable the interpretation of the obtained results. Additionally, the subjects are expected to gain benefits from the clinical trials, except for special circumstances described in ICH Guideline E6, section 4.8.14.

2.6.1. Ethics Committee of the Institution – Independent Ethics Committee

The role and competency of the ethics committee, as described in the ICH Guideline E6, is of key importance to the protection of subjects. In considering the Protocol encompassing the child population, the ethics committee shall have members or experts with knowledge in ethical, clinical and psychosocial issues related to children.

2.6.2. Inclusion of Subjects in Clinical Trials of a Medicine

Subjects, and/or their parents or relatives, shall in no way be improperly lead towards participation in the trials. Reimbursements and living expenses may be within the framework of paediatric clinical trials expenses. Reimbursements shall be approved by the ethics committee.

During the implementation of trials on children, demographic representatives of the country or region, and the disease being tested shall be encompassed (the sample shall be representative), except where there are justified reasons for their limited participation in testing.

2.6.3. Consent

As a general rule, children are legally incapable of providing willing consent for participation in trials. Therefore, their participation depends on the decisions of parents, or legal guardians, taking on the responsibility for the participation of the child in clinical trials. The parent or legal guardian shall be fully familiarized with the testing and the obtaining of their consent shall be pursuant to the law. All participants should be introduced to the trials as thoroughly as possible, using language and terms they understand. If possible, the participants should provide consent for participation in trials (the age of consent should be declared by the ethics committee, pursuant to the law). Participants mentally mature enough should sign and date a special consent form, or an acceptance statement form. In both cases, the participants shall be familiar with their right to refuse participation, and/or to withdraw from participation at any time. Attention should be given to signs of excessive suffering in patients unable to clearly voice their suffering. Although the decision of the subject to withdraw from testing in severe and life-threatening therapy trials must be respected, there exists the chance of occurrences that, according to investigator and parent or guardian opinion may endanger the welfare of the child if it withdraws from testing. In such cases, the further consent of the parent or legal guardian is sufficient for the child to continue in the trials. Individual, i.e. older adolescents (the age is established by law) may provide consent themselves.

Data that may be collected in a less vulnerable population providing consent for participation in medicine trials should not be collected in vulnerable populations, and/or from patients unable to provide voluntary consent. Testing on handicapped or children from social institutions should be limited to those diseases and health states mostly or exclusively limited to these populations, and/or circumstances where their disease or health state is expected to considerably impact the pharmacokinetic or pharmacodynamic characteristics of the medicine.

2.6.4. Minimizing Risk

Whatever the importance of the medicine trials in proving or disproving its value, it may hurt the subject even when the entire social community benefits from the trials. Efforts should be made to prevent this. Prior to the start of clinical trials, investigators should have full insight into all preclinical and clinical data on the medicine toxicity (listed in the Investigator's Brochure). In order to minimize risk in paediatric clinical trials, the personnel implementing it should be well trained and experienced in medicine testing on children, including recognizing and processing potential adverse events for this population.

When designing paediatric trials, all efforts should be made to reduce the number of participants and procedures to a minimum, pursuant to good design for the specific trials. Mechanisms should be established for the rapid termination of testing, in case of unexpected danger.

2.6.5. Minimizing Patient Suffering

Frequent invasive procedures may hurt and scare children. Discomfort may be minimized if the trials are designed and implemented by investigators with experience in treating children.

Protocols and trials shall be conceived and designed specifically for the child population (not merely adapted from the Adult Protocol) and shall be approved by the ethics committee, as described under section 2.6.1.

Practical considerations that may provide a positive subject experience in clinical trials of the medicine and the minimum discomfort include:

- Staff with knowledge and experience in working with children and child needs, including skills in the implementation of paediatric procedures;
- Physical space with furniture, toys, day-care activities and food, adjusted to the age group;
- Implementation of trials in a familiar environment, such as the hospital or clinic wherein the subjects are regularly treated to healthcare services;
- Methods for reducing discomfort related to the implementation of procedures such as:
 - Local anaesthesia prior to the introduction of an intravenous catheter,
 - Application of permanent catheters, instead of frequent venal punctures for blood sampling,
 - Simultaneous sampling of blood (envisaged by Protocol) and routine clinical samples.

