Translation from Bulgarian

ORDINANCE № 10 OF 2008 ON THE DOCUMENTS REQUIRED FROM THE PRINCIPAL/COORDINATING INVESTIGATOR OR SPONSOR FOR OBTAINING AN ETHICS COMMITTEE STATEMENT AND ON THE PROCEDURE FOR SAFETY MONITORING OF MEDICAL DEVICES DURING CLINICAL INVESTIGATIONS AND ASSESSMENT OF THE CLINICAL DATA COLLECTED DURING SUCH INVESTIGATIONS (TITLE AMENDED IN STATE GAZETTE, ISSUE 31 OF 2009, EFFECTIVE AS OF 21 MARCH 2010)

Issued by the Ministry of Health

Promulgated in SG, issue 46 of 16 May 2008, amended in SG, issue 31 of 24 April 2009

Section I

General Provisions

Article 1 (Supplemented SG issue 31 of 2009, effective as of 21 March 2010). This ordinance defines the contents of the documents required for obtaining an Ethics Committee statement pursuant to Article 47 of the Law on Medical Devices (LMD) and the procedure for safety monitoring of medical devices during clinical investigations and assessment of the clinical data collected during such investigations.

Section II

Required documents for obtaining a clinical investigation authorization

Article 2. To obtain a statement from the Ethics Committee, the person referred to in Article 46 of LMD has to submit the following administrative documents in accordance with Article 48, paragraph 1 (1) of LMD:

1. A valid request;

2. A list of all Competent Authorities and Ethics Committees to which an authorization/ statement request/notice has been submitted;

3. A list of all planned medical centres, investigators and investigating teams in Bulgaria;

4. Name and address of the clinical investigation monitor;

5. A written authorization letter for the person submitting the application on behalf of the sponsor, if the applicant is not the sponsor of the clinical investigation;

6. A certificate of current registration of the sponsor and applicant within the European Union, issued by a Competent Authority.

Article 3. Pursuant to Article 48, paragraph 1 (2) of LMD, the information about the subjects of the clinical investigation has to include:

1. The information specified in Article 37, paragraph 1 (1) and (2) of LMD, intended for the subject;

2. A written informed consent form signed by the subject of the clinical investigation;

3. Description of the procedures for recruiting subjects for the clinical investigations;

4. Description of the procedures for obtaining an informed consent from a legal representative in the cases specified in Articles 37, 38 and 39 of LMD;

5. An ethical justification for the recruitment of subjects who are incapable of giving an informed consent as in the cases specified in Article 39 and 40 of LMD;

6. A copy of any other information which will be used in the recruitment of subjects and/or will be provided to subjects before or during the clinical investigation.

Article 4. (1) The documents related to the clinical investigation protocol as specified in Article 48, paragraph 1 (3) of LMD, have to include:

1. A clinical investigation protocol, as last amended;

2. A summary of the protocol in Bulgarian;

3. An assessment of the scientific value of the investigation by an expert in the field, if available, and justification of the clinical investigation project and the proposed protocol;

4. An ethical evaluation of the protocol by the principal or coordinating investigator of the potential risks for the health of subjects when using a medical device not included in the protocol.

(2) The clinical investigation protocol has to contain:

1. Assessment of the expected benefits and the potential risks under Article 34 (3) of LMD, as well as methods and ways of eliminating or reducing risks, if they cannot be prevented;

2. A list of inclusion and exclusion criteria;

3. Justification of the choice of subjects, especially in the cases when these subjects are incapable of giving their informed consent or belong to other vulnerable patient groups;

4. Description of the procedures for recruiting subjects and obtaining an informed consent from subjects who are temporarily or permanently incapable of giving their informed consent, or when consent is to be obtained from an independent witness;

5. Description of the protocol and procedures for providing further medical care for the subjects after the end of the investigation;

6. Procedures for supervision of the investigation;

7. The protocol for publication of collected data;

8. Description of procedures ensuring confidentiality;

9. Document(s) containing codes identifying the subjects and information on any further treatment or measures that have to be undertaken in case of emergency;

10. A report form provided during the investigation, and a final report form in accordance with Article 57, paragraph 1 of LMD;

11. A report form for reporting incidents/potential incidents related to the device, which occurred during the clinical investigation.

