COMMISSION IMPLEMENTING REGULATION (EU) 2017/556

of 24 March 2017

on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014 of the European Parliament and of the Council

(Text with EEA relevance)

THE EUROPEAN COMMISSION,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC ([1]), and in particular Article 78(7) thereof,

Whereas:

(1) Regulation (EU) No 536/2014 lays down the legal framework for the conduct of clinical trials on medicinal products for human use in the Union to ensure that the rights, safety and well-being of the subjects are protected, and the data generated in clinical trials are robust and reliable. In particular, the sponsor of a clinical trial and the investigator are to ensure that the clinical trial is conducted in accordance with the relevant protocol and the principles of good clinical practice. Compliance with the applicable legal requirements, the protocol and the principles of good clinical practice, including with standards relating to data integrity and ethical conduct of the clinical trial, is to be verified by means of inspections conducted under the responsibility of the Member State where the inspection takes place.

(2) The inspection in the context of clinical trials may concern good manufacturing practices as regards the manufacturing of the investigational medicinal products or good clinical practice as regards the conduct of clinical trials. Article 63 of Regulation (EU) No 536/2014 empowers the Commission to adopt delegated acts specifying the detailed arrangements for good manufacturing practice inspections as regards investigational medicinal products. Therefore, this Regulation should only lay down detailed arrangements for good clinical practice inspections procedures and requirements regarding training and qualifications of good clinical practice inspectors.

(3) Member States may conduct inspections of clinical trials performed in third countries, either because a clinical trial is related to a clinical trial authorised in the Union or because the data of the clinical trial is being referred to in a clinical trial authorisation application in the Union. Those inspections should allow verifying whether such clinical trials were conducted in accordance with standards equivalent to Union standards. Inspections of clinical trials in third countries may also be conducted in order to verify whether the clinical trials, whose results are referred to in marketing authorisation applications in the Union, meet the ethical requirements set out in Regulation (EU) No 536/2014. Therefore, provisions on detailed arrangements for the inspection procedures should apply also to inspections conducted outside the Union in accordance with Regulation (EU) No 536/2014.

(4) The International Conference on Harmonisation ('ICH') reached a consensus in 1995 to provide a harmonised approach for good clinical practice. Pursuant to Article 47 of Regulation (EU) No 536/2014, the ICH guidelines should be appropriately taken into account by the sponsor when drafting the clinical trial protocol and conducting the clinical trial. To the extent that those guidelines are compatible with the relevant Union law and EU guidelines, inspectors should refer to the ICH guidelines, taking into account the characteristics of each trial.

(5) Member States should be required to set up quality systems to ensure that the inspection procedures are observed and consistently monitored. A well-functioning quality system should comprise an organisational structure, clear processes and procedures, including the standard operating procedures to be followed by inspectors when performing their tasks, clearly defined details of the inspectors' duties and responsibilities and ongoing training requirements, as well as adequate resources and mechanisms which aim at eliminating non-compliance.

([1]) OJ L 158, 27.5.2014, p. 1.

(6) It is necessary to enable inspectors to ensure the practical effectiveness of provisions on good clinical practice. That objective should be reflected in the minimum requirements for the qualification of inspectors, in particular as regards their education and training. For the same reasons, detailed rules on inspection procedures should be laid down.

(7) In order to safeguard the effectiveness of inspection, the inspectors should be granted the necessary powers of access to the premises and data. This includes in particular any laboratory used for analysis in the clinical trial, any contract research organisation's facilities or the sponsor's premises. They should also be empowered to contact the trial subjects in justified cases.

(8) In order to ensure the compliance with arrangements for good clinical practice inspections and in accordance with Article 77 of Regulation (EU) No 536/2014 Member States should take corrective measures if necessary. When during an inspection a major non-compliance or breach is identified, or the inspectors' investigatory powers are not recognised by the sponsors, Member States should have recourse to penalties.

(9) In order to ensure the protection of confidential information, in particular personal data of clinical trial subjects related to their health as well as commercially confidential information, the inspectors and experts involved in inspections should be bound by the highest standards of confidentiality and the applicable requirements of the Union law, national laws and international agreements. The inspectors and experts involved in inspections should comply with the requirements of Directive 95/46/EC of the European Parliament and of the Council ([1]) when processing personal data.

