DECISION
No. 2/22.04.2014

on approval of Regulations for authorisation of sites for conduct of clinical trials on medicinal products for human use

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health no. 374/02.04.2014, in accordance with the Regulation for the organisation and operation of the NAMMD Scientific Council, Article 8 (1), hereby adopts through written procedure the following

DECISION

Single article - Regulations for authorisation of sites for conduct of clinical trials on medicinal products for human use are approved, in accordance with the Annex which is integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,
Acad. Prof. Dr. Leonida Gherasim

ANNEX
to SCD no. 2/22.04.2014

Regulations for authorisation of sites for conduct of clinical trials on medicinal products for human use

CHAPTER I
Introduction

Article 1. – These regulations enable application of provisions of Article 4 (2) d) of Government Decision no. 734/2010 on organisation and operation of the National Agency for Medicines and Medical Devices, of Government Decision no. 63/2002 on approval of Good Laboratory Practice principles, their inspection and assessment of compliance with these principles as well as inspection and assessment of their compliance concerning tests performed upon chemical substances, as amended, of Order of the Minister of Public Health no. 904/2006 on harmonisation of member states legislation, regulations and administrative measures on approval of rules relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, of Order of the Minister of Public Health no. 903/2006 on approval of the Principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

CHAPTER II
General provisions

Article 2. - (1) Evaluation of medicinal products for human use by means of clinical trials, with or without therapeutic benefit, can only be conducted at sites authorised by the National Agency for Medicines and Medical Devices.

(2) Issuance of the Authorisation for conduct of *clinical trials with therapeutic benefit/phase I clinical trials or bioequivalence clinical trials* (in accordance with the draft provided in Annex 1) is proof of fulfilment of conditions for authorisation.

(3) Sites holding Authorisation for conduct of Phase I clinical trials are also allowed to perform bioequivalence clinical trials.

Article 3 - (1) The manager of the site submits the application for authorisation to the National Agency for Medicines and Medical Devices, specifying the name of the healthcare facility/legal person, clinic(s), department(s), clinical/paraclinical laboratories etc. within the healthcare facility involved in the application.

(2) The application for authorisation is accompanied by the documents attesting fulfilment of conditions for grant of a certain type of Authorisation for conduct of clinical trials, as shown under Articles 5 (2), 9 and 18.

Article 4 - (1) The authorisation issued by the National Agency for Medicines and Medical Devices is valid available for two years and may be extended upon request by the respective site.

(2) – The National Agency for Medicines and Medical Devices is notified on any amendment during the authorisation validity period, likely to change the data underlying grant of authorisation.

(3) – In such circumstances, the site applies for update of the authorisation granted by the National Agency for Medicines and Medical Devices so as to reflect implementation of intervening changes, without change of the validity period.

CHAPTER III

Special provisions

SECTION 1

Authorisation of clinical trials with therapeutic benefit

Article 5. - (1) Assessment of medicinal products through clinical trials with therapeutic benefits can only be performed at specialised healthcare sites performing an activity compliant with CAEN codes 8610 – Hospital activities and 7219 – Other research and experimental development on natural sciences and engineering or 8622 – Specialist medical practice activities.

(2) The National Agency for Medicines and Medical Devices grants the Authorisation for conduct of clinical trials with therapeutic benefit, after assessment of the following documents:

a) the healthcare authorisation for operation of a medical facility;

b) a document attesting registration of the healthcare facility as provider of activities under CAEN code 7219 – Other research and experimental development on natural sciences and engineering.

c) a membership certificate granted by a professional organisation for healthcare professionals involved in clinical trials;

d) the List of Standard Operating Procedures (see Annex 2 for the minimal list of Standard Operating Procedures) or certification of implementation of a quality management system in accordance with ISO standards in force for clinical

trials; certification becomes mandatory one year following entry into force of these regulations;

e) the documents describing the secured IT infrastructure for data management and archiving of the clinical trial dossier;

f) the list of staff qualified to act as main investigator, together with the attached proof of confirmation of respective titles (senior physician or specialist physician with a minimum 3-year experience) and curriculum vitae;

g) proof of existence of an emergency service within the respective site or of a contract for emergency medical services signed with specialised sites.

Article 6. – Qualified staff needs to be hired at the proposed site for conduct of clinical trials with therapeutic benefit (e.g. general physicians, healthcare specialists trained in the area targeted by the clinical trials, physicians in training in clinical/surgery fields, clinical pharmacologists, appropriate auxiliary staff).

