VELFERÐARRÁÐUNEYTIÐ

Ministry of Welfare

REGULATION
concerning the manufacture of medicinal products, No. 893/2004,
as amended by Regulation No. 1100/2010.

1. Scope.
Article 1

This Regulation concerns the manufacture of medicinal products and investigational drugs for human or veterinary use.

The term "medicinal product" covers medicinal products for which a marketing authorisation has been granted in Iceland, medicinal products specially authorised by the Icelandic Medicines Agency, medicinal products or investigational drugs to be used for clinical trials, and officinal formulae. This includes proprietary medicinal products, herbal remedies, medicinal gasses, radiopharmaceuticals, pre-mixes for medicated feedingstuffs, homoeopathic medicinal products, and active substances for the production of pharmaceuticals, as well as any product caught by the definition of Article 5 of the Medicinal Products Act, No. 93/1994, as amended, and the provisions of Directive 2001/83/EC of the European Parliament and of the Council.

The provisions of this Regulation also cover the production of starting materials for the manufacture of medicinal products, and of medicinal products for exportation.

2. Definitions.
Article 2

In this Regulation, the following terms shall have the respective meanings indicated below:

1. "Good manufacturing practice": Those quality assurance procedures that ensure that medicinal products are always manufactured and tested in accordance with quality requirements appropriate to the drug in question.
2. "Medicinal product": Any substance or compound corresponding to the definition of a medicinal product laid down in Article 5 of the Medicinal Products Act, No. 93/1994, as amended.
3. "Investigational drug": Any pharmaceutical form of an active substance or placebo undergoing testing or used as control in a clinical trial, including products for which a marketing authorisation has already been issued, but are used or combined (specially combined or packaged) in a way different from the approved one, or which are used for indications not covered by the authorisation or to gain more information about the authorised form, *cf.* item t, paragraph 1, Article 2, of Regulation No. 443/2004 on clinical drug trials on humans.
4. "Manufacturer": The holder of a manufacturing authorisation as provided for in Articles 34 and 35 of the Medicinal Products Act, No. 93/1994, as amended.
5. "Manufacture": Any act performed in relation to the purchase of substances and products in addition to production operations such as weighing, mixing, filling, packaging, labelling, quality control, approval and storage, as well as appropriate monitoring.

6. “Qualified person”: A competent and qualified person, *cf.* paragraph 2, Article 11, who is responsible for the final approval of each production batch of a medicinal product and fulfils minimum requirements as regards scientific and technical knowledge.
7. “Quality assurance for medicinal products”: Accumulated measures designed to ensure that the medicinal products or investigational drugs are of a quality appropriate to their intended use.
8. “Blinding”: Concealing the identity of an investigational drug according to the instructions of the researcher.
9. “Unblinding”: Revealing the identity of a “blinded” medicinal product.
10. “Validation”: Demonstrating, through appropriate observations, that a method, process, piece of equipment, substance, operation or system in fact produces the intended results.
11. “Control report”: A document signed by the qualified person on behalf of a manufacturer or contractor, and certifying that the medicinal product has been produced according to the principles of good manufacturing practice for medicinal products and achieves the level of quality required by the marketing authorisation.

3. General provisions regarding the manufacture of medicinal products.

Article 3

Only those holding a manufacturing authorisation may perform one or more parts of the manufacturing process of a medicinal product, including investigational drug. This applies equally to the manufacturers of medicinal products for exportation. [Manufacturing authorisation is not requested due to mixing of investigational drugs for the use of or for packaging in hospitals, healthcare centres or doctors’ surgeries, if the process is performed by pharmacologists or parties authorised to do so, in accordance with good manufacturing practice for medicinal products, and the investigational drugs are only to be used in the institution in question.][1)]

The manufacture of medicinal products for human or veterinary use and of investigational drugs shall in all respects comply with the principles of good manufacturing practice for medicinal products.

The importation of medicinal products, including investigational drugs, from countries outside the EEA is governed by the provisions of Article 16 of Regulation No. 699/1996 on the importation and wholesale distribution of medicinal products, as amended.

[1)] Regulation No. 1100/2010, Article 1.

Licensing.

Article 4

[Applications for an authorisation to manufacture medicinal products shall be addressed to the Icelandic Medicines Agency.][1)]

Each manufacturing authorisation is valid only for the site where the activities are to be carried out. For a manufacturing authorisation to be granted the activities must comply with the requirements of this Regulation.

[1)] Regulation No. 1100/2010, Article 2.

Article 5

Applications for an authorisation to manufacture medicinal products, [including investigational drugs],[1)] shall be accompanied by the following information:

1. name, address, National Registry ID, and telephone number of the company;
2. name, address, National Registry ID, and telephone number of the person filing the application on behalf of the company;
3. address where the manufacture and quality control take place;
4. a general description of the planned activities;
5. drawings of premises;
6. an overview of the main equipment;
7. an overview of the medicinal products and pharmaceutical forms to be manufactured;
8. a breakdown of the processes used for the manufacture of medicinal products in the company;
9. an overview of the essential features of the company‘s quality assurance system;
10. the name, qualifications and professional background of the technical manager;

11. the name, qualifications and professional background of the qualified person, if different from the technical manager.

[1)] *Regulation No. 1100/2010, Article 3.*

Article 6

The Icelandic Medicines Agency shall review each application based on the information provided and on the conditions laid down in this Regulation and any other relevant provisions.

[The Icelandic Medicines Agency shall][1)] complete their review of the application within 90 days of its receipt.

