

SUBSIDIARY LEGISLATION 458.47

GOOD CLINICAL PRACTICE AND REQUIREMENTS FOR MANUFACTURING OR IMPORT AUTHORISATION OF INVESTIGATIONAL MEDICINAL PRODUCTS (HUMAN USE) REGULATIONS

26th May, 2006

LEGAL NOTICE 119 of 2006, as amended by Legal Notice 234 of 2022.

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| <p>1. (1) The title of these regulations is the Good Clinical Practice and Requirements for Manufacturing or Import Authorisation of Investigational Medicinal Products (Human Use) Regulations.</p> <p>(2) These regulations shall apply in conjunction with the Clinical Trials Regulations and the Good Manufacturing Practice in respect of Medicinal and Investigational Medicinal Products for Human Use Regulations.</p> | <p>Title and scope.</p> <p>S.L. 458.43
S.L. 458.42</p> |
| <p>2. (1) The following provisions shall apply to investigational medicinal products for human use:</p> <ul style="list-style-type: none">(a) the principles of good clinical practice and detailed guidelines in line with those principles, as referred to in Article 1(3) of Directive 2001/20/EC, for the design, conduct and reporting of clinical trials on human subjects involving such products;(b) the requirements for authorisation of the manufacture or importation of such products, as provided for in Article 13(1) of Directive 2001/20/EC;(c) the detailed guidelines, provided for in Article 15(5) of Directive 2001/20/EC, on the documentation relating to clinical trials, archiving, qualifications of inspectors and inspection procedures. <p>(2) (a) When applying the principles, detailed guidelines and requirements aforementioned, the Licensing Authority, hereinafter referred to as "the Authority", shall take into account the technical implementing modalities provided for in the detailed guidance published by the Commission in The Rules Governing Medicinal Products in the European Union.</p> <p>(b) When applying the principles, detailed guidelines and requirements referred to in subregulation (1) to non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry, the Authority may introduce specific modalities in order to take into account the specificity of these trials as far as regulations 8 to 19 are</p> | <p>Application of provisions.</p> |

concerned.

(3) The Authority may take into account the special position of trials whose planning does not require particular manufacturing or packaging processes, carried out with medicinal products with marketing authorisations within the meaning of Directive 2001/83/EC, manufactured or imported in accordance with the same Directive and conducted on patients with the same characteristics as those covered by the indication specified in the marketing authorisation.

(4) Labelling of investigational medicinal products intended for trials of that nature may be subject to simplified provisions laid down in the good manufacturing practice guidelines on investigational medicinal products:

Provided that the Authority shall inform the Commission as well as the other Member States of any specific modalities implemented in accordance with this subregulation.

Good clinical practice for the design, conduct, recording and reporting of clinical trials.

3. (1) The rights, safety and well being of the trial subjects shall prevail over the interests of science and society.

(2) Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks.

(3) Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects.

(4) The necessary procedures to secure the quality of every aspect of the trials shall be complied with.

(5) The available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial.

(6) Clinical trials shall be conducted in accordance with the latest published version of the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association.

(7) The protocol referred to in point (h) of Article 2 of Directive 2001/20/EC shall provide for the definition of inclusion and exclusion of subjects participating in a clinical trial, monitoring and publication policy.

(8) The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.

(9) All clinical trial information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.

Ethics Committees.

4. (1) Each Ethics Committee established under Article 6(1) of Directive 2001/20/EC shall adopt the relevant rules of procedure

necessary to implement the requirements set out in that Directive and, in particular, in Articles 6 and 7 thereof.

(2) The Ethics Committees shall, in every case, retain the essential documents relating to a clinical trial, as referred to in Article 15(5) of Directive 2001/20/EC, for at least three years after completion of that trial. They shall retain the documents for a longer period, where so required under other applicable requirements.

(3) Communication of information between the Ethics Committees and the Authority shall be ensured through appropriate and efficient systems.

5. (1) A sponsor may delegate any or all of his trial-related functions to an individual, a company, an institution or an organisation: Sponsors.

Provided that in such cases, the sponsor shall remain responsible for ensuring that the conduct of the trials and the final data generated by those trials comply with Directive 2001/20/EC as well as Directive 2005/28/EC.

(2) The investigator and the sponsor may be the same person.

6. (1) The information in the investigator's brochure, referred to in Article 2(g) of Directive 2001/20/EC, shall be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial. This shall also apply to any update of the investigator's brochure. Investigator's brochure.

(2) If the investigational medicinal product has a marketing authorisation, the Summary of Product Characteristics may be used instead of the investigator's brochure.

(3) The investigator's brochure shall be validated and updated by the sponsor at least once a year.

7. (1) Authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall be required for both total and partial manufacture of investigational medicinal products, and for the various processes of dividing up, packaging or presentation: Manufacturing or import authorisation. Amended by: L.N. 234 of 2022.