The ethics committee shall consider the number of venal punctures acceptable for obtaining blood samples envisaged by Protocol and ensure the personnel implementing the trials clearly understand the procedure in case the permanent catheter becomes unusable in time. The right of the subject to refuse further participation in treatment procedures shall be respected, except for cases described under section 2.6.3.

EDITORIAL NOTE: *The forms can be downloaded in PDF format on-line, by clicking the following link:*

[Forms 1 - 4](#)

ANNEX 1

CONTENTS OF THE PROTOCOL FOR CLINICAL TRIALS

The Protocol shall contain all the sections listed below. However, information related to the site may be listed on separate pages of the Protocol or in a separate contract, while certain information listed below may be part of other documents linked to the Protocol, such as the Investigator's Brochure.

1. General information

1.1. Protocol name, identification number and date. All amendments shall likewise bear an amendment number and date.

1.2. Name and address of the sponsor and monitor (if the monitor address differs from the sponsor address).

1.3. Names and titles of persons authorized to sign the Protocol and amendments to the Protocol for the sponsor.

1.4. Name, title and contact details (address and telephone number) of the investigator entrusted by the sponsor for the trials.

1.5. Names and titles of investigators responsible for the implementation of the trials and addresses and telephone numbers of sites.

1.6. Name, title and contact details (address and telephone number) of the qualified external consultant responsible for making key medical (or dental) decisions at the site (unless they are an investigator).

1.7. Name and address of laboratories and other medical and/or technical services and/or institutions involved in the trials.

2. Basic information

2.1. Name and description of the investigational medicine.

2.2. Synopsis of the potentially significant results of preclinical trials, as well as the results of other clinical trials important for the planning of the trials.

2.3. Description and elaboration of the methods of application, dosage, regime and duration of therapy.

2.4. Statement of the trials being implemented pursuant to the Protocol, Good Clinical Practice guidelines and regulations.

2.5. Description of the subject structure involved in the trials.

2.6. References and data of importance for trials confirming the rational basis for testing.

3. Goals and purpose of the trials

Detailed description of the goals and purpose of the trials.

4. Testing plan

The scientific integrity of the testing and validity of data obtained by testing depend considerably on the testing plan. The description of the testing plan encompasses:

4.1. Detailed description of primary results and secondary results, if any, to be measured during testing.

4.2. Description of the type of testing (e.g. double blind, placebo controlled, randomized) and a schematic diagram of the testing plan, procedures and phases.

4.3. Description of measures undertaken to reduce, or avoid bias, including:

a) Randomization,

b) Coding.

4.4. Description of the therapy, dosage and dosage regimen of the investigational medicine. Includes a description of the doses, packaging and labelling of the investigational medicine.

4.5. Expected time of participation for the subject and a description and duration of all individual test phases, including the monitoring period, if envisaged.

4.6. Description of operational procedures for the termination or cessation of testing for subjects, parts of the trials, or the entire trials.

4.7. Procedures for keeping records on the use of the investigational medicine, including the comparative medicine, if any.

4.8. Maintenance of randomization codes and procedures for their discovery.

4.9. Determining the data to be directly entered into case report forms (e.g. without previous written or electronic data records) and considered source data.

5. Selection and exclusion of subjects from the trials.

5.1. Criteria for including subjects in the trials.

5.2. Criteria for non-inclusion of subjects in the trials.

5.3. Criteria for the exclusion of subjects from the trials (completion of therapy with the investigational medicine, and/or the treatment being tested) and special procedures:

a) How and when should a subject be excluded from trials or therapy with the investigational medicine;

b) Type of data required on the excluded subjects and the timeframe for obtaining it;

c) Whether and how the subjects need replacing;

d) Period during which the subjects excluded from therapy with the medicine or treatment being tested are to be monitored.