(3) The protocol has to be signed by the sponsor and the principal investigator of

each of the proposed medical centres.

Article 5. (1) Pursuant to Article 48, paragraph1 (4) of LMD, the documents related to the tested device have to contain:

1. Investigator's brochure containing full and scientifically justified information on the product, which is required for an objective evaluation of the risk-benefit ratio associated with the proposed clinical investigation;

2. A summary of all clinical investigations conducted so far with the medical device in question;

3. Summarized information from existing literature and an expert evaluation supporting the justification of the intended use of the device and the clinical investigation design;

4. A general description of the device and its components;

5. A description of the materials used in the composition and manufacturing of the device;

6. A description of the operation of the device, including information from scientific literature, instructions for use and assembly of the device, potential risks, counter indications, warnings, etc.;

7. A description of the intended use of the medical device;

8. A summary and assessment of in vitro and/or ex vivo data, including preclinical data, such as biological tests, non-clinical laboratory tests and tests on animals;

9. A summary of the clinical experience with the device or with other devices with similar intended use;

10. A list of the fully or partially applied standards and a description of the solutions adopted to ensure conformity to the essential requirements, when these standards are not applied or are only partially applied;

11. Risk analysis results.

(2) The sponsor has to keep the investigator's brochure up to date by modifying it each time new information is supplied during the clinical investigation and provide it to the investigators.

Article 6. (1) The documents on the technical possibilities of the medical centre and the professional qualification of the investigators under Article 48, paragraph 1 (5) of LMD, have to include:

1. A description of the required equipment and/or technical requirements for implementing the protocol;

2. Documents proving the technical possibilities of the proposed medical centre to implement the protocol;

3. (Amended SG issue 31 of 2009, effective as of 21 March 2010) A curriculum vitae and/or other documents certifying the training and qualification of the members of the investigating team.

(2) The documents specified in paragraph 2 above have to be drawn up by the head of the medical centre in which the procedure described in the protocol and requiring specific equipment is planned to take place.

Article 7. The documents related to the administrative organization and funding of the investigation referred to in Article 48, paragraph 1 (6) of LMD have to contain:

1. An insurance agreement covering the liability of the sponsor and of the principal/coordinating investigator for any material or non-material damages caused to the subjects during or in relation to the clinical investigation;

2. Information on indemnity and compensation in case of death or injury of a subject during the clinical investigation;

3. A contract signed by the sponsor and the subjects in the clinical investigation specifying the compensation (travel and subsistence costs) when such is provided for in accordance with Article 34, paragraph 5 of LMD;

4. A contract signed by the sponsor and the investigator(s);

5. A contract signed by the sponsor and the medical centre(s);

6. Information on the funding source of the study when the sponsor is a non-profit entity.

Section III

Required documents for amendment of clinical investigation authorization

Article 8. (Amended in SG issue 31 of 2009, effective as of 21 March 2010) A substantial amendment under Article 54, paragraph 1 of LMD means a change in the details specified in Annex I.

Article 9. (1) When planning substantial amendments to the clinical investigation and the documents under Article 48, paragraph 1 of LMD, the sponsor, or a duly authorized representative, has to submit a written request to the Ethics Committee as provided for in Article 54 of LMD.

(2) This request has to be accompanied by the following documents:

1. A cover letter;

2. A summary of the proposed amendments;

3. A list of updated documents;

4. Updated documents under Article 2 - 7, specifying the amendments;

5. Pages of the documents with highlighted changes for comparison of the current texts and the proposed amended texts;

6. A justification of the amendments;

7. A copy of the clinical investigation request under Article 2 with highlighted changes both in electronic format and on paper.