(10) Commission Directive 2005/28/EC ([2]) should be repealed in order to ensure that only one set of rules applies to the conduct of good clinical practice inspections of clinical trials, including clinical trials governed by Directive 2001/20/EC of the European Parliament and of the Council ([3]). However, in order to ensure consistency with Article 98 of Regulation (EU) No 536/2014 setting up a transitional period maintaining, as regards certain requests for authorisation of a clinical trial, the applicability of Directive 2001/20/EC, Directive 2005/28/EC should, with the exception of its Chapters 5 and 6 referring to good clinical practice inspection procedures and inspectors, remain applicable during that transitional period to all clinical trials authorised on the basis of Directive 2001/20/EC.

(11) This Regulation should become applicable at the same time as Regulation (EU) No 536/2014.

(12) The measures provided for in this Regulation are in accordance with the opinion of the Standing Committee on Medicinal Products for Human Use,

HAS ADOPTED THIS REGULATION:

CHAPTER I

GENERAL PROVISIONS

Article 1

Scope

This Regulation applies to inspections of:

(a) clinical trials conducted in the Union, including clinical trial sites related to those trials but located outside the Union;

([1]) Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data (OJ L 281, 23.11.1995, p. 31).

([2]) Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirement for authorisation of the manufacturing or importations of such products (OJ L 91, 9.4.2005, p. 13).

([3]) Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (OJ L 121, 1.5.2001, p. 34).

(b) clinical trials referred to in the applications for clinical trial authorisations pursuant to Article 25(5) of Regulation (EU) No 536/2014;

(c) clinical trials conducted in third countries and referred to in marketing authorisation applications in the Union.

Article 2

Time frame for inspections

Inspections may take place in any of the following circumstances:

(a) before, during or after the conduct of a clinical trial;

(b) as part of the verification of applications for marketing authorisation;

(c) as a follow-up to the granting of a marketing authorisation.

Article 3

Quality system

1. Each Member State shall set up a properly designed quality system ensuring that the inspection procedures are observed and consistently monitored.

Member States shall maintain those quality systems up to date.

2. Each inspector shall have access to and comply with standard operating procedures, details of their duties, responsibilities and training requirements.

CHAPTER II

INSPECTORS

Article 4

Qualifications, training and experience

1. Inspectors shall have completed education at university level, or have equivalent experience, in medicine, pharmacy, pharmacology, toxicology or other fields relevant to the principles of good clinical practice.

2. Inspectors shall receive appropriate training, including participation in inspections. Their training needs, necessary to maintain or improve their skills, shall be assessed regularly by a person appointed for that task.

3. Inspectors shall have knowledge of principles and processes that apply to the development of medicinal products and clinical research and have knowledge of applicable Union and national legislation and guidelines on the conduct of clinical trials and the granting of marketing authorisations.

4. Inspectors shall have the ability to make professional judgments in relation to the compliance with applicable Union and national legislation and guidelines. They shall be able to assess data integrity as well as aspects related to ethical conduct of clinical trials.

5. Inspectors shall be familiar with the procedures and technical methods for the recording and management of clinical data, and with the organisation and regulation of the healthcare systems in the relevant Member States and, where appropriate, in third countries.

6. Inspectors shall be able to assess the degree of risk as regards the safety of the subjects enrolled in the clinical trial as well as the data integrity.

7. Inspectors shall be aware of the applicable rules as regards confidentiality and protection of personal data.

8. Member States shall keep records of the qualifications, training and experience of each inspector and maintain those records up-to-date for as long as inspector is in active duty.

Article 5

Conflict of interest and impartiality

1. Inspectors shall be free from any influence which could affect their impartiality or their judgement.

2. Inspectors shall not have conflicts of interest. In particular, they shall be independent of all of the following parties:

(a) the sponsor;

(b) the investigators involved in the clinical trial;

(c) persons financing the clinical trial;

(d) any other party involved in the conduct of the clinical trial.

3. Each inspector shall make an annual declaration of their financial interests and other links to the parties to be potentially inspected. That declaration shall be taken into consideration for the purposes of assigning an inspector to a specific inspection.

CHAPTER III

INSPECTION PROCEDURES

Article 6

Subject matter of inspections

Inspectors shall verify the compliance with the requirements of Regulation (EU) No 536/2014, including protection of the rights and well-being of the clinical trial subjects, the quality and integrity of data generated in clinical trial, the compliance with principles of good clinical practice, including the ethical aspects and the relevant national legislation.

