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NB: Unofficial translation, legally binding only in Finnish and Swedish

Finnish Medicines Agency Administrative Regulation

GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS AND THE REQUIREMENTS FOR THE MANUFACTURING OF INVESTIGATIONAL MEDICINAL PRODUCTS

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Legal basis

Medicines Act (395/1987) Section 9 (3) as amended by Act 1200/2013, Section 11 (4) as amended by Act 1258/2021, Section 10 (3) as amended by Act 1112/2010 and section 15a (4) and (7) as provided by law 985/2021.

Target groups

Pharmaceutical factories
Units manufacturing investigational medicinal products
Hospital pharmacies and dispensaries manufacturing investigational medicinal products
Clinical trial sponsors

Period of validity

The regulation will enter into force on June 29, 2022, and will remain so until further notice

Regulations repealed

Administrative regulation of Finnish Medicines Agency 5/2019
Administrative regulation of Finnish Medicines Agency 8/2019

Implemented EU legislation

Directives on good manufacturing practice for medicinal products:

- European Commission Directive (EU) 2017/1572 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 (32017L1572, OJ L 238, 16.9.2017, p. 44)
- Commission Directive 91/412/EEC laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products (31991L0412, OJ L 228, 17.8.1991, p. 70)

General directive on medicinal products for human use and the prevention of the entry into the legal supply chain of falsified medicinal products:

- Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (32001L0062, OJ L 311, 28.11.2001, p. 67), as amended by Directive 2004/27/EC of the European Parliament and of the Council (32004L0027, OJ L 136, 30.4.2004, p. 34) and Directive 2011/62/EU of the European Parliament and of the Council (32011L0062, OJ L 174, 1.7.2011, p. 74).

Directly binding EU legislation

Veterinary Medicinal Products Regulation:

- Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/8/EC (32019R0006, OJ L 4, 7.1.2019, p. 43)

Clinical Trial Regulation:

- Regulation (EU) 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use and repealing Directive 2001/20 / EC (32014R0536, OJ L 158, 27.5.2014, p. 1)

Delegated regulation on good manufacturing practice for investigational medicinal products:

- Commission Delegated Regulation (EU) 2017/1569: supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying the principles and guidelines of good manufacturing practice for investigational medicinal products for human use and the arrangements for inspections (32017R1569, OJ L 238, 16.9.2017, p. 12)

Regulation on good manufacturing practice for active substances for medicinal products for human use:

- Commission Delegated Regulation (EU) 1252/2014 supplementing Directive 2001/83 / EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for active substances in medicinal products for human use (32014R1252, OJ L 337, 25.11.2014, p. 1). 1).

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1 General

Finnish Medicines Agency, Fimea (hereafter Fimea) lays down the principles of good manufacturing practice for the industrial manufacturing of medicinal products for human and veterinary use and lays down more detailed regulations on the duties of a Qualified Person. Batch certification of a medicinal product by qualified person and the release of the batch for distribution are parts of manufacturing.

In addition, Fimea lays down administrative regulations on the language requirements for the labeling of investigational medicinal products and on the requirements concerning manufacturing of investigational medicinal products in hospital pharmacies and dispensaries.

2 Scope of the regulation

This administrative regulation applies to holders of a Manufacturing Authorization in according to section 8 of the Medicines Act, to units manufacturing investigational medicinal products referred to in section 15a (1) of the Medicines Act, and to hospital pharmacies and dispensaries manufacturing investigational medicinal products referred to in section 15a(4) of the Medicines Act.

This administrative regulation shall also apply to the production and quality control of authorized herbal medicinal products and homeopathic preparations, as well as registered traditional herbal medicinal products and homeopathic preparations.

The administrative regulation does not apply to the reconstitution of medicines.

3 Definitions

For the purposes of this administrative regulation:

Good Manufacturing Practice (GMP) for medicinal products means the arrangements and procedures for the manufacturing and quality assurance of medicinal products that ensure that the medicinal products meet all the requirements regarding manufacturing.

Qualified Person (QP) means a person referred to in section 9 (3) and section 15a (2) of the Medicines Act.

