1. SCOPE

This guideline is prepared to provide guidance on format and content of application to be made to Ministry for conducting the clinical trial; submission and content of notifications related to documentation regarding quality and Manufacturing of investigational product, any toxicological and pharmacological test; protocol and clinical information regarding investigational product including the Investigator's brochure; proposed significant amendments to be made in the protocol, and notification regarding termination of clinical trial.

2. FORMAT AND CONTENT OF APPLICATION AND NOTIFICATIONS

2.1. Application for Clinical Trial Permission

2.1.1. Application is done according the related legislation by sponsor or its legal representative, and if there is no sponsor, by principal investigator or by coordinator for multi-center trials.

2.1.2. In order to receive Ministry permission after the received scientific and ethical approval application is made to General Directorate for Pharmaceuticals and Pharmacy for clinical trials to be conducted with medical devices, for bioavailability/bioequivalence (BA/BE) studies, for comparability studies of bio-similar products, for Phase I, Phase II, Phase III, and Phase IV drug clinical trials, for clinical trials to be conducted with advanced treatment medicinal products, for observational drug studies, for observational medical device studies, for efficacy and safety studies to be conducted with cosmetic raw materials or products, and for clinical trials to be conducted with traditional herbal medicinal products. In order to receive Ministry permission following scientific and ethical approval, for clinical trials to be conducted with non-industrial advanced medicinal products application is made to General Directorate of Treatment Services for clinical trials to be conducted with industrial advanced medicinal products, for gene treatment clinical trials, for stem-cell transplantation trials, for organ and tissue transplantation trials, and for new surgery method trials.

2.1.3. According the kind of clinical trial, application should be made along with appendixes with respect to the list indicated in APPENDIX-1 and by completing fully the appropriate application form and application cover letter samples published on the website of General Directorate for Pharmaceuticals and Pharmacy (www.iegm.gov.tr). "Basic Information to be Submitted in Applications" is listed at APPENDIX-1.

2.1.4. The signed documents required to be included in the application file should be originally signed.

2.1.5. If the trial is international, sponsor or its legal representative, and if there is no sponsor, principal investigator or coordinator for multi-center trials, should submit a list of other health authorities that they have submitted the same application to. If there are differences in the related trial protocol as compared with the practice in our country, this should be indicated with its justifications.

2.1.6. If the application holder is not the sponsor of the trial, the original copy of the

signed letter about the authorization of the legal representative acting on behalf of sponsor by the sponsor should be included in the application file.

2.1.7. First application file and the application during the trial continues should be prepared in file colors indicated below:

- **2.1.7.1.** Red for phase I clinical trials,
- **2.1.7.2.** Yellow for phase II clinical trials,
- **2.1.7.3.** Blue for phase III clinical trials,
- **2.1.7.4.** Black for phase IV clinical trials,
- **2.1.7.5.** White for observational drug studies,
- **2.1.7.6.** Orange for comparative studies related to BA/BE and bio-similar products,
- **2.1.7.7.** White for other kind of studies,
- **2.1.7.8.** Purple for import,
- **2.1.7.9.** Green for inspection request.

2.1.8. The original bank receipt and its copy should be added to the application file regarding the payment of the application fee which is published on the website of the related General Directorate.

2.1.9. No application fee payment is required for specialty thesis or trials for academic purposes. However, the documentation of approval of Head of Department or Chief of the Clinic that confirms the trial is a specialty thesis or for academic purposes should be added to the application file.

2.1.10. The application holder should do the submission by using the application cover letter samples published at the website of the related General Directorate.

2.1.11. In case of no available cover letter sample related to the volunteer, submission letter should contain the protocol number of the sponsor (if any), the institution and name of the investigator (the coordinator for multi-center trials), and the full title of the trial should be indicated on the cover letter.

2.1.12. In the application cover letter text, special subjects regarding the submission such as special trial populations, “first-in-man” application of a new active substance, extraordinary investigational products, extraordinary trial designs, sub studies should be called attention to and the locations of the related information and documents in the submission file should be indicated.

2.1.13. The submission forms are standard and they are published on the website of General Directorate for Pharmaceuticals and Pharmacy. The related forms are updated by General Directorate of Pharmaceuticals and Pharmacy when required and the current version of the form should be considered be used in the application.

2.1.14. The sponsor of the trial or its legal representative, if there is no sponsor, the principal investigator or the coordinator for multi-center trials should complete the appropriate submission form accurate, sign it, and deliver it to the related General Directorate along with a cover letter and its attachments.

