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From:	Secretary-General of the European Commission, signed by Mr Jordi AYET PUIGARNAU, Director
date of receipt:	23 May 2017
To:	Mr Jeppe TRANHOLM-MIKKELSEN, Secretary-General of the Council of the European Union
No. Cion doc.:	C(2017) 3368 final
Subject:	COMMISSION DELEGATED REGULATION (EU) .../... of 23.5.2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections

Delegations will find attached document C(2017) 3368 final.

Encl.: C(2017) 3368 final



Brussels, 23.5.2017
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COMMISSION DELEGATED REGULATION (EU) .../...

of 23.5.2017

supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections

(Text with EEA relevance)

EXPLANATORY MEMORANDUM

1. CONTEXT OF THE DELEGATED ACT

A new 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/EC¹ will replace the current 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 use².

Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use³ covers both "finished" medicinal products for human use and investigational medicinal products for human use. Directive 2003/94/EC will not apply to clinical trials conducted according to Regulation (EU) No 536/2014 and in order to ensure that investigational medicinal products used for those clinical trials are of required quality, new provisions for good manufacturing practice for investigational medicinal products for human use are necessary.

Regulation (EU) No 536/2014 requires that the Commission shall adopt delegated acts to specify the principles and guidelines of good manufacturing practice to ensure the quality of investigational medicinal products for human use and arrangements for inspections.

2. CONSULTATIONS PRIOR TO THE ADOPTION OF THE ACT

With a view to preparing this Delegated Regulation, the Commission discussed with the ad hoc group on clinical trials, the expert group for this Delegated Regulation, at its meetings on 1 December 2014 and on 8 February 2016. The ad hoc group on clinical trials were consulted in a written procedure in April 2016.

Furthermore, Member States experts on Good Manufacturing Practice of medicinal products in the context of the Good Manufacturing Practice/Good Distribution Practice Inspectors Working Group were also consulted in March 2015.

A public consultation took place from 28 August to 24 November 2015. In the public consultation, 26 responses were received from stakeholder organisations, individual companies, regional authorities and national competent authorities in Europe and outside of Europe.

The draft proposal of the Regulation was subject to public consultation via the Better Regulation portal from the 13th of January to the 10th of February 2017. The European Commission received 6 contributions from stakeholders representing both

¹ OJ L 158, 27.5.2014, p. 1.

² OJ L 121, 1.5.2001, p. 34.

³ OJ L, 262, 14.10.2003, p. 22.

industry and regulatory authorities. The feedback received lead to small amendments of the proposed text in order to further clarify the sponsor and manufacturer responsibilities in particular with regards to rapid unblinding and quality control, requirements applicable to third country manufacturers of investigational medicinal products as well as requirements in regards to the validation process.

3. LEGAL ELEMENTS OF THE DELEGATED ACT

The legal basis for this Delegated Regulation is Article 63(1) of Regulation (EU) No 536/2014.

This Delegated Regulation supplements Regulation (EU) No 536/2014 by specifying the principles and guidelines of good manufacturing practice in respect of investigational medicinal products for human use and arrangements for inspections.

COMMISSION DELEGATED REGULATION (EU) .../...

of 23.5.2017

supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections

(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/EC⁴, and in particular Article 63(1) thereof,

Whereas:

- (1) The good manufacturing practice for investigational medicinal products for human use ensures that there is consistency between batches of the same investigational medicinal product used in the same or different clinical trials, and that changes during the development of an investigational medicinal product are adequately documented and justified. The manufacturing of investigational medicinal products presents additional challenges comparing to the manufacturing of authorised medicinal products because there are no fixed routines, there is a variety of clinical trial designs and consequently packaging designs. Those challenges are due to the need, often, of randomisation and to disguise the identity of the investigational medicinal products for the purpose of clinical trial (blinding). The toxicity, potency and sensitising potential of investigational medicinal products for human use may not be fully understood at the time of the trial, and the need to minimise all risks of cross-contamination is therefore of even greater importance than for authorised medicinal products. Because of this complexity, the manufacturing operations should be subject to a highly effective pharmaceutical quality system.
- (2) Good manufacturing practice as regards both medicinal products authorised to be placed on the market and investigational medicinal products are based on the same principles. The same manufacturing sites will often manufacture both investigational and medicinal products authorised to be placed on the market. For that reason the principles and guidelines of good manufacturing practice for investigational medicinal products for human use should be aligned as much as possible with those applicable to medicinal products for human use.