Reconstitution of investigational medicinal product means the action or actions that must be performed for the medicinal product before it is ready for administration for the subject.

An investigational medicinal product is a medicinal product which is being tested or used as a reference referred in Article 2 (5) of Regulation (EU) No 536/2014, including placebo.

Auxiliary medicinal product means a medicinal product used for the needs of a clinical trial, but not as an investigational medicinal product, as described in Article 2 (8) of Regulation (EU) No 536/2014

4 Relationship with other regulations and guidelines

Good manufacturing practices for medicinal products other than those referred to in sections 8 and 15a of the Medicines Act, are laid down in Fimea´s administrative regulations for Manufacturing of Medicines for Pharmacies, and for Activities of Hospital Pharmacies and Dispensaries.

5 Good manufacturing practices in the industrial manufacturing and duties of the Qualified Person

5.1 Industrial manufacturing

Manufacturing of medicinal products for human use shall comply with Commission Directive (EU) 2017/1572 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.

Manufacturing of active substances used in the manufacture of medicinal products for human use is regulated by Commission Delegated Regulation (EU) 1252/2014.

Manufacturing of veterinary medicinal products must comply with the good manufacturing practice laid down in Directive 91/412 / EEC.

The Guide to Good Manufacturing Practice for Medicinal Products: Part I and Part II with Annexes, and Part IV are hereafter referred to as the GMP Guide (https://ec.europa.eu/health/documents/eudralex/vol-4_en) explains in more detail how the activities related to the industrial production and quality control of medicinal products and active substances should be organized in order to meet the requirements of good manufacturing practice.

The Pharmaceutical Inspection Convention and Pharmaceutical Co-operation Scheme PIC/S and the World Health Organization WHO websites provide useful guidelines and examples to support the practical implementation of good manufacturing practices (http://www.picscheme.org, http://www.who.int/medicines/publications). The instructions and examples are not binding.

5.2 Manufacture of excipients

The industrial manufacturer of medicinal products for human use shall, on the basis of a risk assessment, set appropriate good manufacturing practices for excipients used in the manufacture of medicinal products. The risk assessment must be carried out in accordance with the general guidelines adopted by the European Commission for this purpose and must take into account the requirements of other appropriate quality systems, the source and the intended use of the excipients, and previous quality deficiencies. The manufacturer of the medicinal product must ensure that the relevant good

manufacturing practice is followed. All activities to set up and to verify appropriate good manufacturing practice for excipients shall be documented.

5.3 Duties of Qualified Person

The duties of an Qualified Person are defined in Article 51 of the Medicinal Products Directive 2001/83/EC (2011/62/EU) for medicinal products for human use and in Article 97 (6) to (8) of Regulation (EU) 2019/6 for veterinary medicinal products. The job description is supplemented in Annex 16 of the GMP Guide *Certification by a Qualified Person and Batch Release*, and Part IV *Guidelines is Good Manufacturing Practice specific to Advanced Therapy Medicinal Products.*

In addition to the provisions of Article 30t of the Medicines Act and Commission Delegated Decree (EU) 2016/161, the Qualified Person shall ensure and verify in a documented manner (certify) that the batch of the medicinal product has been manufactured in accordance with the marketing authorization in force in the country of destination and according to at least good manufacturing practices for medicines that comply with European Union rules. This presupposes that the Qualified Person has access to the information of all actors involved in the manufacture and supply of the medicinal product or veterinary medicinal product, of active substances, excipients and packaging materials used in the manufacturing, regardless of where these actors are located. Only actors in accordance with the rules adopted in the European Union may be present in the production and supply chain. This means, among other things, that a batch of a medicinal product or of veterinary medicinal product may be stored only in the premises mentioned in the license referred to in section 8 of the Medicinal Products Act before it the batch certified and released for distribution.

A certified batch does not need to be re-certified as long as the batch remains within the European Economic Area and is accompanied by an appropriate certificate of certification.

6 Manufacturing of investigational medicinal products for human use

6.1 Language requirements for labeling

The labeling of investigational and auxiliary medicinal products is regulated in Chapter X of the Clinical Trial Regulation 536/2014. The labeling must be in Finnish and, if necessary, in Swedish. If the medicine package is not given to the subject but the medicine is administered by the study staff, the labeling may alternatively be in English.