2.1.15. The sponsor of the trial and/or its legal representative, if there is no sponsor, the principal investigator or the coordinator for multi-center trials undertake by signing the related submission form that the submitted information is sufficient and attached documents reflect the available information accurately, that the initiation of the clinical trial applied for is found logical according their own opinions, and that they accept the initiation of the trial.

2.2. Trial Protocol/Plan

2.2.1. Trial protocol/plan is the document describing the purpose and design of the clinical trial, statistical methods to be applied, and procedures pertaining to the trial in detail.

2.2.2. The content and format of the trial protocol/plan should comply with the related Good Clinical Practice guidance.

2.2.3. The protocol submitted in the attachment of the trial file should include the version number of the protocol, the full title of the trial. For protocol amendments including all changes the updated version number and date or the acronym title or the title given to this protocol by the sponsor; should be signed by the sponsor and by the principal investigator (by the coordinator for multi-center trials).

2.2.4. In case there will be a situation for volunteers who cannot provide written volunteer informed consent form, the trial protocol/plan should also include a justification regarding the situation.

2.2.5. If the trial protocol/plan and protocol/plan amendment are prepared in different languages except English, the Turkish translation of all text should also be delivered. If the trial protocol/plan and protocol/plan amendment are in English, the original protocol/plan and the Turkish translation of the synopsis of protocol/plan and protocol/plan amendment should be delivered.

2.3. Investigator's Brochure

2.3.1. The content, format, and the methods to be provided in the Investigator's Brochure should comply with the related legislation.

2.3.2. It should include clinical and non-clinical data pertaining to investigational product or products.

2.3.3. The Investigator's Brochure should be prepared by including all available information and evidences that will support the rationale of the clinical trial submitted and the safety of the investigational product usage in the trial.

2.3.4. If the Investigator's Brochure and its amendment are prepared in different languages except English, the Turkish translation of all text should also be delivered. If the Investigator's Brochure and its amendment are in English, the delivery of the original text is sufficient.

2.4. Investigational Product File

2.4.1. The submission of investigational product file is not mandatory. However, in cases deemed as required, the Ministry may request the investigational product file or its related sections.

2.4.2. The investigational product file includes the non-clinical studies, and the quality including its clinical usage information's related to the reference products and placebos of any investigational product to be used in the clinical trial.

2.4.3. The Investigator's Brochure may cross reference the non-clinical and clinical information of the investigational product. In this case, summaries of non-clinical information and clinical information should be presented preferably in tables. This table should provide sufficient information to people who will perform the evaluation for them to decide related to the potential toxicity of the investigational product and to its usage safety in the trial to be conducted.

2.4.4. If there are some special cases requiring a detailed expert opinion or discussion except the ones normally included in the Investigator's Brochure in non-clinical and/or clinical data, the sponsor may provide this non-clinical and/or clinical information as a part of the investigational product file.

2.4.5. A comprehensive investigational product file should include the documents related to the quality, the Manufacturing, and the control of the investigational product, the non-clinical data, and the summaries of the clinical data. The main titles are listed in the appendix of the guideline. However, it should be also accepted that presenting the information in all titles will not be possible for each investigational product.

2.4.6. The file will be dependent on many factors such as the nature of the investigational product, the stage of development, the population of the trial, the nature and seriousness of the disease, including the duration of exposure to the investigational product.

2.4.7. When data should be removed, scientific justifications related to this should be submitted; if there is no suitable title for this, a new section should be added.

2.4.8. Sponsor should submit summaries about chemical, pharmaceutical, and biological data related to any investigational product. The titles related to this are presented in the appendix of the guideline.

2.4.9. The investigational product of the sponsor, to be used in the clinical drug trial, should be produced pursuant to Good Manufacturing Practice (GMP) principles and to GMP Guideline.

2.4.10. Sponsor should submit summaries of non-clinical pharmacological and toxicological data related to any investigational product to be used in the clinical drug trial. If this data is not available, the justification for this should be indicated. Moreover, a reference list regarding on-going trials and related literature references should be submitted. Upon request, sponsor should also submit the copies of fully comprehensive data and references regarding trials. It is preferred that data are presented in tables and short information emphasizing main points accompanies this table. The summaries of on-going trials should ensure the compliance of the trial and the performance of the assessment of the trial conduct according to an acceptable protocol.