⁴ OJ L 158, 27.5.2014, p. 1.

- (3) In accordance with Article 61(5) of Regulation (EU) No 536/2014 certain processes do not require the authorisation referred to in Article 61(1) of that Regulation. In line with Article 63(2) of Regulation (EU) No 536/2014 good manufacturing practice for investigational medicinal products does not apply to those processes.
- (4) For the manufacturer to be able to comply with good manufacturing practice for investigational medicinal products, cooperation between the manufacturer and the sponsor is necessary. Likewise, for the sponsor to comply with the requirements of Regulation (EU) No 536/2014 cooperation with the manufacturer is necessary. Where the manufacturer and the sponsor are different legal entities, the obligations of the manufacturer and sponsor vis-à-vis each other should be specified in a technical agreement between them. Such an agreement should provide for the sharing of inspection reports and exchange of information on quality issues.
- (5) Investigational medicinal products imported into the Union should be manufactured by applying quality standards at least equivalent to those in the Union. For this reason, only products manufactured by a third country manufacturer that is entitled or authorised to do so in accordance with the laws of the country where the manufacturer is located, should be allowed to be imported into the Union.
- (6) All manufacturers should operate an effective quality assurance system of their manufacturing or import operations. Such a system in order to be effective requires the implementation of a pharmaceutical quality system. Good documentation constitutes an essential part of a quality assurance system. The documentation system of manufacturers shall enable the history of the manufacture of each batch and any changes introduced during the development of an investigational medicinal product to be traced.
- (7) Principles and guidelines of good manufacturing practice for investigational medicinal products should be set out in relation to quality management, personnel, premises, equipment, documentation, production, quality control, outsourced operations, complaints and recall, and self-inspections.
- (8) It is appropriate to require a product specification file which brings together and contain all of the essential reference documents to ensure that investigational medicinal products are manufactured according to good manufacturing practice for investigational medicinal products and the clinical trial authorisation.
- (9) Due to the special characteristics of advanced therapy investigational medicinal products, the provisions on good manufacturing practice should be adapted to those products in accordance with a risk-based approach. As regards the advanced therapy medicinal products marketed in the Union, Article 5 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council⁵ provides for such adaptation. The Commission guidelines referred to in Article 5 of Regulation (EC) No 1394/2007 should also set out the requirements on good manufacturing practice applicable to advanced therapy investigational medicinal products.

⁵ Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121).

- (10) In order to ensure conformity with the principles and guidelines of good manufacturing practice for investigational medicinal products, provisions on inspections by the competent authorities of the Member States should be established. Member States should not be obliged to inspect third country manufacturers of investigational medicinal products routinely. The need for such inspections should be established according to a risk based approach but third country manufacturers should be inspected at least if there is a suspicion that the investigational medicinal products are not manufactured by applying quality standards at least equivalent to those applicable in the Union.
- (11) Inspectors should consider the Commission guidelines on good manufacturing practice for investigational medicinal products for human use. To achieve and maintain mutual recognition of inspection findings in the Union and facilitate the cooperation of the Member States, commonly recognised standards on the conduct of inspections on good manufacturing practice for investigational medicinal products in the form of procedures should be developed. The Commission guidelines and these procedures should be maintained and regularly updated, according to technical and scientific developments.
- (12) During inspections of a site the inspectors should check whether a site respects good manufacturing practice as regards both investigational medicinal products and medicinal products authorised to be placed on the market. For that reason, and in order to ensure the effective supervision, procedures and powers to carry out inspections to verify that good manufacturing practice for investigational medicinal products for human use is followed should be aligned as much as possible to those for medicinal products for human use.
- (13) To ensure that inspections are effective, inspectors should be appropriately empowered.
- (14) Member States should be able to take action in case of non-compliance with good manufacturing practice for investigational medicinal products for human use.
- (15) The competent authorities 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 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 to eliminate non-compliance.
- (16) This Regulation should apply from the same date as Commission Directive (EU) .../...⁶,