6. Subject treatment

6.1. Therapy to be applied, including the names of all medicines, dosages, dosage regimen, application method and treatment duration, including a monitoring period for the subject, for all investigational medicines for all therapy groups, and/or for all segments of the trials.

6.2. Allowed use of medicines and/or therapies (including urgent ones) allowed prior and during the trials.

6.3. Procedures for monitoring subject compliance.

7. Efficacy assessment

7.1. Establishing efficacy parameters.

7.2. Methods and period for the assessment, recording and analysis of efficacy parameters.

8. Safety assessment

8.1. Establishing safety parameters.

8.2. Methods and period for the assessment, recording and analysis of safety parameters.

8.3. Procedures for stimulating reporting on adverse events and relevant diseases, as well as procedures for their recording and reporting.

8.4. Method and duration of monitoring subjects after adverse events.

9. Statistical data

9.1. Description of statistical methods to be used, including the time planned for data processing during testing.

9.2. Number of subjects planned for inclusion in the trials. If the trials are multicentre trials, the number of planned subjects for all sites should be listed. The reason for the careful choice of sample size, i.e. number of subjects includes impact on the significance of the trials and clinical justification.

9.3. Degree of significance to be used.

9.4. Criteria for completing the trials.

9.5. Procedure for explaining deficiencies and unused and false data.

9.6. Procedures for reporting all deviations from the statistical plan (any deviation from the statistical plan should be described and elaborated in the Protocol, and/or the final report).

10. Direct access to source data and documents

The sponsor should secure for the Protocol or other written document to indicate that the investigators, and/or institutions will provide for direct access to source data and documents in order to conduct trials monitoring, auditing, assessments by the ethics committee of the institution and controls undertaken by the Agency.

11. Quality control and quality assurance.

12. Ethical aspects of the trials

Description of the ethical aspects related to the clinical trials.

13. Use of data and documentation management

14. Finances and insurance

Methods of financing and insurance should only be listed unless they are listed in a separate contract.

15. Publishing policy

The agreement on publishing the results of the trials should only be listed unless it is listed in a separate contract.

16. Annexes

ANNEX 2

CONTENTS OF THE INVESTIGATOR'S BROCHURE

The Investigator's Brochure (hereinafter: Brochure) is a set of clinical and preclinical data on the investigational medicine, of importance for clinical testing on humans.

The Brochure shall contain a title page and non-disclosure agreement.

The title page shall list the name of the sponsor, the identification of the investigational medicine (identification number, chemical name, INN or generic name, protected name, if any), as well as the date of issue for the Brochure.

The number of the valid Brochure is listed, along with the date and number of the Brochure issue being replaced.

The sponsor may include a statement notifying the investigator to consider the Brochure a confidential document and use it solely for informing the investigation team, as well as for delivery to the ethics committee and the Agency.

The Brochure shall also contain the following chapters, documented with accessible data from literature:

1. Contents

2. Synopsis

Provide a brief synopsis (up to two pages, if possible), listing the available significant physical-chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic and clinical properties of the investigational medicine.

3. Introduction

Brief introductory chapter containing the chemical name (INN or generic name, protected name, if any) of the investigational medicine, all active substances, pharmacological group and classification in the group, rational basis for implementing the trials and envisaged prophylactic, therapy or diagnostic efficacy. The introductory chapter should set up the principles to be used for assessing the results of testing the investigational medicine.

4. Physical-chemical, pharmaceutical properties and formulation

List the active substance of the investigational medicine (including the chemical, and/or structural formula) and a brief synopsis of the significant physical-chemical and pharmaceutical properties. In order to provide for undertaking relevant safety measures during clinical trials, the given formulation of the medicine to be used should be elaborated, including all excipients, if clinically significant. Complete an instruction for the storage and management of certain pharmaceutical forms of the medicine.