2.4.11. Sponsor should submit the non-clinical information in titles included in the guideline appendix as much as possible. The titles are not mandatory and not limited to this list. If any, in cases including deviation(s) and/or omitting(s), sponsor should provide a critical analysis regarding available data and should submit a summary reflecting data related to on-going trials and an evaluation related to the product safety with respect to the clinical trial to be conducted.

2.4.12. All trials should be conducted according to the most advanced protocols currently accepted. Moreover, as much as possible, Good Laboratory Practice (GLP) requirements should be met. Sponsor should justify the deviations from

these principles and should present a declaration related to the GLP status of all trials.

2.4.13. Test materials used in toxicity studies should represent the qualitative and quantitative impurity profiles. Preparation of test materials should be subject to control, and thus, should support the validity of the study.

2.4.14. Sponsor should submit the summaries of all available information obtained as a result of the clinical trials conducted previously with investigational products and of the studies conducted on humans. Although the titles pertaining to these are presented in the appendix of the guideline, more information should be submitted as much as possible. The titles are not mandatory and should not be limited to this list.

2.4.15. All trials should be conducted in compliance with Good Clinical Practice (GCP) principles and a declaration for the conduct of the trials according to GCP rules should be confirmed by the sponsor. If this is not possible, sponsor should submit an explanation or a justification.

2.4.16. Sponsor should submit an integrated summary, analyzing non-clinical data and clinical data critically with respect to potential risks and benefits of the study to be conducted. The text should also include the reasons for premature termination of any study. These subjects should be taken into consideration especially for evaluating the trials related to children and limited volunteers. The purpose of non-clinical pharmacology and toxicity tests is to demonstrate the main risks of the product to be investigated. Sponsor should use the related pharmacological, toxicological, and pharmacokinetic results as a basis of extrapolation to refer to the potential risks in humans. Sponsor should integrate all available data, should analyze the pharmacological and toxicological effects of the investigational product, and should demonstrate its possible mechanisms. When possible, the safety margin of the investigational product should be discussed based preferably on AUC and Cmax data instead of dose applied. The clinical significance, the effect in clinical trials, and the reliability of any finding in non-clinical and clinical trials should be indicated.

2.4.17. If the investigational product is licensed / permitted in our country and includes the same form, the same indications and a dosage regime covered by Summary of Product Characteristics (SmPC) or by information leaflet; sponsor may submit the available version of SmPC or information leaflet approved by the Ministry. However, additional non-clinical data and/or clinical data should be submitted to support that the usage is safe for a new indication, in a new volunteer population, and in new dosage regime.

3. METHOD FOR NOTIFICATION OF AMENDMENTS AND FOR RECEIVING PERMITTION

3.1. After the initiation of the clinical trial, an amendment on its conduct may be permitted.

3.2. For all amendments to be performed related to the trial as indicated in the related legislation as required to have permission, the means amendments cannot be applied without the permission of the Ministry. However, when sponsor and/or investigator are required to take emergency safety prevention to protect the volunteers from an immediate hazard, this action can be permitted without notification to the Ministry. However, afterwards the Ministry should be informed immediately.

3.3. Significant amendments in the conduct of the trial may result from the protocol or from the new information regarding scientific documents supporting the trial. Examples regarding significant amendments are included in the appendix of the guideline.

3.4. Sponsor should handle cases one by one, should evaluate whether the amendment is significant or not, and should submit it with the appropriate current form and cover letter sample published at the website of the General Directorate of Pharmaceuticals and Pharmacy.

3.5. In cases, a significant amendment affects more than one protocol for a specific investigational product, sponsor or its legal representative should indicate this on the cover letter and should notify the related General Directorate by including also a list containing the sponsor protocol number and the full title of the trial and in a way for the notification to include all affected protocols.

3.6. The disapproval of applications does not rule out the right of the application holder for re-submission of the information.