HAS ADOPTED THIS REGULATION:

CHAPTER I

⁶ [Commission Directive (EU) .../... supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for medicinal products for human use (OJ ...)].

GENERAL PROVISIONS

Article 1 **Subject matter**

This Regulation specifies the principles and guidelines of good manufacturing practice for investigational medicinal products for human use the manufacture or import of which requires an authorisation as referred to in Article 61(1) of Regulation (EU) No 536/2014 and lays down arrangements for inspections of manufacturers in relation to compliance with good manufacturing practice in accordance with Article 63(4) of that Regulation.

Article 2 **Definitions**

For the purposes of this Regulation, the following definitions shall apply:

- (1) 'manufacturer' means any person engaged in activities for which an authorisation is required in accordance with Article 61(1) of Regulation (EU) No 536/2014;
- (2) 'third country manufacturer' means any person established in a third country and engaged in manufacturing operations in that third country;
- (3) 'product specification file' means a reference file containing, or referring to files containing, all the information necessary to draft detailed written instructions on processing, packaging, quality control, testing and batch release of an investigational medicinal product and to perform batch certification;
- (4) 'validation' means action of proving, in accordance with the principles of good manufacturing practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results.

CHAPTER II

GOOD MANUFACTURING PRACTICE

Article 3 **Conformity with good manufacturing practice**

1. The manufacturer shall ensure that manufacturing operations are carried out in accordance with good manufacturing practice for investigational medicinal products specified in this Regulation and subject to an authorisation as referred to in Article 61(1) of Regulation (EU) No 536/2014.
2. When importing an investigational medicinal products, the holder of the authorisation referred to in Article 61(1) of Regulation (EU) No 536/2014 shall ensure that the products have been manufactured by applying quality standards at least equivalent to those laid down by this Regulation and in Regulation (EU) No 536/2014, and that the third country manufacturer is authorised or entitled to in accordance with the laws of that country to manufacture that investigational medicinal products in that third country.

Article 4
Compliance with clinical trial authorisation

1. The manufacturer shall ensure that all manufacturing operations for investigational medicinal products are carried out in accordance with the documentation and information provided by the sponsor pursuant to Article 25 of Regulation (EU) No 536/2014 and as authorised in accordance with the procedure laid down in Chapter II, or if documentation and information was subsequently amended, in Chapter III of above mentioned Regulation (EU) No 536/2014.
2. The manufacturer shall regularly review his manufacturing methods in the light of scientific and technical progress and experience gained by the sponsor during the development of the investigational medicinal product.

The manufacturer shall inform the sponsor of his reviews of the manufacturing methods.

Where, following a review, an amendment to the clinical trial authorisation is necessary, the application for the amendment shall be submitted in accordance with Article 16 of Regulation (EU) No 536/2014 where the change to the clinical trial is a substantial modification or the amendment shall be carried out in accordance with Article 81(9) of that Regulation where the change to the clinical trial is not a substantial modification.

Article 5
Pharmaceutical quality system

1. The manufacturer shall establish, implement and maintain effective organised arrangements to ensure that the investigational medicinal products are of the quality required for their intended use. Those arrangements shall include the establishment of a good manufacturing practice and a quality control.
2. Senior management and personnel from different departments shall participate in the establishment of the pharmaceutical quality system.