Article 7. – (1) The proposed site for conduct of clinical trials with therapeutic benefit must meet the requirements for areas, utilities, facilities and devices, mentioned in legislation in force, namely Order of the Minister of Health no. 914/2006 on approval of the Norms regarding the conditions to be fulfilled by a hospital in order to receive the sanitary authorisation for operation, Order of the Minister of Health and Family no. 1338/2007 on approval of the Norms on the functional structure of medical and dental offices.

(2) The proposed site for conduct of clinical trials with therapeutic benefit must own licensed and secured IT systems.

(3) The proposed site for conduct of clinical trials with therapeutic benefit must comply with requirements on archiving areas for clinical trial dossiers compliant with provisions of Order of the Minister of Health no. 903/2006 on approval of the Principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as requirements for authorisation of manufacturing or importation of such products as well as Scientific Council Decision no. 51/2006 on approval of Guidance on the content of the trials master file and archiving.

Article 8. – In case the proposed site does not allow for conduct of assays, tests, clinical and paraclinical investigations, these can be performed as per agreement with other sites authorised/accredited by authorised bodies.

SECTION 2
Authorisation for conduct of Phase I clinical trials

Article 9. – Clinical assessment of medicinal products through Phase I clinical trials can only be performed at sites specially authorised for this purpose, performing activities in accordance with CAEN code 7219 – Other research and experimental development on natural sciences and engineering.

Article 10. – The following sites may apply for Authorisation for conduct of Phase I clinical trials:

a) medical sites provided with their own bioanalytical laboratory, specialised in pharmacokinetic determinations;

b) medical sites signatory of a collaboration agreement with bioanalytical laboratories specialised in pharmacokinetic determinations, covering at least the validity period of the authorisation;

c) bioanalytical laboratories specialised in pharmacokinetic determinations, signatory of a collaboration agreement with a medical site, covering at least the validity period of the authorisation;

d) bioanalytical laboratories specialised in pharmacokinetic determinations, provided with a clinical site in line with provisions of this Decision;

e) legal entities signatory of collaboration agreements with a bioanalytical laboratory specialised in pharmacokinetic determinations and with a medical site, covering at least the validity period of the authorisation;

f) legal entities signatory of collaboration agreements with a medical site, providing proof of contract at the time of submission of an application for authorisation of a clinical trial with a bioanalytical laboratory specialised in pharmacokinetic determinations, covering at least the validity period of the authorisation, when a conditional authorisation shall be granted.

Article 11. – The National Agency for Medicines and Medical Devices grants an Authorisation for conduct of Phase I clinical trials, after verification of the following documents:

a) the healthcare authorisation for operation of a medical facility;

b) a document attesting registration of the applicant as service provider under CAEN code 7219 – Other research and experimental development on natural sciences and engineering.

c) a membership certificate granted by a professional organisation for healthcare professionals involved in clinical trials;

d) list of its Standard Operating Procedures (see Annex 2 for the minimal list of Standard Operating Procedures) or certification of implementation of a quality management system in accordance with ISO standards in force for clinical trials; certification becomes mandatory one year following entry into force of these regulations;

e) the documents describing the secured IT infrastructure for data management and archiving of the clinical trial dossier;

f) the list of staff qualified to act as main investigator, together with the attached proof of confirmation of respective titles (senior physician or specialist physician with a minimum 3-year experience) and curriculum vitae;

g) proof of an emergency service within the respective site, in accordance with Annex 3;

h) proof of a bioanalytical laboratory, certified for Good Laboratory Practice (GLP) by the Romanian competent authority, or of a contract with a certified/accredited laboratory;

i) employment/collaboration agreement with a clinical pharmacologist with at least 3 years experience in this field;

Article 12. – Qualified staff should be hired at sites proposed for conduct of Phase I clinical trials (general physicians, medical specialists trained in the area targeted by clinical trials, physicians in training in clinical or surgery areas, clinical pharmacologists, appropriate auxiliary staff).

Article 13. – (1) The sites proposed for conduct of Phase I clinical trials must meet the requirements for areas, utilities, facilities and devices, mentioned in legislation in force, namely in Order of the Minister of Health no. 914/2006 on approval of the Norms regarding conditions to be met by a hospital for functioning authorisation.