List all other structural similarities with other known medicines.

5. Pre-Clinical Trials

List the results as a synopsis of all the significant preclinical pharmacological, toxicological, pharmacokinetic studies of the investigational medicine. The synopsis should explain the methodology used, results and deliberation of the significant findings of the investigational medicine and potential adverse and unexpected reactions to the medicine in humans.

If known and available, the information may include:

- Types of test animals used for preclinical trials;
- Number and sex of animals in all groups;
- Dosage unit (e.g. mg/kg);
- Dosage regimen;
- Application method;
- Duration of application, and/or medicine use;
- Information on the systemic division;
- Duration of monitoring after therapy;
- Results, including the following aspects:
 - Nature and frequency of pharmacological or toxicological reactions,
 - Degree or intensity of pharmacological or toxicological reactions,
 - Time of reaction withdrawal,
 - Reaction duration,
 - Relationship between dosage and reaction.

In order to improve clarity, the data should be displayed in tables.

The following chapters should be used for an analysis of the key findings from preclinical studies, including the noticed reactions in altered doses, potential extrapolation to humans and all other aspects to be studied on humans. If possible, the findings of efficient and non-toxic dosages on the same animal species should be compared (consider the therapy index). The significance of this information should be stressed in planning doses for humans. If possible, comparisons should be made based on medicine blood or tissue levels, not based on a dosage unit (e.g. mg/kg).

5.1. Preclinical pharmacology

A synopsis of the pharmacological properties of the investigational medicine should be listed, and, if they exist, properties of metabolites discovered after animal studies. Such a synopsis should contain studies usable as a basis for estimating potential therapy effects (e.g. method of medicine activity, bonds with receptors and selective bonding), as well as those usable for assessing safety (e.g. special studies for assessing pharmacological activities, except those wherein the achievement of therapy efficacy is studied).

5.2. Pharmacokinetics and product metabolism in animals

Provide a synopsis of the pharmacokinetics and biological transformation and disposition of the medicine being tested in all test species. Resorption and local and systemic bioavailability of the investigational medicine and its metabolites should be considered in analysing the results, along with their relationship to pharmacological and toxicological data obtained from animal testing.

5.3. Toxicology

The synopsis should describe the toxic effects of the medicine from significant studies implemented on various animal species, and should contain the following elements:

- Individual dose;
- Repeat dose;
- Carcinogenicity;
- Special tests such as irritation and allergic potential;
- Reproductive toxicology;
- Genotoxicity (mutagenicity);

6. Effects of the investigational medicine on humans

Provide a detailed overview of known reactions to the medicine, including information on the pharmacokinetics, metabolism, pharmacodynamics, i.e. doses and efficacy, safety, and other pharmacological effects. Where possible, a synopsis of all clinical trials should be provided, along with information on the results of medicine use different to that envisaged in clinical trials, such as experiences from markets in countries where the medicine is on the market.

6.1. Pharmacokinetics and medicine metabolism in humans

If available, provide a synopsis of data on the pharmacokinetics of the investigational medicine, including the following:

- Pharmacokinetics (including, if possible, metabolism, resorption, bonds with plasma proteins, division and elimination);
- Bioavailability of the medicine (absolute, or relative, if possible) for various pharmaceutical forms;
- Special groups within the population (e.g. sex, age, damage to functions of certain organs);
- Interactions (e.g. interactions medicine – medicine and nutrition impact);
- Other pharmacokinetic data (e.g. results of tests implemented in various population groups during clinical trials).

