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MINISTRY OF HEALTH

DECREE, 31 March 2008

Definition of the minimum requirements which Contract Research Organisations (CRO) shall satisfy in order to work within clinical trials on medicinal products.

THE MINISTER OF HEALTH

Having regard to the Ministerial Decree of 15 July 1997, <Adoption of the European Union guidelines implementation of good clinical practice in the conduct of clinical trials of medicinal products for human use>, published in the ordinary supplement of the Official Journal no. 191 of 18 August 1997;

Having regard to Legislative Decree no. 211 of 24 June 2003 published in the ordinary supplement of the Official Journal no. 184 of 9 August, 2003, concerning the <Transposition of 2001/20/EC Directive relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use>;

Having regard, in particular, to article 20, paragraph 3 of the aforementioned Legislative Decree no. 211 of 24 June 2003, which foresees that with a Decree by the Ministry of Health the minimum requirements are established that private organisations must satisfy when they are delegated by sponsors to perform any or all of the trial-related functions in compliance with good clinical practice, without prejudice to the sponsor's responsibility for the correlated research, and considering that said organisations are considered Contract Research Organisations (CRO) pursuant to paragraph 1.20 of Attachment 1 of the aforementioned Ministerial Decree of 15 July 1997;

Having regard to Ministerial Decree of 17 December, 2004, <Prescriptions and conditions of a general nature, referring to the conduct of clinical trials with medicinal products, with special reference to those designed to enhance clinical practice as an integral part of health and medical care>;

Having regard to Legislative Decree no. 200 of 6 November 2007, published in the ordinary supplement of the Official Journal no. 261 of 9 November 2007, <Implementation of 2005/28/EC Directive which lays down 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>;

Having regard, in particular, to article 6 of paragraph 3, of the aforementioned Legislative Decree no. 200 of 6 November 2007, which disciplines the possibilities of delegating the sponsor's functions to a facility that satisfies the established minimum requirements;

HEREBY ISSUES:

Article 1.

Scope

1. This Decree establishes the minimum requirements that shall be satisfied by private organisations, pursuant to article 20, paragraph 3 of Legislative Decree no. 211 of 24 June 2003 and from hereinafter referred to as Contract Research Organisations (CRO).

Article 2.

Definitions

1. For the purpose of this Decree the following definitions shall apply:

a) Contract Research Organisation (CRO): a company, an institution or a private organisation contracted by the sponsor to perform any or all of his trial-related functions (protocols design, selection of clinical sites and investigators, selection and use of monitors, elaboration of reports, statistical analysis, preparation of the documentation to be submitted to competent authorities etc.) as foreseen by good clinical practice, without prejudice to the sponsor's responsibility for the correlated trial;

b) good clinical practice (GCP): the standards pursuant to Attachment 1 of the Ministerial Decree of 15 July 1997 and Legislative Decree no. 200 of 6 November 2007, which were referred to in the premise;

c) sponsor of the clinical trial: a company, institute or organisation that takes the responsibility for the initiation, management and in case the financing of clinical trials. The person who, in addition to taking the aforementioned responsibilities, undertakes the role of investigator at the structure pursuant to article 1, paragraph 2, letter a) of the Decree by the Ministry of Health of 17 December 2004, is also considered a sponsor, but only in the cases in which such research is for non-commercial purposes within institutional tasks;

d) monitor: the person who oversees the progress of a clinical trial at the clinical sites, in order to guarantee that the trial is conducted in accordance with the protocol, the Standard Operating Procedures (SOP), the applicable regulatory requirements, good clinical practice (GCP) and who is responsible for the activities of monitoring the trials as provided in Attachment 1 of the Ministerial Decree of 15 July 1997;

e) Quality Assurance (QA): the combination of planned and systematic actions that are established to ensure:

1) that the trials entrusted to the CRO are conducted and that the data is generated, documented (recorded) and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements;

2) that all the activities of the CRO satisfy the quality requirements.

f) verifying or auditing: a systematic and independent examination of trial related activities and documents to determine whether the trial/clinical site related activities were conducted and the data was recorded, analysed and accurately reported according to the protocol, the CRO's and the sponsor's Standard Operating Procedure (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements;

g) director responsible for verifying or auditor: the person who takes the responsibility and the relating coordination of the activities of the CRO pertaining to check or auditing;

h) medical or scientific director: the person who takes the technical-scientific responsibility and the relating coordination of the activities of the CRO pertaining to the aspects of a medical or scientific nature;

i) qualified statistician: the person who takes the technical scientific responsibility and the relating coordination of the activities of the CRO pertaining to the aspects of a statistical nature.

Article 3.