(2) The proposed site for conduct of clinical trials with therapeutic benefit must own licensed and secured IT systems.

(3) The sites proposed for conduct of Phase I clinical trials must comply with requirements on archiving areas for clinical trial dossiers compliant with provisions of Order of the Minister of Health no. 903/2006 on approval of the Principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products as well as Scientific Council Decision no. 51/2006 on approval of Guidance on the content of the trials master file and archiving.

Article 14. - (1) In case the proposed site does not allow for conduct of assays, tests, clinical and paraclinical investigations, these can be performed as per agreement with other sites authorised/accredited by authorised bodies.

(2) The applicant must certify existence of an on-site emergency service.

Article 15. – The applicant healthcare facility must be provided with the following:

a) a dedicated section allowing for simultaneous care of at least 8 healthy volunteers/patients;

b) conditions proper for medical examination and surveillance for collection and storage of samples;

c) staff qualified for provision of emergency medical care.

Article 16. - Bioanalytical laboratories specialised in pharmacokinetic determinations must be certified/accredited. For trials performed in Romania only, bioanalytical laboratories specialised in pharmacokinetic determinations must hold an authorisation for Good Laboratory Practice (GLP), granted by the National Agency for Medicines and Medical Devices, in accordance with Government Decision no. 63/2002, as amended.

Article 17. - Phase I clinical trials shall be coordinated by a clinical pharmacologist employed as per Article 11 i).

SECTION 3
Authorisation for conduct of bioequivalence clinical trials

Article 18. - (1) Clinical evaluation of medicinal products through bioequivalence clinical trials can only be performed at sites specially authorised for this purpose in accordance with CAEN 7219 code – Other research and experimental development on natural sciences and engineering.

2) Holding an Authorisation for conduct of bioequivalence clinical trials does not entitle the holder to conduct Phase I clinical trials as well.

Article 19. – The following sites may apply for an authorisation for conduct of bioequivalence clinical trials:

a) medical sites provided with their own bioanalytical laboratory, specialised in pharmacokinetic determinations;

b) medical sites signatory of a collaboration agreement with a bioanalytical laboratory specialised in pharmacokinetic determinations, covering at least the validity period of the authorisation;

c) bioanalytical laboratories specialised in pharmacokinetic determinations, signatory of a collaboration agreement with medical site, covering at least the validity period of the authorisation;

d) bioanalytical laboratories specialised in pharmacokinetic determinations, provided with a clinical site in accordance with the provisions of this Order;

e) legal entities signatory of collaboration agreements with a bioanalytical laboratory specialised in pharmacokinetic determinations and with a medical site, covering at least the validity period of the authorisation.

Article 20. – The National Agency for Medicines and Medical Devices grants an Authorisation for conduct of bioequivalence clinical trials, after assessment of the following documents:

a) the healthcare authorisation for operation of a medical facility;

b) a document attesting registration of the applicant as service provider under CAEN code 7219 – Other research and experimental development on natural sciences and engineering

. c) free practice license of healthcare professionals involved in clinical trials;

d) list of its Standard Operating Procedures (see Annex 2 for the minimal list of Standard Operating Procedures) or certification of implementation of a quality management system in accordance with ISO standards in force for clinical trials; certification becomes mandatory one year following entry into force of these regulations;

e) the documents describing the secured IT infrastructure for data management and archiving of the clinical trial dossier;

f) the list of staff qualified to act as main investigator, together with the attached proof of confirmation of respective titles (senior physician, clinical pharmacologist or specialist physician, with a minimum 3-year experience) and curriculum vitae;

g) proof of existence of an emergency site in accordance with Annex 3;

h) proof of a bioanalytical laboratory, authorised for Good Laboratory Practice (GLP) by the National Agency for Medicines and Medical Devices, or of a contract signed with such laboratory;

i) employment/collaboration agreement with a clinical pharmacologist with at least 3 years experience in this field;

Article 21. – (1) The sites proposed for conduct of bioequivalence clinical trials must comply with requirements concerning areas, utilities, facilities and devices, stipulated by regulations in force, namely Order of the Minister of Health no. 914/2006 and Scientific Council Decision no. 15/07.06.2010 on approval of the Guideline on the investigation of bioequivalence.

(2) Sites proposed for conduct of bioequivalence clinical trials must hold authorisations and secured IT systems.