6.2 Units manufacturing investigational medicinal products referred to in section 15a (1) of the Medicines Act

Good manufacturing practices for investigational medicinal products, including the release of the investigational medicinal product for study purposes, are regulated in the Commission's in Delegated Regulation (EU) 2017/1569: *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.*

The Regulation is supplemented by the guidance published on 8 December 2017 *Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second paragraph of the Article 63(1) of Regulation (EU) No 536/2014.*

6.3 Manufacturing of investigational medicinal products in a hospital pharmacy and dispensary

6.3.1 Manufacturing limitations

Manufacturing of investigational medicinal products in hospital pharmacy and dispensary is limited to the following activities defined in the Clinical Trial Regulation:

a) re-labeling or re-packaging
b) preparation of radiopharmaceuticals used as diagnostic investigational medicinal products
c) the preparation of medicinal products referred in the following points of Directive 2001/83/EC, Article 3:
    1. Point 1 (Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient) and
    2. Point 2 (Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question)

A hospital pharmacy or dispensary may manufacture investigational medicinal products for subjects participating the study from its own unit, as well as for other subjects participating the same study in other Finnish hospitals, health centers or clinics.

The manufacturing of investigational medicinal products must comply with the approved clinical trial submission (documentation concerning the investigational medicinal product).

6.3.2 Manufacturing requirements

6.3.2.1 General

Unless otherwise laid out in this regulation, Fimea´s administrative regulations Manufacturing of Medicines for Pharmacies, and Activities of Hospital Pharmacies and Dispensaries shall be followed.

The hospital pharmacy and dispensary must have a designated pharmacist [with Master´s degree] responsible for the manufacturing of investigational medicinal products. The pharmacist must be trained in a documented way with the regulations and guidelines in force for clinical trials on medicinal products, and with the special features of the pharmaceutical form to be prepared.

The pharmacist responsible for the manufacturing of investigational medicinal products may delegate individual tasks to pharmacists [with Master´s degree], or to pharmacists [with Bachelor´s degree], if they have

documented training on clinical trials on medicinal products, and on the requirements of the sponsor for the study in question.

Before a hospital pharmacy or dispensary decides to start manufacturing of investigational medicinal products, it must notify Fimea of the manufacturing of the investigational medicines. The notification is needed only once. The notification shall include the assessment of the scope of the planned activity, the starting date and information of the pharmacist responsible for the manufacture of the investigational medicinal products (name and contact information).

Fimea must be notified of any change in the pharmacist responsible for the manufacture of investigational medicinal products or of any substitutions lasting more than 3 months.

The manufacturing, quality control and release of investigational medicinal products for study use shall be instructed in accordance with the standard operating instructions of the hospital pharmacy and dispensary, approved by the pharmacist responsible for the manufacture of investigational medicinal products. By release of investigational medicinal products for study use, the pharmacist responsible for the manufacturing of investigational medicinal products shall confirm that the investigational medicinal product has been manufactured in accordance with the regulations and guidelines in force, and in accordance with the instructions given by the clinical trial sponsor.

The manufacturing and packaging of investigational medicinal products must have adequate controls in place at different stages to prevent mix-up of the medicinal products, in particular when investigational medicinal products are blinded. The handling of investigational medicinal batches the manufacturing and packaging premises must be limited to one batch at a time, and the number of packages to be handled in the premises must be ensured by yield calculations. In addition, adequate line clearance checks of the manufacturing and packaging premises and equipment must be performed before and after the medicinal products are handled.

If open products are handled in a hospital pharmacy or dispensary, it is even more important than normal to prevent cross-contamination from medicines in research phase with other medicines. If necessary, for example campaign production can be used; manufacturing or packaging of a series of consecutive batches with identical formulation, followed by thorough cleaning of premises and equipment before handling of new medicines with a different formulation. To assess the risk of cross-contamination risk of investigational medicinal products, the hospital pharmacy or dispensary should cooperate with the clinical trial sponsor.