Article 6
Personnel

1. At each manufacturing site, the manufacturer shall have a sufficient number of competent and appropriately qualified personnel at his disposal to ensure that the investigational medicinal products are of the quality required for their intended use.
2. The duties of managerial and supervisory staff, including the qualified persons, responsible for implementing and operating good manufacturing practice shall be set out in their job descriptions. Their hierarchical relationships shall be set out in an organisation chart. The organisation chart and the job descriptions shall be approved in accordance with the manufacturer's internal procedures.
3. The staff referred to in paragraph 2 shall be given sufficient authority to discharge their responsibility correctly.

4. The personnel shall receive initial and on-going training covering in particular the following areas:
 - (a) the theory and application of the concept of pharmaceutical quality;
 - (b) good manufacturing practice.

The manufacturer shall verify the effectiveness of the training.

5. The manufacturer shall establish hygiene programmes, including procedures relating to health, hygiene practice and clothing of personnel. The programmes shall be adapted to the manufacturing operations to be carried out. The manufacturer shall ensure that the programmes are observed.

Article 7 ***Premises and equipment***

1. The manufacturer shall ensure that premises and manufacturing equipment are located, designed, constructed, adapted and maintained to suit the intended operations.
2. The manufacturer shall ensure that the premises and manufacturing equipment are laid out, designed and operated in such a way as to minimise risk of error and permit effective cleaning and maintenance in order to avoid contamination, cross contamination and any other adverse effect on the quality of the investigational medicinal product.
3. The manufacturer shall ensure that those premises and equipment to be used for manufacturing operations which are critical to the quality of the investigational medicinal products are subjected to appropriate qualification and validation.

Article 8 ***Documentation***

1. The manufacturer shall establish and maintain a documentation system recording the following, where appropriate having regard to the activities undertaken:
 - (a) specifications;
 - (b) manufacturing formulae;
 - (c) processing and packaging instructions;
 - (d) procedures and protocols, including procedures for general manufacturing operations and conditions;
 - (e) records, in particular covering the various manufacturing operations performed and batch records;
 - (f) technical agreements;

(g) certificates of analysis;

The documents specific to any investigational medicinal product shall be consistent with the product specification file as relevant.

2. The documentation system shall ensure the data quality and integrity. Documents shall be clear, free from error and kept up to date.
3. The manufacturer shall retain the product specification file and batch documentation for at least five years after the completion or discontinuation of the last clinical trial in which the batch was used.
4. When documentation is stored using electronic, photographic or other data processing systems, the manufacturer shall first validate the systems to ensure that the data will be appropriately stored during the period of storage laid down in paragraph 3. Data stored by those systems shall be made readily available in readable form.
5. The electronically stored data shall be protected against unlawful access, loss or damage of data by techniques, such as duplication, back-up and transfer onto another storage system. Audit trails, meaning records of all relevant changes and deletions in those data, shall be maintained.
6. The documentation shall be provided to competent authority upon request.

Article 9 **Production**

1. The manufacturer shall carry out production operations in accordance with pre-established instructions and procedures.

The manufacturer shall ensure that adequate and sufficient resources are made available for the in-process controls and that all process deviations and product defects are documented and thoroughly investigated.

2. The manufacturer shall take appropriate technical or organisational measures to avoid cross contamination and unintentional mixing of substances. Particular attention shall be paid to the handling of investigational medicinal products during and after any blinding operation.
3. The manufacturing process shall be validated in its entirety, as far as is appropriate, taking into account the stage of product development.

The manufacturer shall identify the process steps that ensure the safety of the subject, such as sterilisation, and the reliability and robustness of the clinical trial data generated in the clinical trial. Those critical process steps shall be validated and regularly re-validated.

All steps in the design and development of the manufacturing process shall be fully documented.

Article 10
Quality control

1. The manufacturer shall establish and maintain a quality control system under the authority of a person who has the requisite qualifications and is independent of production.

That person shall have access to one or more quality control laboratories appropriately staffed and equipped to carry out the examination and testing of starting materials and packaging materials and the testing of intermediate and finished investigational medicinal products.