Provided that by way of derogation from sub-regulation (1), the Licensing Authority shall allow investigational medicinal products to be imported from parts of the United Kingdom other than Northern Ireland without such an authorisation provided that all of the following conditions are fulfilled:

- (a) the imported investigational medicinal products have undergone certification of batch release either in the Union, as provided for in paragraph 3, point (a) of Article 13 (1) of Directive 2001/20/EC, or in parts of the United Kingdom other than Northern Ireland in compliance with the requirements set out in paragraph

3, point (b) of the same Directive;

(b) the imported investigational medicinal products are only made available in Malta.

(2) Such authorisation shall be required even if the products manufactured are intended for export.

(3) Authorisation shall also be required for imports from non-EU Member States into Malta.

(4) Authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall not be required for reconstitution prior to use or packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in Malta to carry out such processes and if the investigational medicinal products are intended to be used exclusively in those institutions.

Requirements to
obtain
authorisation.

8. (1) In order to obtain the authorisation, the applicant must meet at least the following requirements:

(a) specify in his application the types of medicinal products and pharmaceutical forms to be manufactured or imported:

Provided that for the purposes of this paragraph, "types of medicinal products" include blood products, immunological products, cell therapy products, gene therapy products, biotechnology products, human or animal extracted products, herbal products, homeopathic products, radiopharmaceutical products and products containing chemical active ingredients;

(b) specify in his application the relevant manufacture or import operations;

(c) specify in his application, where relevant as in the case of viral or non-conventional agents' inactivation, the manufacturing process;

(d) specify in his application the place where the products are to be manufactured or have at his disposal, for their manufacture or importation, suitable and sufficient premises, technical equipment and control facilities complying with the requirements of Directive 2003/94/EC as regards the manufacture, control and storage of the products;

(e) have permanently and continuously at his disposal the services of at least one qualified person as referred to in Article 13(2) of Directive 2001/20/EC.

(2) The applicant shall provide with his application documentary evidence that he complies with subregulation (1).

Issuing of
authorisation.

9. (1) The Authority shall issue the authorisation only after verifying the accuracy of the particulars provided by the applicant pursuant to regulation 8 by means of an inquiry carried out by its

agents.

(2) The Authority shall take all appropriate measures to ensure that the procedure for granting an authorisation is completed within ninety days from the receipt of a valid application.

(3) The Authority may require from the applicant further information concerning the particulars supplied pursuant to regulation 8(1), including in particular information concerning the qualified person at the disposal of the applicant in accordance with regulation 8(1)(e):

Provided that where the Authority exercises that right, the application of the time-limits aforementioned shall be suspended until the additional data required have been supplied.

10. (1) In order to ensure that the requirements laid down in regulation 8 are complied with, authorisation may be made conditional on the carrying out of certain obligations imposed either when authorisation is granted or at a later date.

Compliance with and applicability of authorisation.

(2) An authorisation shall apply only to the premises specified in the application and to the types of medicinal products and pharmaceutical forms specified in that application pursuant to regulation 8(1)(a).

11. The holder of the authorisation shall at least comply with the following requirements:

Holder to comply with requirements.

- (a) have at his disposal the services of staff that comply with the legal requirements as regards manufacture and controls;
- (b) dispose of the investigational and authorised medicinal products only in accordance with the legislation in force;
- (c) give prior notice to the Authority of any changes he may wish to make to any of the particulars supplied pursuant to regulation 8(1) and, in particular, to inform the Authority immediately if the qualified person referred to in Article 13(2) of Directive 2001/20/EC is replaced unexpectedly;
- (d) allow agents of the Authority access to his premises at any time;
- (e) enable the qualified person referred to in Article 13(2) of Directive 2001/20/EC to carry out his duties, for example by placing at his disposal all the necessary facilities;
- (f) comply with the principles and guidelines for Good Manufacturing Practice for medicinal products as laid down by Community law.

12. If the holder of the authorisation requests a change in any of the particulars referred to in regulation 9(1)(a) to (e), the time taken for the procedure relating to the request shall not exceed

Change in authorisation.

	thirty days. In exceptional cases, this period of time may be extended to ninety days.
Suspension etc., of authorisation.	13. The Authority shall suspend or revoke the authorisation, as a whole or in part, if the holder of the authorisation fails at any time to comply with the relevant requirements.
The trial master file and archiving.	14. (a) The documentation referred to Article 15(5) of Directive 2001/20/EC as the trial master file shall consist of essential documents, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated. Those documents shall show whether the investigator and the sponsor have complied with the principles and guidelines of good clinical practice and with the applicable requirements and, in particular, with Annex I to Directive 2001/83/EC. (b) The trial master file shall provide the basis for the audit by the sponsor's independent auditor and for the inspection by the Authority. (c) The content of the essential documents shall be in accordance with the specificities of each phase of the clinical trial.
Retention of documents.	15. (1) The sponsor and the investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion. (2) They shall retain the documents for a longer period, where so required by other applicable requirements or by an agreement between the sponsor and the investigator. (3) Essential documents shall be archived in a way that ensures that they are readily available, upon request, to the Authority. (4) The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.
Transfer of data ownership.	16. Any transfer of ownership of the data or of documents shall be documented. The new owner shall assume responsibility for data retention and archiving in accordance with the preceding regulation.
Archives.	17. (1) The sponsor shall appoint individuals within its organisation who are responsible for archives. (2) Access to archives shall be restricted to the named individuals responsible for the archives. (3) The media used to store essential documents shall be such that those documents remain complete and legible throughout the required period of retention and can be made available to the competent authorities upon request. (4) Any alteration to records shall be traceable.