3.7. Notification regarding the amendment should include the following information at minimum:

3.7.1. "Application Cover Letter Sample" appropriate for the subject published at the website of the General Directorate of Pharmaceuticals and Pharmacy

3.7.2. Current application form including the following basically, however as published at the website of the General Directorate of Pharmaceuticals and Pharmacy:

3.7.2.1. Full title of the clinical trial, protocol code number of the sponsor,

3.7.2.2. Sponsor and/or its legal representative,

3.7.2.3. Number, date, and/or version of the amendment.

3.7.3. Explanation of the amendment;

3.7.3.1. Indication of amendments by underlining, if possible, the summary of the documents amended,

3.7.3.2. Number and date of updated version.

3.7.4. Sponsor information including the followings:

3.7.4.1. If possible, submission of a summary of data,

3.7.4.2. If possible, updated overall risk benefit assessment,

3.7.5. Possible results for volunteers included in the trial and the assessment of these results.

3.8. If new situations may possibly affect the safety of the volunteers during the conduct of the trial or during the development of the investigational product, sponsor or investigator may be required to take appropriate emergency safety prevention to protect volunteers against this condition that might arise. These safety measures (such as temporary interruption of the trial) may be also implemented without previously taking permission of the Ministry. Sponsor or investigator should immediately inform the related General Directorate on the new conditions that might develop, on preventions taken against these, and on plans regarding of other actions. This informing should be by fax at first stage and afterwards in a written report format.

3.9. Sponsor should inform the related General Directorate when the clinical trial is interrupted (such as interruption of new volunteer recruitment into the trial and/or discontinuation of treatment of volunteers in execution stage of the trial) within 15 (fifteen) days by using the current form published on the website of the General Directorate of Pharmaceuticals and

Pharmacy. As long as the Ministry does not grant permission to the re-initiation of the trial, the trial cannot be initiated.

4. TEMPORARY INTERRUPTION OF THE TRIAL

4.1. If the Ministry determines that one of the conditions, available while permitting the trial, has been removed during the conduct of the trial, the Ministry interrupts the trial immediately. In cases of not fulfillment of these conditions within the period indicated or of understanding that this fulfillment is not possible or of endangering volunteer health during this period, the trial is terminated directly.

4.2. In cases including no obvious risk for the volunteers, the opinions of the sponsor and/or the investigator related to the subject may be requested. In this case, the sponsor or investigators should send their opinions related to the subject to the Ministry within seven days.

4.3. If the trial is terminated following the decision of temporary interruption; the sponsor should inform by using the current form regarding the notification of the termination of the trial and published at the website of General Directorate of Pharmaceutical and Pharmacy.

4.4. If the Ministry has justifications in the direction of non-compliance by the sponsor / its legal representative / investigator / another person related to the conduct of the trial with the obligations indicated, the Ministry may determine the actions required to be taken by the sponsor for compensating the violation of these obligations. The action plan should include an implementation calendar and the date on which the sponsor will report the progression and the completion of the implementation to the related General Directorate. The Ethics Committee should also be informed about this action plan. In these cases, the sponsor should implement the action plan specified by the related General Directorate and should provide immediately the information related to the progression and the completion of the trial in accordance with the calendar implemented and specified.

5. NOTIFICATION OF TERMINATION OF CLINICAL TRIAL

5.1. The sponsor of the clinical trial or its legal representative, if there is no sponsor, principal investigator or coordinator for multi-center trials should inform the related General Directorate about the termination of the clinical trial.

5.2. Sponsor or its legal representative, if there is no sponsor, principal investigator or coordinator for multi-center trials should notify the termination of the clinical trial by using the current form and cover letter sample published at the website of the General Directorate of Pharmaceuticals and Pharmacy.

5.3. Sponsor or its legal representative, if there is no sponsor, principal investigator or coordinator for multi-center trials should notify Ethics Committee and Ministry the termination of the trial within 90 (ninety) days after the termination the clinical trial.

5.4. If the clinical trial cannot be initiated on the date indicated in the application file although the permission is granted by the Ministry, the reasons of not being able to initiate should be notified to the related General Directorate within fifteen days; this period may be extended by the related General Directorate when required.

5.5. A section indicating the matters related to the termination of the trial should be included in the trial protocol/plan; whatever the reason is, any amendment made here should be notified pursuant to the related legislation. The last visit date of the last volunteer recruited in the trial can be described as the termination of the trial. Any exceptional condition should be justified in the protocol/plan.

5.6. If sponsor decides not to initiate the trial or decides not to re-initiate after interrupting the trial, the Ministry should be informed; a letter, explaining briefly the protocol, the protocol code number of the sponsor, and the reasons of not initiating and terminating the trial, should be delivered.

5.7. Sponsor or its legal representative, if there is no sponsor, principal investigator or coordinator for multi-center trials should submit to the Ministry the summary of the clinical trial final report within one year after the termination of the trial and should comply with the legislation related to Good Clinical Practice.

5.8. The notification for the termination of the trial should be made by using the current form and cover letter sample published at the website of the General Directorate of Pharmaceuticals and Pharmacy.