2. The manufacturer shall ensure that the quality control laboratories comply with information provided in the application dossier, referred to in Article 25(1) of Regulation (EU) No 536/2014, as authorised by Member States.
3. When investigational medicinal products are imported from third countries, analytical control in the Union shall not be mandatory.
4. During the final control of the finished investigational medicinal product, and before its release by the manufacturer, the manufacturer shall take into account:
 - (a) analytical results;
 - (b) production conditions;
 - (c) the results of in-process controls;
 - (d) the examination of the manufacturing documents;
 - (e) the conformity of the product with its specifications;
 - (f) conformity of the product with the clinical trial authorisation;
 - (g) examination of the final finished packaging.

Article 11
Retention of samples used for quality control

1. The manufacturer shall retain sufficient samples of each batch of bulk formulated product, of key packaging components used for each finished investigational medicinal product batch and of each batch of finished investigational medicinal product for at least two years after the completion or discontinuation of the last clinical trial in which the batch was used.

Samples of starting materials, other than solvents, gases or water, used in the manufacturing process shall be retained by the manufacturer for at least two years after the release of the investigational medicinal product. However, this period may be shortened where the period of stability of the starting material, as indicated in the relevant specification, is shorter.

In all cases samples shall be maintained by the manufacturer at the disposal of the competent authority.

2. Upon application of the manufacturer, the competent authority may grant a derogation from paragraph 1 in relation to the sampling and retention of starting material and for certain products manufactured individually or in small quantities, or when their storage could raise special problems.

Article 12 ***Responsibilities of the qualified person***

1. The qualified person referred to in Article 61(2)(b) of Regulation (EU) No 536/2014 shall be responsible for the following:
 - (a) where investigational medicinal products are manufactured in the Member State concerned, verifying that each production batch has been manufactured and checked in compliance with the requirements of good manufacturing practice for investigational medicinal products laid down in this Regulation and the information provided pursuant to Article 25 of Regulation (EU) No 536/2014, taking into account the guidelines referred to in Article 63(1) of that Regulation;
 - (b) where investigational medicinal products are manufactured in a third country, verifying that each production batch has been manufactured and checked in accordance with quality standards at least equivalent to those laid down in this Regulation and the information provided pursuant to Article 25 of Regulation (EU) No 536/2014 taking into account the guidelines referred to in Article 63(1) of that Regulation.

The qualified person shall certify in a register or equivalent document provided for that purpose that each production batch complies with the requirements laid down in paragraph 1.

2. The register or equivalent document shall be kept up to date as operations are carried out and shall remain at the disposal of the competent authority for at least five years after the completion of or the formal discontinuation of the last clinical trial in which the product batch was used.

Article 13 ***Outsourced operations***

1. Where a manufacturing operation or operation linked thereto is outsourced, the outsourcing shall be the subject of a written contract.
2. The contract shall clearly lay down the responsibilities of each party. It shall lay down an obligation for the party to whom the operations are outsourced to follow good manufacturing practice and set out the manner in which the qualified person responsible for certifying each batch is to discharge his responsibilities.

3. The party to whom the operations are outsourced shall not subcontract any of the operations entrusted to him under the contract without written consent from the contract giver.
4. The party to whom the operations are outsourced shall comply with the principles and guidelines of good manufacturing practice applicable to the operations concerned and shall submit to inspections carried out by the competent authority pursuant to Article 63(4) of Regulation (EU) No 536/2014.

Article 14

Complaints, product recall and emergency unblinding

1. The manufacturer shall, in cooperation with the sponsor, implement a system for recording and reviewing complaints together with an effective system for recalling investigational medicinal products which have already entered the distribution network promptly and at any time. The manufacturer shall record and investigate any complaint concerning a defect and shall inform the sponsor and the competent authority of the Member States concerned of any defect that could result in a recall or abnormal restriction on supply.

All trial sites shall be identified and, in so far as possible, the countries of destination shall be indicated.