General minimum requirements

1. The CRO in order to operate must satisfy at least the following general requirements:

a) requirements of an organisational and structural nature:

1) articles of the CRO and relating statute consistent with the objective of the CRO itself;

2) a list of the activities that the CRO accepts to perform;

3) a functional organigramme and a nominative organigramme wherein the career briefs responsible for the activities of the CRO are specified as well as the personnel assigned to these positions;

4) there must be a medical director or a scientific director with respectively a degree in medicine and a degree in a scientific discipline that pertains to the tasks to be performed by the CRO, with documented experience of at least two years in one or more medical or scientific fields pertaining to the CRO;

5) there must be personnel who is suitably qualified and in an adequate number to perform the activities foreseen;

6) the CRO must have operative headquarters that are suitably structured to ensure the correct undertaking of the activities to be performed by the CRO, and secure filing of confidential documents.

b) quality requirements:

1) a standard operating procedure must be drawn up for the activities that the structure has agreed to perform;

2) a quality assurance system must be set up and defined according to the ISO norms or equivalent standards, which must be implemented and maintained and related quality manuals must exist;

3) documented quality assurance (QA) activities must be performed;

4) a quality assurance director must be present who has a degree and proven experience of at least one year of practice in the sector, who must also have undergone at least 15 days of theoretical training during the last two years in the sector of quality assurance in general as well as specific pertaining to the activities of the CRO;

5) an annual program must be arranged, documented and implemented for training personnel, both employees and consultants;

6) all the CRO activities must comply with GCP;

7) a suitable documentation system must be set up in order to ensure that all the CRO activities can be traced;

c) requirements to up-to-date the personnel:

1) the CRO personnel must partake in at least 10 days of refresher courses annually on subject matters pertaining to the functions they carry out, unless provided otherwise.

Article 4.

Requirements for monitoring activities

1. Should the CRO carry out activities of monitoring, they must be equipped with the related personnel who satisfy at least the following requirements:

a) a degree in a medical/scientific discipline that pertains to the type of work to be carried out;

b) at least 10 days of theoretical training during the 12 months preceding the beginning of the monitoring activities pertaining to the following topics:

1) methodology and regulations relating clinical trials;

2) GCP;

3) Good manufacturing practice (GMP) with specific reference to the investigational medicinal product being tested;

4) pharmacovigilance;

5) quality and quality assurance systems;

6) monitoring tasks pursuant to paragraph 5.18 of Attachment 1 to the Ministerial Decree of 15 July 1997;

c) at least 30 days of monitoring activities as an assistant to an expert monitor during the 12 months preceding the beginning of the autonomous monitoring activities. Such assisting must be performed for at least 50% of the visits at the clinical sites before a trial commences, during the trial, and after the conclusion of a trial;

d) at least 6 months of activity in the 12 months preceding the beginning of the autonomous monitoring activities within the sector of control or surveillance of

medicinal products or clinical trials; as an alternative an additional 60 days of the activities described in letter c) during the 12 months preceding the beginning of the autonomous monitoring activities; as an alternative the completion of a masters program in clinical trials or regulatory science or in an equivalent discipline;

e) specific training on the type of trials that the monitoring pertains to.

2. Those who, during the thirty months preceding the date of this Decree, have performed the functions of monitor of clinical trials as described in paragraph 5.18 of Attachment 1 to the Ministerial Decree of 15 July 1997, which can be demonstrated by at least 110 days of documented monitoring or auditing activities, at least 50% of which were carried out through visits in clinical sites, are exempt from having to possess the requirements of paragraph 1, letters a), b), c) and d) and they may continue to carry out their activities, without prejudice to what is foreseen by paragraph 4.

3. The CRO must make use of monitors who, in addition to the requirements of paragraph 1 and 2, will partake in specific annual refresher courses of a duration not inferior to 10 days pertaining to one or more of the following subjects:

a) methodology and regulations relating clinical trials;

b) GCP;

c) GMP with specific reference to the investigational medicinal product being tested;

d) quality systems;

e) pharmacovigilance;

f) clinical-scientific topics that pertain to clinical trials;

g) other subjects pertaining to the tasks to be carried out.

4. For the auditing of trials or clinical sites that use advanced technological systems, such as for example, electronic case report forms (e-CRF), it is necessary to demonstrate to have undergone suitable training and refresher courses in the specific sector.

Article 5.

Requirements for auditing of trials or clinical sites

1. Should the CRO carry out activities of auditing of trials or clinical sites, he must have the related personnel who satisfy at least the following requirements:

a) a degree;

b) at least 10 days of theoretical training during the 12 months preceding the beginning of the auditing activities pertaining to the following subjects:

1) quality and quality assurance systems;

2) methods and regulations relating clinical trials;

3) GCP;

4) Good manufacturing practice (GMP) with specific reference to the investigational medicinal product being tested ;

5) pharmacovigilance;

6) auditor's tasks pursuant to paragraph 5.19 of Attachment 1 to the Ministerial Decree of 15 July 1997;

c) at least 30 days of auditing activities as an assistant to an expert auditor during the 12 months preceding the beginning of the autonomous auditing activities;

d) at least 6 months of activity in the 12 months preceding the beginning of the autonomous auditing activities in the sector of control or surveillance of medicinal products or clinical trials; as an alternative, an additional 60 days of the activities described in letter c) or 60 days of activities as a monitor performed during the 12 months preceding the beginning of the autonomous auditing activities;

e) specific training trial pertaining to the auditing.