5.9. When the trial is terminated prematurely, at least the following information should be submitted at the end of the clinical trial report:

5.9.1. Justification regarding premature termination of the trial,

5.9.2. When the trial is terminated, the number of volunteers currently in treatment,

5.9.3. When the trial is terminated, proposed patient management for volunteers on treatment,

5.9.4. Assessment of trial results.

6. SUPERSEDED REGULATIONS

Guideline Regarding Application Format for Application to Ministry in Clinical Trials effective with the Consent dated 20.12.2010 and numbered 7905 has been superseded.

7. EFFECTIVE DATE

This Guideline is effective as of date of approval.

8. APPENDIXES

APPENDIX–1: BASIC INFORMATION REQUIRED TO BE SUBMITTED DURING APPLICATIONS

Related cover letter published at the website of the General Directorate of Pharmaceuticals and Pharmacy, if there is no cover letter sample related to the subject, cover letter prepared in the

form indicated at Article 2.1.11 of this Guideline

1. Current application form and its appendixes published at the website of the General Directorate of Pharmaceuticals and Pharmacy
2. If available, copies of Ethics Committee decisions in countries, except our country (The Turkish translations of the decisions taken in languages except English should also be delivered.)
3. If any, preliminary evaluation made by principal investigator
4. If any, investigational product file (submission is not mandatory)
5. If available, analysis certificate regarding the investigational product
6. If available, viral safety information and data

APPENDIX–2: TITLES FOR QUALITY DATA OF INVESTIGATIONAL PRODUCT

1. Investigational Product
1.1. General information
1.2. Terminology
1.3. Structure
1.4. General Characteristics

2. Manufacture
2.1. Manufacturer(s)
2.2. Description of Manufacturing Process and Process Controls
2.3. Control of Materials
2.4. Controls of Critical and Intermediates Steps
2.5. Process Validation and/or Evaluation
2.6. Manufacturing Process Development
2.7. Characterization
2.7.1. Elucidation of Structure and other Characteristics
2.7.2. Impurity
2.7.3. Control of Drug Substance
2.7.3.1. Specification
2.7.3.2. Analytical Procedures
2.7.3.3. Validation of Analytical Procedures
2.7.3.4. Batch Analyses
2.7.3.5. Justification of Specification
2.8. Reference Standards or Materials
2.9. Container Closure System

2.10. Stability
2.11. Drug Product
2.11.1. Description and Composition of the Drug Product
2.11.2. Pharmaceutical Development
2.11.3. Components of the Drug Product
2.11.3.1. Drug Substance
2.11.4. Excipients
2.11.4.1. Drug Product
2.11.4.1.1. Formulation Development
2.11.4.1.1.1. Overages
2.11.4.1.1.2. Physicochemical and Biological Properties
2.11.4.1.1.3. Manufacturing Process Development
2.11.4.1.1.4. Container Closure System
2.11.4.1.1.5. Microbiological Attributes
2.11.4.1.1.6. Compatibility
2.11.4.2. Manufacture
2.11.4.2.1. Manufacturer (s)
2.11.4.2.2. Batch Formula
2.11.4.2.3. Description of Manufacturing Process and Process Controls
2.11.4.2.4. Controls of Critical Steps and Intermediates
2.11.4.2.5. Process Validation and/or Evaluation
2.11.4.3. Control of Excipients
2.11.4.3.1. Specifications
2.11.4.3.2.Analytical Procedures
2.11.4.3.3. Validation of Analytical Procedures
2.11.4.3.4. Justification of Specifications
2.11.4.3.5. Excipients of Human or Animal Origin
2.11.4.3.6. Novel Excipients
2.11.4.4. Control of Drug Product
2.11.4.4.1. Specification(s)
2.11.4.4.2. Analytical Procedures
2.11.4.4.3. Validation of Analytical Procedures
2.11.4.4.4. Batch Analyses
2.11.4.4.5. Characterisation of Impurities
2.11.4.4.6. Justification of Specification(s)
2.11.4.5. Reference Standards or Materials
2.11.4.6. Container Closure System
2.11.4.7. Stability

3. Appendix
3.1. Facilities and Equipment
3.2. Adventitious Agents Safety Evaluation
3.3. Novel Excipients
3.4. Re-arrangement and Solvents for Diluents