In the case of an authorised investigational medicinal product, the manufacturer shall, in cooperation with the sponsor, inform the marketing authorisation holder of any defect that could be related to that product.

2. Where blinding of investigational medicinal products is required by the protocol of a clinical trial, the manufacturer in conjunction with the sponsor shall implement a procedure for the rapid unblinding of blinded products, where this is necessary for a prompt recall as referred to in paragraph 1. The manufacturer shall ensure that the procedure discloses the identity of the blinded product only in so far as it is necessary.

Article 15

Self-inspection by the manufacturer

The manufacturer shall conduct regular inspections as part of the pharmaceutical quality system in order to monitor the implementation and respect of good manufacturing practice. He shall take any necessary corrective action and to put in place any necessary preventive measures.

The manufacturer shall maintain records of all such inspections and any corrective action or preventive measures subsequently taken.

Article 16

Advanced therapy investigational medicinal products

The good manufacturing principles shall be adapted to the specific characteristics of the advanced therapy medicinal products when used as investigational medicinal products.

Investigational medicinal products, which are at the same time advanced therapy medicinal products, shall be manufactured in accordance with the guidelines referred to in Article 5 of Regulation (EC) No 1394/2007.

CHAPTER III

INSPECTIONS

Article 17

Supervision by inspection

1. By means of regular inspections as referred to in Article 63(4) of Regulation (EU) No 536/2014 the Member State shall ensure that holders of an authorisation as referred to in Article 61(1) of that Regulation comply with the principles of good manufacturing practice laid down in this Regulation and takes into account the guidelines referred in second subparagraph of Article 63(1) of Regulation (EU) No 536/2014.
2. Without prejudice to any arrangements which may have been concluded between the Union and third countries, a competent authority may require a third country manufacturer to submit to an inspection as referred to in Article 63(4) of Regulation (EU) No 536/2014 and this Regulation. This Regulation applies *mutatis mutandis* to such inspections in third countries.
3. Member States shall carry out inspections of third country manufacturers to ensure that investigational medicinal products imported into the Union are manufactured by applying quality standards at least equivalent to those laid down in the Union.

The Member States are not obliged to routinely inspect third country manufacturers of investigational medicinal products. The necessity of such inspections shall be based on an assessment of risk, but shall take place at least if the Member States have grounds for suspecting that the quality standards applied to the manufacture of the investigational medicinal products imported into the Union are lower than those laid down in this Regulation and in the guidelines referred to in the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014.

4. Inspections may, if necessary, be unannounced.
5. Following an inspection, an inspection report shall be drawn up by the inspector. Before the report is adopted by competent authority, the manufacturer shall be afforded an opportunity to submit comments in relation to the findings of the report.
6. Where the findings of the final report show that the manufacturer complies with the good manufacturing practice for investigational medicinal products, the competent authority shall within a period of 90 days of the inspection issue a certificate of good manufacturing practice to the manufacturer.
7. The competent authority shall enter the certificate of good manufacturing practice which they issue into the Union database referred to in Article 111(6) of Directive 2001/83/EC.

8. Where the outcome of the inspection is that the manufacturer does not comply with good manufacturing practice for investigational medicinal products, the competent authority shall enter this information into the Union database referred to in Article 111(6) of Directive 2001/83/EC.
9. The competent authority shall, upon receipt of reasoned request, send the inspection reports referred to in paragraph 5 electronically to the competent authorities of other Member States or to the European Medicines Agency ('the Agency').
10. The competent authority shall enter the information relating to the authorisation referred to in Article 61(1) of Regulation (EU) No 536/2014 in the Union database referred to in Article 111(6) of Directive 2001/83/EC.

Article 18
Cooperation and coordination of inspections

The competent authorities shall cooperate with each other and with the Agency in relation to inspections. They shall share information with the Agency on both inspections planned and conducted.