Article 10. (1) (Amended SG issue 31 of 2009, effective as of 21 March 2010) When planning substantial amendments to the clinical investigation and the documents referred to in Article 50, paragraph 1 of LMD, the sponsor, or a duly authorized representative, has to submit a written request for the said amendments to the Bulgarian Drug Agency (BDA).

(2) This request has to be supported by the documents specified in Article 9, paragraph 2 (1 – 7), the declaration specified in Article 50, paragraph 4 of LMD, and a copy of the Ethics Committee statement when it becomes available.

(3) Another document that has to be submitted is the request specified in Article 50, paragraph 1 of LMD, containing updated information reflecting the proposed amendments, and a copy with highlighted changes both in electronic format and on paper.

Article 11. (1) The documents for obtaining authorization or amending a clinical investigation have to be submitted in Bulgarian and/or English.

(2) The documents specified in Article 2, paragraphs 1 and 2, Article 3, paragraphs 1, 2 and 6, Article 4, paragraph 1 (2), Article 6, paragraph 1, (1), (2) and (3), Article 7, Article 10, paragraph 1, and Article 18 have to be submitted in Bulgarian as well.

(3) The request under Article 10, paragraphs 1 and 3 has to be submitted in English as well.

Article 12. (1) The Executive Director of the Bulgarian Drug Agency (BDA) has to issue an order for the approval of the requests specified in Articles 2, 9 and 10.

(2) These requests have to be submitted in electronic format and on paper.

(3) The electronic copies must be submitted in the format established for clinical investigations that need to be entered in the European database.

(4) The sponsor, or a duly authorized representative, has to certify that the electronic and paper copies of the requests contain identical information.

Section IV

Procedure for safety monitoring of medical devices during clinical investigations and assessment of clinical data collected during such investigations (Title amended in SG, issue 31 of 2009, effective as of 21 March 2010)

Article 13. The sponsor has to collect and conduct continuous assessment of the safety of the tested medical devices, taking into consideration:

1. Any additional information on the risks for the medical device which may pose a risk to the health or safety of the subjects in the clinical investigation, or information that might lead to an amendment to the clinical investigation protocol;

2. The investigator's reports and assessment of any adverse effect or event in terms of the cause and effect relationship and the seriousness of such effects;

3. Each serious adverse event assessed by the investigator as possibly related to the tested device must be properly handled and reported.

Article 13a (New SG issue 31 of 2009, effective as of 21 March 2010) (1) The assessment of the clinical data collected during a clinical investigation of devices referred to in Article 2, paragraph 1 (3) of LMD, has to be carried out in compliance with Annex II.

(2) The assessment of the clinical data collected during a clinical investigation of active implantable devices has to be carried out in compliance with Annex III.

Article 13b (New SG issue 31 of 2009, effective as of 21 March 2010) (1) The clinical investigation has to be supervised by an investigator who is:

1. A medical doctor or a dentist qualified to use the tested device and specially trained to work with it;

2. Familiar with the methods and requirements for conducting the clinical investigation;

3. Familiar with the principles and requirements for obtaining an informed consent.

(2) The investigating team has to be properly qualified and experienced, and to have undergone special training for completing the operations involved in the investigation.

(3) Supervision of the clinical investigation is performed by the sponsor or a duly authorized representative as specified in Article 42, paragraph 1 or 2 of LMD, or by a monitor appointed by the sponsor.

(4) During the clinical investigation, the medical doctor or dentist has to monitor the health of the subject and to take any medical measures that may be required.

(5) The sponsor is liable for any damages to the health of a patient or a patient's

death caused during or in relation to the clinical investigation, when the investigation is carried out in compliance with the requirements and procedures specified in the protocol approved by the Ethics Committee.

(6) The principal or the coordinating investigator are liable for any damages to the health of the patient or the patient's death caused during or in relation to the clinical investigation, when the requirements and procedures specified in the protocol approved by the Ethics Committee have not been observed.