18. (1) The inspectors, appointed by the Authority pursuant to Article 15(1) of Directive 2001/20/EC, shall be made aware of and maintain confidentiality whenever they gain access to confidential information as a result of good clinical practice inspections in accordance with applicable Community requirements, national laws or international agreements. Inspectors.

(2) The Authority shall ensure that inspectors:

- (a) have completed education at university level, or have equivalent experience, in medicine, pharmacy, pharmacology, toxicology or other relevant fields;
- (b) have received appropriate training, that their training needs are assessed regularly and that appropriate action is taken to maintain and improve their skills;
- (c) have knowledge of the principles and processes that apply to the development of medicinal products and clinical research.

(3) Inspectors shall:

- (a) have knowledge of applicable Community and national legislation and guidelines applicable to the conduct of clinical trials and the granting of marketing authorisations; and
- (b) be familiar with the procedures and systems for recording clinical data, and with the organisation and regulation of the healthcare system in the relevant Member States and, where appropriate, in third countries.

(4) The Authority shall maintain up-to-date records of the qualifications, training and experience of each inspector.

(5) Each inspector shall be provided with:

- (a) a document setting out standard operating procedures and giving details of the duties, responsibilities and ongoing training requirements. Those procedures shall be maintained up to date; and
- (b) suitable means of identification.

(6) Each inspector shall sign a statement declaring any financial or other links to the parties to be inspected. That statement shall be taken into consideration when inspectors are to be assigned to a specific inspection.

19. In order to ensure the presence of skills necessary for specific inspections, the Authority may appoint teams of inspectors and experts with appropriate qualifications and experience to fulfill collectively the requirements necessary for conducting the inspection. Inspectors to have proper qualifications.

20. (1) Good clinical practice inspections may take place on any of the following occasions: Inspection procedures.

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

- (b) as part of the verification of applications for marketing authorisation; and
- (c) as a follow-up to the granting of authorisation.

(2) In accordance with Article 15(1) and (2) of Directive 2001/20/EC, inspections may be requested and coordinated by the European Medicines Agency (hereinafter referred to as "the Agency") within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council, especially in connection with clinical trials relating to applications through the procedure established by Regulation 726/2004.

(3) Inspections shall be conducted in accordance with the inspection guidance documents developed to support the mutual recognition of inspection findings within the Community.

(4) Improvement and harmonisation of inspection guidance shall be achieved by the Authority, in collaboration with the Commission and the Agency, through joint inspections, agreed processes and procedures and sharing of experience and training.

Duties of the
Authority.

21. (1) The Authority shall:

- (a) make publicly available in Malta the documents relating to the adoption of good clinical practice principles;
- (b) establish the legal and administrative framework within which good clinical inspections operate, with definitions of the powers of inspectors for entry into clinical trial sites and access to data; and
- (c) ensure that, on request and where appropriate, inspectors of the competent authority of other Member States also have access to the clinical trial sites and data.

(2) The Authority shall provide for sufficient resources and shall in particular appoint an adequate number of inspectors to ensure effective verification of compliance with good clinical practice.

(3) The Authority shall establish the relevant procedures for verification of good clinical practice compliance. The procedures shall include the modalities for examining both the study management procedures and the conditions under which clinical trials are planned, performed, monitored and recorded, as well as follow-up measures.

(4) The Authority shall establish the relevant procedures for the following:

- (a) appointing experts for accompanying inspectors in case of need;
- (b) requesting inspections/assistance from other Member States, in line with Article 15(1) of Directive 2001/20/EC and for cooperating in inspections in another Member State; and

(c) arranging inspections in third countries.

(5) The Authority shall maintain records of national and, if applicable, international inspections including the good clinical practice compliance status, and of their follow-up.

(6) The Authority shall ensure that national inspection procedures are in compliance with the guidance documents published by the Commission.

(7) The Authority shall lay down all necessary rules to ensure that confidentiality is respected by inspectors and other experts. With regard to personal data, the requirements of Directive 95/46/EC of the European Parliament and of the Council shall be respected.

(8) Inspection reports shall be made available by the Authority only to the recipients referred to in Article 15(2) of Directive 2001/20/EC, in accordance with national laws and regulations and subject to any arrangements concluded between the Community and third countries.