6.2. Safety and efficacy

List a synopsis of information on safety, pharmacodynamic properties, efficacy of the investigational medicine (and the metabolism, if needed), as well as information on the dosage dependence of the reaction obtained in previous human testing (healthy volunteers, and/or patients). Analyse the significance of all that data. When numerous clinical trials have been completed, a clear data presentation from several trials can be achieved by using the safety synopsis and efficacy per indication. A summary table overview of adverse reactions to the medicine from all clinical trials (including those for all tested indications) may be very significant. The important differences occurring in relation to the sample and incidence of the adverse reaction to the medicine should be considered for various indications or subgroups.

The Brochure shall provide a description of the potential differences and adverse reactions to the medicine that may be foreseen based on earlier experiences with the investigational medicine and medicines in the same ATC group. Warnings and special measures that need to be taken as part of the tested use of the medicine shall be listed.

6.3. Market experience

List countries wherein the medicine obtained an authorization for placement on the market, countries where the authorization was refused, where the medicine was withdrawn from the market, or where the authorization was terminated. Any significant information obtained from the market shall be explained (e.g. formulation, dosage, method of application, adverse reactions to the medicine).

7. Synopsis of data and investigator instructions

Comprehensive analyses of preclinical and clinical data and information from various sources on the medicine being tested are listed, if possible. The investigator is thus provided with the most informative presentation of the available data, with an assessment of the impact of this information on future clinical trials.

When available, the published data on medicines in the same ATC group should be considered. This may additionally help the investigator predict adverse reactions to the medicine or other problems in clinical trials.

The data in this chapter shall clearly present the potential risks and adverse reactions to the medicine, as well as special tests, notes and alert measures that may be required during clinical trials. The data shall be based on existing physical-chemical, pharmaceutical, pharmacological, toxicological and clinical data on the investigational medicine. The investigator should be provided with instructions on recognizing and treating potential overdose and adverse reaction cases, based on earlier experiences in humans and the pharmacology of the investigational medicine.

ANNEX 3

CONTENTS OF THE REPORT ON THE COMPLETED CLINICAL TRIALS

The report on the completed clinical trials shall contain the following elements:

1. Title page

The title page shall contain the following information:

- Name (of the trials);
- Name of the active substance of the investigational medicine;
- Tested indication;
- If the title is unclear on the issue, a brief description (one or two sentences) of the testing method (randomized, cross, comparative, placebo controlled, open, single blind, double blind), comparison (placebo, active control, dependence of dosage and effect), therapy duration, dosage and subject population group;
- Sponsor name
- Protocol identification (Protocol number);
- Test phases;
- Date of starting trials (including the first subject, or pursuant to another verifiable definition);
- Date of early completion of testing, if exists;
- Date of completion of testing (completion of data for the last subject);
- Name and title of the principal investigator or the testing coordinator, and/or the external consultant responsible for medical decisions named by the sponsor;
- Name of the company or sponsor, name of the person responsible for the report by the sponsor (list the name a contact details of the person entrusted by the company, and/or the sponsor, for issues that might arise during the assessment of the testing report);
- Confirmation that the testing was conducted pursuant to the Guidelines of Good Clinical Practice, including the archival of essential documentation;
- Date of creating the report (listing all previous reports on the same study, with names and dates).

2. Brief contents

Provide brief contents (maximum three pages) encompassing a brief overview of the clinical trials. The brief contents shall, in addition to the text and p-values, contain numerical data and an illustrated overview of the results.

3. Contents of the report on individual completed clinical trials

The contents encompass:

- Chapter page number, including summary tables, image and charts,
- List and number of pages in annexes, tables and all case report forms attached.

4. List of abbreviations and definitions

List the abbreviations, definitions of special terms, as well as measurement units used in the report.

5. Ethics (ethics section)

5.1. Institutional Ethics Committee

Provide the positive opinion of the ethics committee of the institution on the trials implemented, as well as a list of all ethics committees that were solicited for opinions and the names of the chairpersons to all boards.

5.2. Statement of the ethical implementation of trials

Provide a statement on having conducted the trials pursuant to ethics principles based on the Declaration of Helsinki on biomedical investigation on humans.