Article 14. (1) The sponsor or investigator has to undertake urgent action for protecting the subjects in the clinical investigation in case of unexpected risks for their safety or health.

(2) If such emergency as described in paragraph 1 occurs, the sponsor has to notify immediately BDA and the Ethics Committee of any action which has been taken and of any reasons which are known to have caused the emergency.

Article 15. (1) The principal investigator has to notify immediately the sponsor, either in writing or orally, of any serious adverse events which occur during the clinical investigation.

(2) After notifying the person specified in paragraph 1 above, the investigator has to submit a detailed report in writing in the format and within the terms set forth in the clinical investigation protocol, where the subject is identified by means of a code as specified in the protocol.

(3) The investigator has to report to the sponsor any adverse events defined in the protocol as critical in relation to safety, in the format and within the terms set forth in the clinical investigation protocol.

(4) In multi-centre investigations, the sponsor has to inform all investigators conducting the specific clinical investigation about the reported serious adverse events related to the tested medical device.

Article 16. When the outcome of such adverse events is death, the investigator has to supply the sponsor and the Ethics Committees with any further information that

they may require.

Article 17. The sponsor has to keep detailed records of any serious adverse events reported by the investigators, and to provide them upon request to BDA or the Competent Authorities of the member states in the cases of multi-centre clinical investigations.

Article 18. (1) The sponsor has to submit a report to BDA, the Competent Authorities of all member states in which the clinical investigation takes place, and to the specific Ethics Committee, on any unexpected serious adverse events which occur during the clinical investigation and cause the death or a serious injury or damage to the health of a subject, hereinafter referred to as 'incident', within 7 days of receiving information about it.

(2) The sponsor has to notify the authorities specified in paragraph 1 above of any further information on the case within 8 days of the date of the report.

(3) The sponsor has to submit a report to the authorities specified in paragraph 1 above on any other adverse events which occur during the clinical investigation, other than those specified in paragraph 1 above, hereinafter referred to as potential incidents, within 15 days of receiving information about them.

Article 19. (1) The sponsor has to submit a report to BDA on incidents with medical devices bearing the CE marking, which are applied in combination with the tested medical device during the clinical investigation.

(2) In the cases specified in paragraph 1 above, the sponsor has to notify the manufacturer, or the duly authorized representative, of the incident and of the information submitted to BDA.

(3) In the cases specified in paragraph 2 above, the manufacturer or the duly authorized representative does not have to submit reports on the incidents to BDA.

Article 20. Once a year, the sponsor has to submit to BDA and the respective Ethics Committee a list of all incidents / potential incidents which have occurred during

the past period, as well as a report on the safety of the subjects.

Article 21. (1) The reports on incidents / potential incidents during a clinical investigation have to contain at least the following:

1. Administrative information on the clinical investigation;

2. Information about the sponsor;

3. Information about the duly authorized representative;

4. Information about the source of the details presented in the report;

5. Identification of the medical device;

6. The diagnosis which the device was indicated for and any other concurrent diseases of the subject;

7. The condition of the subject during the clinical investigation and a plan for monitoring his/her health status;

8. Information about the incident/potential incident

(2) The report specified in paragraph 1 above has to be signed by the investigator.

Article 22. (1) The Bulgarian Drug Agency has to record, analyse, and summarize any information provided under Article 20 about any incidents / potential incidents involving medical devices, which occurred during the clinical investigations, and has to take specific measures in compliance with Article 59 of LMD.

(2) The Bulgarian Drug Agency has to submit information on any incidents with medical devices which occurred during clinical investigations, as well as any other information other than the information entered in the European database, whenever such is requested by another member state or by the European Commission.

(3) By completing its obligations under paragraph 1 above, BDA complies with the guidelines published by the European Commission.