All sterilization methods used in the manufacturing of investigational medicinal products must be validated.

Deviations during manufacturing or quality control testing shall be investigated and documented. In addition, it needs to be evaluated if the observed deviations have effect on the quality of the investigational medicinal product. Where possible, the root cause of the deviations should be identified and the recurrence of the similar deviations later should be prevented. Significant deviations that may affect the quality of the batch, shall be evaluated in collaboration with the sponsor and the investigator.

The pharmacist responsible for the investigational medicinal products shall document the rejection or release of the investigational medicinal product batch in which the deviation was observed. If the investigational medicinal product or the starting materials used in the manufacturing do not meet the quality specifications, the batch may not be released for study use.

6.3.2.2 Manufacturing of investigational medicinal products

Each investigational medicinal product to be manufactured shall have a written order from the sponsor or an agreement between the sponsor and hospital pharmacy or dispensary specifying the product to be manufactured, the number of units to be manufactured and the distribution. The hospital pharmacy or dispensary may supply the individual batches of investigational medicines to a person authorized by the investigator based on an order.

Before the manufacturing can start, an investigational medicinal product specific manufacturing and packaging instructions shall be created and the instructions shall be approved by the pharmacist responsible for the manufacturing of the investigational medicinal products. The instructions shall include at least

- the name, pharmaceutical form and strength of the investigational medicinal product,
- the batch size
- the raw materials, utensils and packaging materials used in the
- manufacturing with the required quantities
- designs of labels and/or packaging
- detailed instructions for the different stages of manufacture and packaging.
- the approval of the instruction and the date of approval.

For each manufactured or packaged batch, production and packaging record shall be created, recording at least

- the name, pharmaceutical form and strength of the investigational medicinal product
- batch number,
- the raw materials and utensils used, their quantities and batch numbers, shelf lives and, where appropriate, their quality
- the packaging materials used, their quantities and batch numbers, shelf lives and, where appropriate, their quality
- start and end time of manufacture
- the names of the persons taking part in the manufacturing
- confirmations of persons who have carried out critical manufacturing steps, including line clearance checks at the manufacturing premises before and after manufacturing
- quantity completed and the yield calculations (quantities of materials brought in for manufacturing versus quantity of final products gained)
- quality control results,
- written approval of the pharmacist responsible for the manufacturing of the investigational medicinal product in order to pack the batch
- start and end time of the packaging process
- the names of the persons who carried out the packaging

- confirmations of persons who have carried out critical packaging steps, including line clearance checks at the packaging premises before and after packaging
- quantity completed and the yield calculations (quantities of materials brought in for packaging versus quantity of final products gained)
- written release of the investigational medicinal product batch for study use by the pharmacist responsible for the manufacturing of the investigational medicinal products

7 Guidance and advice

On request, the Finnish Medicines Agency wil provide guidance and advice on the application of this regulation.

8 Period of validity

This administrative regulation will enter into force on June 29, 2022 and will remain so until further notice.

Director General Eija Pelkonen

Head of Section Mervi Saukkosaari

Distribution

Pharmaceutical factories
Units manufacturing investigational medicinal products
Hospital pharmacies and dispensaries

For information

Ministry of Social Affairs and Health
Ministry of Economic Affairs and Employment
Ministry of Agriculture and Forestry
National Institute for Health and Welfare
National Supervisory Authority for Welfare and Health (Valvira)
Finnish Food Authority
National Committee on Medical Research Ethics (TUKIJA)
Hospital districts

Pharma Industry Finland
Finnish Generics Pharmaceutical Association
Finnish Medicines and Health Care Association
Finnish Parallel Drug Importers Foundation
The Association of Finnish Pharmacies
The Finnish Pharmacists' Association
The Finnish Pharmacists' Society
The Finnish Medical Association
Centre for Military Medicine
Finnish Red Cross Blood Service
University of Helsinki, Faculty of Pharmacy
University of Eastern Finland, Faculty of Health Sciences
Åbo Akademi University, Faculty of Science and Technology
The Chemical Industry federation of Finland
The Union of Professionals in Natural, Environmental and Foresty Sciences
Loimu

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