5.3. Information for subjects and their written consent

Describe how and when was written consent for inclusion in the clinical trials obtained from the subjects.

6. Investigation and organizational security of the clinical trials

The division of labour and duties significant for the proposal, implementation, control and assessment of trials is described. A list of investigators at all sites is provided, along with their resumes and professional qualification data. A list of all associates participating in the implementation of clinical trials is also provided. If the volume of the clinical trial is great, only the key data are listed.

7. Introduction

The phase of clinical trials is listed as per the full development of the medicine, basic characteristics of clinical trials (elaborate, goals, target population group, basic primary results). Regulations and recommendations by the competent bodies taken into consideration during the preparation of the clinical trials plan are listed.

8. Goal of the clinical trials

List the overall goals of the trials.

9. Study plan

9.1. General study plan

9.2. Analysis of the study plan, including the choice of control group

9.3. Choice of population group for clinical trials

9.3.1. Criteria for inclusion of subjects in the clinical trials

9.3.2. Criteria for exclusion of subjects from the clinical trials

9.3.3. Subjects excluded from therapy or clinical trials

9.4. Treatment

9.4.1. Applied treatment

9.4.2. Identity of the investigational medicine

9.4.3. Method of assigning subjects to treatment groups

9.4.4. Choice of doses for the investigational medicine

9.4.5. Choice of dosage regimen for all subjects

9.4.6. Coding

9.4.7. Previous and associated therapy

9.4.8. Treatment harmonization

9.5. Efficacy and safety parameters

9.5.1. Establishing efficacy and safety and a schematic overview of the plan

9.5.2. Adequacy of measurement methods

9.5.3. Basic efficacy parameters

9.5.4. Medicine concentration measurements

9.6. Data quality assurance

9.7. Statistical methods planned in the Protocol and establishing sample sizes

9.7.1. Statistical and analytical plan

9.7.2. Establishing sample sizes

9.8. Deviations from the testing or planned analyses

10. Subjects in clinical trials

10.1. Subject records

10.2. Deviations from Protocol

11. Efficacy assessment

- 11.1. Analysis of overall data
- 11.2. Demographic and other primary characteristics
- 11.3. Establishing the homogeneity of treatment
- 11.4. Results of efficacy and table overview of subject data
 - 11.4.1. Efficacy analysis
 - 11.4.2. Statistical, and/or analytical data
 - 11.4.2.1. Covariance regulation
 - 11.4.2.2. Treatment of excluded or lost data
 - 11.4.2.3. Previous analyses and data monitoring
 - 11.4.2.4. Multicentre trials
 - 11.4.2.5. Multiple comparisons/multicentricity
 - 11.4.2.6. Determining “successfully subdued” subjects
 - 11.4.2.7. Tests with active controls intended for establishing equivalence
 - 11.4.2.8. Testing (assessment) of subgroups
 - 11.4.3. Table overview of data on individual responses
 - 11.4.4. Medicine dosage, medicine concentration and efficacy, as well as their interdependence
 - 11.4.5. Interactions medicine-medicine and medicine against the associated disease
 - 11.4.6. Graphical overview of data on the individual effect of the medicine on the subject
 - 11.4.7. Efficacy conclusions
- 12. Safety assessment
 - 12.1. Duration of subject exposure
 - 12.2. Adverse effects
 - 12.2.1. Brief overview of adverse effects
 - 12.2.2. Overview of adverse effects (records on adverse effects)
 - 12.2.3. Analysis of adverse effects
 - 12.2.4. List of adverse effects in subjects
 - 12.3. Deaths, other serious adverse effects and other significant adverse effects.
 - 12.3.1. List of deaths, other serious adverse effects and other significant adverse effects
 - 12.3.1.1. Cases of mortality
 - 12.3.1.2. Other serious adverse effects
 - 12.3.1.3. Other significant adverse effects
 - 12.3.2. Overview of deaths, other serious adverse effects and other significant adverse effects
 - 12.3.3. Analysis and consideration of deaths, other serious adverse effects and other significant adverse effects
 - 12.4. Clinical laboratory testing
 - 12.4.1. List of laboratory measurements for all subjects (16.2.8) and all unusual laboratory findings (14.3.4)
 - 12.4.2. Evaluation of all laboratory parameters
 - 12.4.2.1. Laboratory values
 - 12.4.2.2. Changes to laboratory values for all subjects
 - 12.4.2.3. Clinically significant individual abnormalities
 - 12.5. Vital signs, physical (corporeal) findings and other notes related to subject safety
 - 12.6. Safety conclusions
- 13. Considerations and general conclusions
- 14. Tables, images and charts related to the trials, but not included in the text
 - 14.1. Demographic data
 - 14.2. Efficacy data
 - 14.3. Safety data
 - 14.3.1. Overview of adverse effects
 - 14.3.2. List of deaths, other serious and significant adverse effects
 - 14.3.3. Overview of deaths, other serious and some other significant adverse effects
 - 14.3.4. List of unusual laboratory findings (for all subjects)