Section V

Supervision

Article 23. (1) The clinical investigations conducted in Bulgaria are supervised by inspectors and experts defined in specific orders issued by the Executive Director of BDA.

(2) The supervision covers preliminary inspections, ongoing control and follow-ups.

(3) The sponsor, the principal investigator and the other investigators, the medical centres, the Ethics Committees, the facilities where the tested device is manufactured and inspected, the laboratories, and any documents related to the clinical investigation, are subject to supervision.

Article 24. (1) Supervision of the clinical investigations is carried out in compliance with the standard operating procedures approved by the Executive Director of BDA. These standard operating procedures are drawn up in compliance with the guidelines set by the European Commission.

(2) Each inspection related to a clinical investigation of a medical device has to end with a report which is submitted to the sponsor.

(3) In case of any deficiencies, the clinical investigation is suspended until the moment when the deficiency is remedied or the investigation is terminated.

(4) A report on the inspection of a clinical investigation may be submitted to the investigators, the Ethics Committee in case of multi-centre investigations, the other EU member states and the European Commission.

Additional Provisions

§ 1. For the purposes of this ordinance the following words and phrases shall have the following meanings:

1. 'Adverse effect' is any untoward and unexpected response to the medical device when used in compliance with the manufacturer's instructions, including as a result of inadequacies or deficiencies in the instructions for use or as a result of the user's fault.

2. 'Unexpected deterioration': a case of deteriorating health is considered as

unexpected if the circumstances that led to the event were not accounted for in the risk analysis made by the manufacturer.

3. 'Adverse event' is any untoward event involving a subject in the clinical investigation, which does not necessarily have a causal relationship with the tested medical device.

4. 'Serious adverse event' is an untoward event leading to:

1. Death;

2. Serious damages to the health of the subject in the investigation;

3. Damages to an embryo, death of an embryo, or congenital anomalies or birth defects;

5. 'Serious damages to the health' are:

1. Life-threatening conditions or diseases, or injuries;

2. Persistent disability or loss of a vital function or damage to the structure of the body;

3. Conditions requiring hospitalization or significant prolongation of existing hospitalization;

4. Conditions requiring medical care or surgical intervention to prevent damaged as the ones specified in (2) above.

6. 'Incident' is any malfunction or deterioration in the characteristics and/or performance of a device, as well as any incomplete or inadequate information on the label or in the instructions for use which caused the death or serious damages to the health of the patient, user, or to other people.

7. 'Potential incident' is any malfunction or deterioration in the characteristics and/or performance of a device, as well as any incomplete or inadequate information on the label or in the instructions for use, which could directly or indirectly cause the death or serious damages to the health of a person, but which have been prevented thanks to favourable circumstances or medical intervention.

§ 1a. (New – SG issue 31 of 2009, effective as of 21 March 2010) This ordinance introduces the provisions from Directive 90/385/EEA of the Council on the approximation of the laws of the member states related to active implantable medical

devices (promulgated in the Official Journal, Special Issue 2007, chapter 13, volume 9), last amended by Directive 2007/47/EC (promulgated in OJ, L 247 of 21 September 2007, p. 21 - 55), and from Directive 93/42/EEA of the Council, concerning the medical products (promulgated in OJ, Special issue 2007, chapter 13, volume 11), last amended by Directive 2007/47/EC.

Final Provisions

§ 2. (Supplemented in SG issue 31 of 2009, effective as of 21 March 2010) This ordinance is issued pursuant to Article 32a, Article 48, paragraph 2 and Article 58, paragraph 3 of the Law on Medical Devices.

Final Provisions
OF THE ORDINANCE AMENDING AND SUPPLEMENTING ORDINANCE № 10 OF 2008 ON THE DOCUMENTS REQUIRED FROM THE PRINCIPAL/COORDINATING INVESTOGATOR OR SPONSOR FOR OBTAINING AN ETHICS COMMITTEE STATEMENT AND ON THE PROCEDURE FOR SAFETY MONITORING OF MEDICAL DEVICES DURING CLINICAL INVESTIGATIONS

(Promulgated in SG issue 31 of 2009, effective as of 21 March 2010)

§ 12. This ordinance becomes effective on 21 March 2010.