Article 19
Recognition of inspection conclusions

1. The conclusions reached in the inspection report referred to in Article 17(5) shall be valid throughout the Union.

However, in exceptional cases, where a competent authority is unable, for reasons relating to public health, to recognise the conclusions reached following an inspection under Article 63(4) of Regulation No 536/2014, that competent authority shall forthwith inform the Commission and the Agency. The Agency shall inform the other competent authorities concerned.

2. When the Commission is informed in accordance with the second subparagraph of paragraph 1, it may, after consulting the competent authority which was unable to accept the report, request the inspector who performed the inspection to perform a new inspection. The inspector may be accompanied by two inspectors from other competent authorities which are not parties to the disagreement.

Article 20
Empowerments of the inspectors

1. The competent authority shall provide inspectors with suitable means of their identification.
2. Inspectors shall be empowered to:
 - (a) enter and inspect the premises of the manufacturer and quality control laboratories having carried out checks pursuant to Article 10 for the manufacturer;

- (b) take samples, including for independent tests to be carried out by an Official Medicines Control Laboratory or a laboratory designated for that purpose by the Member State, and
- (c) examine any documents relating to the object of inspection, make copies of records or printed documents, print electronic records and take photographs of the premises and equipment of the manufacturer.

Article 21

Competence and obligations of the inspectors

1. The competent authority shall ensure that the inspectors possess adequate qualifications, experience and knowledge. In particular, the inspectors shall have the following:
 - (a) experience and knowledge of the inspection process;
 - (b) the ability to make professional judgements as to the compliance with the requirements of good manufacturing practice;
 - (c) ability to apply the principles of quality risk management;
 - (d) knowledge of current technologies relevant for inspections;
 - (e) knowledge of the current technologies for the manufacture of the investigational medicinal products.
2. Information acquired as a result of inspections shall remain confidential.
3. The competent authorities shall ensure that inspectors receive the training necessary to maintain or improve their skills. Their training needs shall be assessed regularly by the persons appointed for that task.
4. The competent authority shall document the qualifications, training and experience of each inspector. Those records shall be kept up to date.

Article 22

Quality system

1. The competent authorities shall establish, implement and comply with a properly designed quality system for their inspectors. The quality system shall be updated as appropriate.
2. Each inspector shall be informed of the standard operating procedures and of his duties, responsibilities and on-going training requirements. Those procedures shall be kept up to date.

Article 23
Impartiality of inspectors

The competent authority shall ensure that inspectors are free of any undue influence that could affect their impartiality and judgment.

Inspectors shall be independent, in particular, of:

- (a) the sponsor;
- (b) the management and personnel of the clinical trial site;
- (c) the investigators involved in the clinical trials where the investigational medicinal products manufactured by the inspected manufacturer are used;
- (d) the persons financing the clinical trial in which the investigational medicinal product is used;
- (e) the manufacturer.

Inspectors shall make an annual declaration of their financial interests in the parties inspected or other links to them. The competent authority shall take the declaration into consideration when assigning inspectors to specific inspections.

Article 24
Access to premises

The manufacturer shall allow inspectors access to his premises and documentation at all times.

Article 25
Suspension or revocation of manufacturing authorisation

If an inspection reveals that the holder of an authorisation as referred to in Article 61(1) of Regulation (EU) No 536/2014 fails to comply with good manufacturing practice as set out in Union law, the competent authority may, with regard to this manufacturer, suspend manufacture or imports from third countries of investigational medicinal products for human use, or suspend or revoke the authorisation for a category of preparations or all preparation.

CHAPTER IV

FINAL PROVISIONS

Article 26
Transitional provision

The Member states may continue to apply national transposition measures adopted under Directive 2003/94/EC to the manufacture of investigational medicinal products used in clinical trials governed by Directive 2001/20/EC in accordance with the transitional provisions laid down in Article 98 of Regulation (EU) No 536/2014.

Article 27
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 six 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 or 1 April 2018, whichever is the later.

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

Done at Brussels, 23.5.2017

For the Commission
The President
Jean-Claude JUNCKER