- 15. List of references
- 16. Annexes
 - 16.1. Test data
 - 16.1.1. Protocol, amendments to the Protocol
 - 16.1.2. Case report form (just one page)
 - 16.1.3. List of ethics committees (as well as the name of the chairperson, at the Agency's request), overview of the written information for subjects and written consent form
 - 16.1.4. List and description of investigator and other key participants in the study, including the brief (single-page) resume or relevant overview of training and experiences related to the implementation of clinical trials
 - 16.1.5. Signatures of the principal investigator or investigation coordinator or external consultant of the sponsor based on the Agency's request
 - 16.1.6. List of subjects receiving the investigative active substance, and/or the investigational medicine if several series of the same product are used
 - 16.1.7. Scheme and codes for randomization (subject and treatment type identification)
 - 16.1.8. Certificate on completed audits (if any);
 - 16.1.9. Documentation on the statistical methods
 - 16.1.10. Documentation on the standardization of interlaboratory methods and procedures for quality assurance, if used
 - 16.1.11. Publications stemming from the results of clinical trials
 - 16.1.12. Important publications listed in the report
 - 16.2. Subject data
 - 16.2.1. All subjects breaching the trials
 - 16.2.2. Deviations from Protocol
 - 16.2.3. Subjects excluded from the efficacy analysis;
 - 16.2.4. Demographic data
 - 16.2.5. Compliance and data on medicine concentration (if available)
 - 16.2.6. Individual data on medicine efficacy on the subject
 - 16.2.7. List of adverse effects (for all subjects)
 - 16.2.8. List of laboratory tests for all subjects at the Agency's request
 - 16.3. Case report form
 - 16.3.1. Case report forms for cases of mortality, other serious adverse effects and subject exclusion due to adverse reactions to the investigational medicine
 - 16.3.2. Other attached case report forms
 - 16.4. List of subject data.

**STATEMENT BY THE PRINCIPAL INVESTIGATOR ON THE IMPORT
OF THE MEDICINE FOR CLINICAL TRIALS**

Name of the clinical trials of the medicine/medical device, number and date of issue of the authorization:	
Protocol number for the clinical trials:	
Sponsor and contract research organization:	
Name of the medicine/medical device:	

a) Investigational medicine; b) Comparative investigational medicine; c) Other medicines listed on the clinical trials card.	
Pharmaceutical form and strength of the medicine import is requested for:	
The bearer of the authorization for the medicine, i.e. entry into the Registry of Medical Devices, if the medicine has a medicine authorization in the Republic of Serbia.	
Manufacturer of the medicine/medical device the import is requested for:	
Amount of the medicine and period the medicine/medical device are required for:	
I hereby accept full responsibility in that the medicine/medical device is necessary for the implementation of clinical trials as per the above authorization	

Healthcare institution stamp

Principal investigator
signature

Date