Annex I to Article 8

(Previous Annex to Article 8 - SG issue 31 of 2009, effective as of 21 March 2010)

Amendment of details leading to substantial changes:

1. Amendments to the protocol:

1.1. Amendments to the purpose of the investigation.

1.2. Amendments to the design and/or methods of the investigation, or to the preliminary information on which its scientific value is based.

1.3. Amendments to the following documents required for the investigation:

1.3.1. Informed consent;

1.3.2. Information about the subject;

1.3.3. Information about the legal representative and/or the person who takes care of the subject;

1.3.4. Questionnaires, invitations, letters to the attending physician or other investigators;

1.4. Amendments to the procedure for recruitment of subjects;

1.5. Amendments to the effectiveness indicators;

1.6. Amendments to the protocol for obtaining biological materials for testing;

1.7. Inclusion or exclusion of tests;

1.8. Amendments to the age range for participation;

1.9. Amendments to the inclusion and exclusion criteria.

1.10. Amendments to the procedure for safety monitoring;

1.11. Amendments to the duration of use of the tested product;

1.12. Amendments to the way in which the tested product is used;

1.13. Amendments to the statistical plan;

1.14. Any amendment concerning the safety and the physical and/or mental integrity of the subjects, or the risk/benefit ratio associated with the investigation;

1.15. Amendments to the definition for termination of an investigation;

2. Amendments to the administrative organization of the investigation:

2.1. Change of the sponsor and/or the duly authorized representative;

2.2. Change of the approved medical centre;

2.3. Appointment of a new principal investigator or another major member of the investigating team;

2.4. Inclusion of another medical centre;

2.5. Appointment of a new principal investigator in an approved medical centre;

2.6. Amendments to the terms and conditions of the insurance or the procedures for indemnifying the subjects in the investigation;

2.7. Other significant amendments to the protocol and/or the original documentation submitted with the request;

3. Amendments concerning the quality of the tested medical device:

3.1. Change of the name of the tested product;

3.2. Change of the materials used as primary package;

3.3. Change of the importer of products manufactured outside the European Union;

3.4. Change of manufacturer;

3.5. Amendments to the manufacturing process of any component of the product;

3.6. Major changes of the manufacturing process of the tested product;

3.7. Changes of the characteristics of the tested product when this involves expansion of the acceptable limits and/or exclusion of tests;

3.8. Change of the characteristics of substances which can affect the properties of the product.

3.9. A major change of the composition.

3.10. Limitations on the storage conditions;

3.11. Shortening of the expiration period;

3.12. Amendments to the procedures for testing the product when a new testing method is introduced;

3.13. Amendments to the procedures for testing non-pharmacopoeia substances when a new testing method is introduced;

4. Any changes in the non-clinical data about the tested medical device which may affect the risk/benefit ratio;

5. Any changes in the clinical data about the tested medical device which may affect the risk/benefit ratio.

Annex II to Article 13a, paragraph 1

(New – SG issue 31 of 2009, effective as of 21 March 2010)

Assessment of the clinical data collected during the investigations of devices under Article 2, paragraph 1 (3) of LMD.