(3) The sites proposed for conduct of bioequivalence clinical trials must comply with requirements on archiving spaces for clinical trial dossiers compliant with provisions of Order of the Minister of Health no. 903/2006 on approval of the Principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products and Scientific Council Decision no. 51/2006 on approval of Guidance on the content of the trials master file and archiving.

Article 22. - (1) In case the proposed site does not allow for conduct of assays, tests, clinical and paraclinical investigations, these can be performed as per agreement with other sites authorised/accredited by authorised bodies

(2) The applicant must certify the existence of an on-site emergency service.

Article 23. - The applicant healthcare facility must be provided with the following:

a) a dedicated section allowing for simultaneous care of at least 12 healthy volunteers;

b) conditions proper for medical examination and surveillance for collection and storage of samples;

c) staff qualified for provision of emergency medical care.

Article 24. - Bioanalytical laboratories specialised in pharmacokinetic determinations must hold a GLP certificate issued by the National Agency for Medicines and Medical Devices, in accordance with Government Decision no. 63/2002, as amended, and with Scientific Council Decision no. 15/07.06.2010 on approval of the Guideline on the investigation of bioequivalence.

ANNEX 1
to SCD no. 2/ 22.04.2014

NAMMD HEADER

AUTHORISATION
for conduct of clinical trials
on medicinal product for human use

The National Agency for Medicines and Medical Devices, set up based on Emergency Government Ordinance no. 72/2010 on reorganisation of healthcare facilities and amendment of public health legislation based on Article 4 (2) d) of Government Decision no. 734/2010 on the organisation and operation of the National Agency for Medicines and Medical Devices, Scientific Council Decision no. 2/22.04.2014 on approval of Regulations for authorisation of sites for conduct of clinical trials on medicinal products for human use and according to documentation submitted, hereby grants Authorisation for conduct ***of clinical trials with therapeutic benefit/Phase I/bioequivalence clinical trials*** **to:**

Holder of authorisation:

Headquarters:

Areas of expertise:

Manager:

Number of authorisation:

Notifications:

In accordance with the legislation in force, the National Agency for Medicines and Medical Devices must be notified with regard to any amendment

of data included in the Authorisation for conduct of clinical trials on medicinal products for human use or the authorisation dossier

This authorisation of valid 2 years after grant.

PRESIDENT

ANNEX 2
to SCD no. 2/22.04.2014

Minimal list of Standard Operating Procedures

- Procedure for the stages of clinical trials
- Procedure for subject recruitment and identification
- Procedure for subjects informed consent
- Procedure for establishment of source documents and minimal information
- Procedure for assessment and report of serious adverse events
- Procedure for draft of procedures
- Procedure for organisation of the investigator team and delegation of responsibilities within a clinical trial
- Procedure for trial medication – reception, storage and handling
- Procedure for document archiving

ANNEX 3
to SCD no. 2/22.04.2014

MINIMUM EMERGENCY EQUIPMENT
for emergency services of sites conducting Phase I and bioequivalence clinical trials

1. Monitor of vital functions (TA, EKG, pulse oximeter)
2. Defibrillator (with battery)
3. Injectomate/pump for infusion
4. External heart stimulator
5. Source of medicinal oxygen
6. Cardiopulmonary resuscitation kit
7. PEEP ventilator
8. Surgical vacuum
9. Stethoscope and tensiometer
10. Glucose meter and glucose test strips
11. Ophthalmoscope
12. Reflex hammer

13. Expendables required for treatment of medical emergencies (syringes, sterile and non-sterile surgical gloves, peripheral catheters, intubation probes, laryngeal mask, aspiration probes, duodenal/gastric probes, Foley probes, tracheostomy cannulae, scalpel, infusors etc.)
14. Adjustable beds
15. Alarm system (for calling qualified care)
16. Direct telephone line
17. Medicinal products and solutions for infusion or parenteral use, unless otherwise specified, required for treatment of medical emergencies (physiological serum, Ringer's solution, 5%, 10%, 33% glucose, colloidal solutions, mannitol, analgesics, bronchodilators for inhalation, adrenalin, atropine, diazepam, ketamine, succinylcholine, muscular paralysis inducing drugs for long-term use, hydrocortisone hemisuccinate, dexametazone, nitroglycerin, dobutamine, metoprolol, amiodarone, xylin, heparine, antiemetics, furosemidum, B1 and B6 vitamins, sodium bicarbonate, insulin, aminophyllinum, antihypertensives, clonidine, antispastics).