APPENDIX–3: TITLES FOR NON-CLINICAL PHARMACOLOGICAL AND TOXICOLOGICAL DATA

1. Pharmacodynamics

1.1. Brief Summary
1.2. Primary Pharmacodynamics
1.3. Secondary Pharmacodynamics
1.4. Safety Pharmacology
1.5. Pharmacodynamic interactions
1.6. Discussion and Conclusions

2. Pharmacokinetics
2.1.Brief Summary
2.1.1. Methods of Analysis
2.2. Absorption
2.3. Distribution
2.4. Metabolism
2.5. Excretion
2.6. Pharmacokinetic Drug Interactions
2.7. Other Pharmacokinetic Studies
2.8. Discussion and Conclusions including assessment of toxico-kinetics

3. Toxicology
3.1. Brief Summary
3.2. Single-Dose Toxicity
3.3. Repeat-Dose Toxicity *
3.4. Genotoxicity
3.4.1. In vitro
3.4.2. In vivo*
3.5. Carcinogenicity*
3.6. Reproductive and Developmental Toxicity *
3.7. Local Tolerance
3.8. Other Toxicity Studies
3.9. Discussion and conclusions
* These sections should be supported by toxicokinetic assessments.

APPENDIX–4 Titles for Data Regarding Clinical Trial and Experience Obtained Previously in Humans

1. Clinical Pharmacology

1.1. Brief summary
1.2. Primary effect mechanism
1.3. Secondary pharmacological effects
1.4. Pharmacodynamic interactions

2. Clinical Pharmacokinetics
2.1. Brief summary
2.2. Absorption
2.3. Distribution
2.4. Elimination
2.5. Pharmacokinetics of active metabolites
2.6. Plasma concentration-effect relationship
2.7. Dependencies on dose and time
2.8. Special volunteer populations
2.9. Interactions

3. Exposure of man
3.1. Brief summary
3.2. General explanation regarding safety and efficacy
3.3. Healthy volunteer study
3.4. Volunteer studies
3.5. Previous experience in humans
3.6. Assessment of benefits and risks

4. Appendix

APPENDIX–5 Examples Regarding Matters That Might Require Significant Amendment in Clinical Trials

The amendments indicated below are examples and amendments are not limited to these.

Samples of Basic Significant Amendment

- Physical and mental health of the volunteers,
- Scientific value of the trial,
- System and method on conducting the trial ,
- Quality and safety of the investigational product used in the trial.

Amendments Regarding Trial Protocol/Plan

- Purpose of the trial,
- Design of the trial,
- Volunteer informed consent form (SICF),

- Method/methods of volunteer recruitment for the trial,
- Efficacy measurements,
- Addition or omitting of tests or measurements,
- Number of volunteers,
- Age interval of volunteers,
- Inclusion criteria for the trial,
- Exclusion criteria for the trial,
- Monitoring of volunteer safety,
- Duration of exposure to investigational product,
- Change in dosage of investigational product,
- Change of comparator drug,
- Statistical analysis.

Amendments Regarding Administrative Structuring

- Change of principal investigator,
- Change of coordinating investigator,
- Change of trial site and/or addition of new trial sites,
- Change of sponsor or legal representative,
- Change of contract research organization,

Amendments Regarding Investigational Product

- Change in quality data of investigational product,
- Change in title or code of investigational product,
- Change in internal package material,
- Change in producer of active substance,
- Change in Manufacturing process of active substance,
- Change in specifications of active substance,
- Change(s) in information related to Manufacturing of medical product,
- Change in specifications of medical product,
- Change(s) in specifications of excipients in cases the performance of investigational product is affected,
- Change in shelf life of investigational product,
- Basic change made in formulation,
- Change in storage conditions,
- Change in test methods of active substance,
- Change in test methods of medical product,
- Change in test methods of excipients not related to pharmacopeia.

Amendments Made Related to Pre-clinical Pharmacology and Toxicology Data for Ongoing Trials

- Results of newly made pharmacology tests,
- New interpretation of available pharmacology tests,
- Results of newly performed toxicity tests,
- New interpretation of available toxicity tests,
- Results of new interaction studies.

Amendments Made in Data Regarding Usage During Clinical Trial and in Humans for

Ongoing Trials

- Change pertaining to safety information occurring in the clinical trial process of the investigational product or during its usage in human,
- Results of new clinical pharmacology tests,
- New interpretation of available clinical pharmacology tests,
- Results of new clinical trials,
- New interpretation of available clinical trial data,
- New data obtained from the usage of investigational product in human,
- New interpretation of available data regarding the usage of investigational product in human.