1. General provisions

1.1. The statement and conformity to the requirements refer to the characteristics and the performance of the medical devices according to chapter two of the Ordinance on the essential requirements and procedures for assessment of compliance with the essential requirements for medical products under Article 2, paragraph 1 (3) of LMD, adopted by resolution № 186 of 2007 of the Council of Ministers (promulgated in SG issue 65 of 2007; amended and supplemented in issue 106 of 2008). They are defined for normal conditions of use of the products with further assessment of the side effects and the acceptability of the risk/benefit ratio under the terms of Article 15 of the Ordinance on the essential requirements and procedures for assessment of conformity to the essential requirements for medical products under Article 2, paragraph 1 (3) of LMD. The assessment of this information hereinafter referred to as 'clinical assessment' is carried out in compliance with a specific methodologically relevant procedure, taking account of all applicable harmonized standards. The clinical assessment is based on one or more of the following criteria:

1.1.1. Critical assessment of the specific scientific literature on the safety, performance, design characteristics and the intended use of the product when:

a) The product in question and the product for which the information refers are identical;

b) The information indicates clearly and accurately conformity to the specific essential requirements;

1.1.2. Critical assessment of the results from the clinical investigations;

1.1.3. Critical assessment of the general clinical information under paragraphs

1.1.1 and 1.1.2.

1.2. The information which is generated and used during the clinical assessment has to be kept in compliance with Chapter 8a of LMD.

1.3. Clinical investigations of implantable devices and Class III devices need not be conducted, if there is sufficient proof that the existing clinical data is reliable.

1.4. The clinical investigation and its results have to be recorded. These records have to be included and/or described in detail in the technical characteristics of the product.

1.5. The clinical assessment and the documents related to it have to be regularly updated in compliance with the information received from the monitoring after the product is placed on the market. A clinical monitoring need not necessarily be conducted as part of the protocol after the product is placed on the market, but this has to be properly justified and documented.

1.6. When it is not suitable to prove conformity to the essential requirements on the basis of clinical data, this has to be justified in a document containing the results of the risk management and taking account of the specific nature of the interaction of the device with the human body, to the indicated clinical investigations and the requirements of the manufacturer. The adequacy of the proofs of conformity to the essential requirements by assessment of the work, bench testing, and preclinical assessment, has to be duly justified.

2. Clinical investigations

2.1. Goals

The goals of the clinical investigations are:

- to test if under normal conditions of use the performance of the device will comply with that specified in Article 12 of the Ordinance on the essential requirements and procedures for assessment of conformity to the essential requirements for medical products under Article 2, paragraph 1 (3) of LMD;

- to detect any and all adverse side effects under normal conditions of use and to determine whether they pose a threat by interfering with the expected performance of the device.

2.2. Ethical considerations

The clinical investigations have to be carried out in compliance with the Declaration of Helsinki concerning the ethical principles during clinical investigations on human subjects. All measures concerning human protection have to be taken as provided for in the Declaration of Helsinki, and they are mandatory. This refers to each stage of the clinical investigation, from its conception and justification to the publication of the final results.

2.3. Methods

2.3.1. The clinical investigations have to be conducted in compliance with an appropriate clinical investigation protocol consistent with the latest scientific and technical achievements. They are intended to either validate or refute the manufacturer's claims about the product; these investigations have to include a sufficient number of observations so that they can underpin the scientific validity of their conclusions.

2.3.2. The procedure for conducting such an investigation has to be suitable for the specific product.

2.3.3. The clinical investigations have to be carried out under conditions which are similar to the normal conditions of use of the product.

2.3.4. All relevant characteristics, including those related to the safety, performance, and effects of the product on the patients have to be properly investigated.

2.3.5. The Bulgarian Drug Agency has to provide to the Competent Authorities of the other member states detailed information about any serious adverse events which occur during a clinical investigation conducted in Bulgaria.

2.3.6. The investigations have to be carried out under the supervision of an active practitioner, who is a medical doctor or a dentist, or of another authorized qualified person in a suitable environment.

The medical doctor/dentist or authorized person has to be provided access to the technical and clinical information on the product.

2.3.7. The written report signed by the medical doctor/dentist, or the responsible authorized person, has to contain critical assessment of all data collected during the clinical investigation.