Article 7

Procedures to be established by Member States

1. Member States shall establish the relevant procedures for at least the following:

(a) appointing experts to accompany inspectors, if additional expertise is required for an inspection;

(b) arranging inspections outside the Union;

(c) verification of good clinical practice compliance, including the modalities for examining the study management procedures and the conditions under which the clinical trial is planned, performed, monitored and recorded, as well as follow-up measures, such as a review of an analysis of the root cause of a significant non-compliance and verification of corrective and preventive actions implemented by the sponsor.

Member States shall make those procedures and rules publicly available.

2. Member States shall also define the powers of experts appointed to accompany inspectors.

Article 8

Unannounced inspections

The inspections may, where necessary, be carried out unannounced.

Article 9

Collaboration between Member States

1. Member States shall collaborate with each other, with the Commission and with the European Medicines Agency to develop and improve commonly recognised standards of good clinical practice inspections. This collaboration may take the form of joint inspections, agreed processes and procedures and sharing of experience and training.

2. The Commission shall make publicly available any guidance documents on the commonly recognised standards for the conduct of inspections, developed in collaboration with Member States and the European Medicines Agency.

3. The European Medicines Agency shall process and make available to Member States information on inspections that are envisaged, scheduled, or conducted, in order to assist Member States to ensure the most efficient use of inspection resources when planning their inspections.

4. Member States may request assistance from the national competent authority of another Member State in the matter of inspection.

Article 10

Powers of inspectors

1. Inspections shall be carried out by inspectors appointed by Member States.

In order to ensure the availability of necessary skills for each inspection, Member States may appoint teams of inspectors and appoint experts with appropriate qualifications to accompany inspectors.

2. Inspectors shall be entitled to inspect the clinical trial sites, documents, facilities, records, including individual patients' records, quality arrangements, data and any other resources and entities that are deemed by the competent authority to be related to the clinical trial.

3. When performing an inspection, the inspectors shall be empowered to enter into sites, other related premises, and to access to data, including individual patients' records.

4. Inspectors shall be entitled to make copies of records and hard copies, print-outs of electronic records and take photos of premises and equipment.

5. Inspectors shall be entitled to ask any representative or member of staff of the inspected entity and any party involved in the clinical trial for explanations relating to the subject matter and purpose of the inspection and to record the answer.

6. Inspectors shall be empowered to contact the trial subjects directly, in particular in case of reasonable suspicion that they were not informed adequately of their participation in the clinical trial.

7. Member States shall provide inspectors with suitable means of their identification.

8. Member States shall establish a legal and administrative framework to ensure that inspectors from other Member States, on request and where appropriate, have access to sites, any premise of any entity related to the clinical trial as well as to related data.

Article 11

Recognition of inspection conclusions

Inspectors shall carry out inspections on behalf of the Union. The results of those inspections shall be recognised by all Member States.

In case of divergences between Member States in relation to the verification of compliance with the applicable legislation, the Member States, or the European Medicines Agency within the framework of its powers as provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council [1], shall inform the Commission. The Commission, after consulting those Member States and the European Medicines Agency, may request a new inspection.

Article 12

Resources

Member Sates shall appoint an adequate number of inspectors to ensure effective verification of compliance of clinical trials with applicable requirements, as well as the timely reporting of inspection findings.

Article 13

Inspection reports and records

Without prejudice to the obligation to submit the inspection reports via the EU Portal in accordance with Article 78(6) of Regulation (EU) No 536/2014, Member States shall keep for at least 25 years relevant records of national inspections as well as of the inspections performed outside their territory, including information on the outcome of the inspection as regards good clinical practice compliance status as well as any action taken by the sponsor or Member State in the follow-up of the inspection. The inspection reports submitted through the EU portal shall not contain personal data of clinical trials' subjects.

Article 14

Confidentiality

The inspectors and experts appointed to the inspection team shall maintain the confidentiality of information to which they gain access as a result of good clinical practice inspections.

CHAPTER IV

FINAL PROVISIONS

Article 15

Repeal

Directive 2005/28/EC is repealed from the date referred to in the second paragraph of Article 17.

Article 16

Transitional provisions

Directive 2005/28/EC, except for its Chapters 5 and 6, shall continue to apply to the clinical trials governed by Directive 2001/20/EC pursuant to Article 98 of Regulation (EU) No 536/2014.

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[1] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

Article 17

Entry into force

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

It shall apply from 6 months after the date of publication in the *Official Journal of the European Union* of the notice referred to in Article 82(3) of Regulation (EU) No 536/2014.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels, 24 March 2017.

For the Commission

The President

Jean-Claude JUNCKER