2. Those who, during the thirty months preceding the date of this Decree, have performed the functions of auditor of trials as described in paragraph 5.19 of Attachment 1 of the Ministerial Decree of 15 July 1997, which can be demonstrated by at least 110 days of documented auditing activities, of which at least 50% are carried out through visits in clinical sites, are exempt from having to satisfy the requirements of paragraph 1, letter a), b), c) and d) and may continue to carry out their activities, without prejudice to what is foreseen by paragraph 4.

3. The CRO must make use of auditors who, in addition to the requirements of paragraph 1 and 2, partakes in specific annual refresher courses of a duration not inferior to 10 days on one or more of the following subjects:

a) methodology and regulations relating to clinical trials;

b) GCP;

c) GMP with specific reference to the investigational medicinal product being tested;

d) quality system;

e) pharmacovigilance;

f) clinical-scientific subjects that pertain to clinical trials;

g) other subjects pertaining to the tasks to be carried out.

4. For auditing of trials or clinical sites that use advanced technological systems, such as for example, electronic case report forms (e-CRF) it is necessary to demonstrate to have undergone suitable training and refresher courses in the specific sector.

Article 6.

Requirements for statistical analysis and data management

1. Should the CRO carry out activities of statistical analysis and management of data coming from clinical trials, they must make use of a qualified statistician who has at least the following requirements:

a) degree in statistics discipline or in an equivalent discipline related to his tasks or a degree in a discipline of a scientific type with an adequate training in statistics or university specialization, doctorate or master in a statistical discipline;

b) at least two years of experience on topics pertaining to his responsibilities;

c) annual refresher courses on topics pertaining to his responsibilities;

2. The data management activities must be carried out by qualified personnel and through appropriate software and must be validated according to what is foreseen by GCP.

3. For the activities pursuant to this article, the CRO must be equipped with facilities and informatics systems that are adequate enough to guarantee the physical and logical safety of the data.

Article 7.

Performance and notification of the requirements

1. Since the entrance into force of this decree, only the CRO who satisfy the requirements pursuant to the preceding articles may operate in Italy, without prejudice to what is foreseen by the following paragraphs.

2. Those who at the time of this Decree have performed for at least 2 years the documented functions of Scientific Director, or Quality Assurance Director, pursuant to article 3, may continue such functions even though they do not possess the degree requirements foreseen by the above mentioned article 3.

3. Those who at the time of this Decree have performed for at least two years the documented functions of qualified statistician pursuant to article 6 may continue to perform such functions even though they do not possess the university degrees foreseen by article 6, paragraph 1, letter a).

4. Individual professionals and technical workers who, within their independent professional activities or consulting activities, after having stipulated contracts with the sponsor of the trials or with a CRO, perform single functions referred to in this Decree, must satisfy the same requirements foreseen by this Decree in order to perform said functions and must operate within the quality system of such structures.

5. The CROs who, before the entrance into force of this Decree satisfy the foreseen requirements, in order to continue to operate must provide notification, before the Decree enters into force, of the possession of the aforementioned requirements by means of self-certification drawn up in compliance with a specific Determination by the Director General of AIFA, issued on the same date as this Decree, and to be sent to the GCP inspectorate and the Office for Clinical Trials of the Italian Medicines Agency (AIFA).

6. In the event of the activation of new CROs after the date this Decree enters into force, the notification pursuant to paragraph 5 must be made at least 30 days before the beginning of the activity.

7. The possession of the requirements pursuant to this Decree, notified according to this article must be subject to verification by the AIFA, within the inspection activities pursuant to article 15 of Legislative Decree no. 211 of 24 June 2003 and according to Chapters V and VI of Legislative Decree no. 200 of 6 November 2007.

Article 8.

Legal Representation

1. The CROs with headquarters outside Italy who intend to carry out activities within Italian territory must have legal representation in one of the member states of the European Union and must have requirements that are at least equivalent to those set forth by this Decree.

Article 9.

Effects on marketing authorisation

1. When a sponsor has delegated any or all of his responsibilities to an Italian CRO who does not satisfy the requirements pursuant to this Decree, or to an external CRO who does not have requirements that are at least equivalent to those foreseen by this Decree, the results of the trials shall not be taken into consideration in the evaluation of the request for marketing authorisation. This Decree shall be transmitted to the State Audit Court for registration.

This Decree shall enter into force on the ninetieth day since its publication in the *Official Journal* of the Italian Republic, without prejudice to what is foreseen by article 7, paragraph 5 which shall enter into force on the same day of the publication in the *Official Journal* of the Italian Republic.

Rome, 31 March 2008

The Minister: TURCO

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