Annex III to Article 13a, paragraph 2

(New – SG issue 31 of 2009, effective as of 21 March 2010)

Assessment of the clinical data collected during the testing of active implantable medical devices

1. General provisions

1.1. The statement and conformity to the requirements refer to the characteristics and the performance of the medical devices according to chapter two of the Ordinance on the essential requirements and procedures for assessment of the conformity to the essential requirements for active implantable medical devices, adopted by resolution № 185 of 2007 of the Council of Ministers (promulgated in SG issue 65 of 2007; amended and supplemented in issue 106 of 2008). They are defined for normal conditions of use of the products with further evaluation of the side effects and the acceptability of the risk/benefit ratio under the terms of Article 13 of the Ordinance on the essential requirements and procedures for assessment of the conformity to the essential requirements for active implantable medical devices. The assessment of this information hereinafter referred to as 'clinical assessment' is carried out in compliance with a specific methodologically relevant procedure, with consideration of all applicable harmonized standards. The clinical assessment is based on one or more of the following criteria:

1.1.1. Critical assessment of the specific scientific literature on the safety, operation, design characteristics and the intended use of the product when:

- The product in question and the product for which the information refers are identical; and

- The information indicates clearly and accurately conformity to the specific essential requirements;

1.1.2. Critical assessment of the results from all clinical investigations;

1.1.3. Critical assessment of the general clinical information under paragraphs 1.1.1 and 1.1.2.

1.2. Clinical investigations need not be conducted, if it is duly verified that the existing clinical data is reliable.

1.3. The clinical investigation and the results from it have to be recorded. These records have to be included and/or described in detail in the technical characteristics of the product.

1.4. The clinical assessment and the documents related to it have to be regularly updated in compliance with the information received from the monitoring after the product is placed on the market. A clinical monitoring need not necessarily be conducted as part of the protocol after the product is placed on the market, but this has to be properly justified and documented.

1.5. When it is not suitable to prove conformity to the essential requirements on the basis of clinical data, this has to be justified in a document containing the results of the risk management and with consideration to the specific nature of the interaction of the device with the human body, to the indicated clinical investigations and the requirements of the manufacturer. The adequacy of the proofs of conformity to the essential requirements by assessment of the work, bench testing, and preclinical assessment, has to be duly justified.

1.6. The information which is generated and used in the course of the clinical assessment has to be stored in compliance with Chapter 8a of LMD.

2. Clinical investigations

2.1. Goals

The goals of the clinical investigations are:

- to test if under normal conditions of use the performance of the device will comply with that specified in Article 10 of the Ordinance on the essential requirements and procedures for assessment of conformity to the essential requirements for active implantable medical products;

- to detect any and all adverse side effects under normal conditions of use and to determine whether they pose a threat by interfering with the expected performance of the device.

2.2. Ethical considerations

The clinical investigations have to be carried out in compliance with the

Declaration of Helsinki concerning the ethical principles during clinical investigations on human subjects. All measures concerning human protection have to be taken as provided for in the Declaration of Helsinki, and are mandatory. This is valid for each stage of the clinical investigation, from its very conception and justification to the publication of the final results.

2.3. Methods

2.3.1. The clinical investigations have to be conducted according to the stages of the clinical investigation protocol which are intended to either validate or refute the manufacturer's claims about the product. These investigations have to include a sufficient number of observations which can underpin the scientific validity of their conclusions.

2.3.2. The procedure for conducting such an investigation has to be suitable for the specific product.

2.3.3. The clinical investigations have to be carried out under conditions which are similar to the normal conditions of use of the product.

2.3.4. All relevant characteristics, including those related to the safety, performance, and effects of the product on the patients have to be properly investigated.

2.3.5. The Bulgarian Drug Agency has to provide to the Competent Authorities of the other member states detailed information about any serious adverse events which occur during a clinical investigation conducted in Bulgaria.

2.3.6. The investigations have to be carried out under the supervision of a qualified medical practitioner or an authorized person in a suitable environment. The medical doctor has to be given access to the technical information on the product.

2.3.7. The written report signed by the respective practitioner has to contain critical assessment of all data collected during the clinical investigation.