If the Icelandic Medicines Agency considers that the information submitted with the application is insufficient, it shall address a written request for further information to the applicant. The 90-day time limit is then to be extended by the amount of time that elapses between the time the information was requested and the time it is received by the Icelandic Medicines Agency.

Before granting a manufacturing authorisation, the Icelandic Medicines Agency shall carry out a control at the applicant's premises in order to verify that the submitted information is correct.

[1)] *Regulation No. 1100/2010, Article 4.*

Article 7

An authorisation to manufacture medicinal products and investigational drugs may be made subject to conditions, and may also be limited in time.

Article 8

The holder of an authorisation shall seek the permission of the Icelandic Medicines Agency for any planned changes to the factors on the basis of which the authorisation was granted, *cf.* Article 5.

[The Icelandic Medicines Agency shall][1)] process applications for such changes within 30 days. In exceptional cases this time limit may be extended to 90 days.

[1)] *Regulation No. 1100/2010, Article 4.*

Article 9

If the qualified person leaves the employment of the manufacturer, the Icelandic Medicines Agency shall be notified of this fact and of the identity of the new qualified person without delay.

Article 10

The Icelandic Medicines Agency shall issue a certificate attesting that the holder of the manufacturing authorisation fulfils all requirements to manufacture medicinal products within the European Economic Area.

The certificate shall specify which processes and medicinal products are covered by the authorisation, as well as the name of the qualified person and the address of the manufacturing site.

The Icelandic Medicines Agency shall also issue a manufacturing certificate at the request of an exporter or the authorities of an importing country.

The certificates shall be issued in accordance with applicable European Economic Area rules and/or the rules of the World Health Organisation.

Manufacturing.

Article 11

Companies engaged in the manufacturing of medicinal products, including investigational drugs, shall employ a technical manager who must be a qualified pharmacologist or possess at least equivalent qualifications.

The company shall employ a qualified person who can also be the technical manager.

Article 12

All manufacturing processes shall respect the principles and guidelines of good manufacturing practice for medicinal products.

Directions applicable to the manufacture of medicinal products can be found in the guidelines of good manufacturing practice for medicinal products and the accompanying annexes.

Article 13

The European Pharmacopoeia applies in Iceland in its English version, *cf.* Article 6 of the Medicinal Products Act, No. 93/1994, as amended, and its requirements are the minimum requirements applicable to medicinal products.

In addition to the provisions contained in this Regulation and the European Pharmacopoeia, the manufacture of medicinal products shall take place according to the Danish Pharmaceutical Standards (DLS) and other applicable pharmaceutical standards, *cf.* Article 6 of the Medicinal Products Act, No. 93/1994, as amended.

Article 14

The manufacturer must adhere to the manufacturing processes on the basis of which the marketing authorisation was granted.

The manufacturer shall review the manufacturing methods at regular intervals taking into account recent scientific and technological developments. The approval of the Icelandic Medicines Agency shall be sought for any modifications to manufacturing processes for medicinal products that are brought about by changes to the factors on the basis of which the marketing authorisation was granted.

The provisions of this Article also apply, where appropriate, to the manufacture of investigational drugs, *cf.* Article 11 of Regulation No. 443/2004 on clinical drug trials on humans.

Quality management.

Article 15

All manufacturers shall establish an efficient quality management system for its operations that actively involves the company‘s personnel.

Organisation and personnel.

Article 16

In order to ensure the quality of the medicinal products manufactured, the company shall have an adequate number of personnel possessing the appropriate qualifications and experience to carry out the tasks entrusted to them.

Each company shall be able to present an organisational chart of its activities, as well as written descriptions of the tasks and responsibilities of individual employees, as appropriate.

The organisational chart and the descriptions of tasks and responsibilities shall clearly indicate the division of responsibilities between employees.

Personnel must have adequate knowledge of the regulatory provisions applying to medicinal products in Iceland, as well as of provisions governing their activities.

Article 17

Key personnel shall have adequate authority to fulfil any obligations falling under their responsibilities.

Article 18

The manufacturer shall carry out the training of personnel according to written procedures.

Personnel shall receive the necessary training and records shall be kept of all training given to individual employees or groups of employees.

Article 19

Written procedures shall apply to the hygiene of personnel and to health checks. The procedures shall be adapted to the activities carried out in the company.

The procedures shall at least relate to the health, hygiene practices and clothing of personnel.

Records shall be kept of the implementation of these procedures.

Premises and equipment.

Article 20

Premises and equipment must be designed, adapted and maintained to suit the intended operations.

The layout and design of premises and equipment, and all procedures, must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.

Article 21

Premises and equipment which are critical to the quality of the products shall be subjected to appropriate validation.

Documentation.

Article 22

Every manufacturer shall have a system of documentation. The system shall be based on specifications for starting materials, packing materials, intermediate products, bulk products and finished products; formally authorised manufacturing formulae and processing instructions stating the composition, methods of production and appropriate quality control of intermediate and finished products; general guidelines on methods used and concerning equipment, hygiene, processing and quality control.

Separate formulae shall exist for each batch size manufactured.

Documents shall be clear, free from errors and up to date.

Article 23

A batch processing record must be kept for each batch manufactured. It shall contain information making it possible to trace the entire manufacturing process.

All batch processing records shall be retained for at least one year after the expiry date of the batch.

Article 24

Where electronic, photographic or other similar data processing methods are used, the manufacturer shall validate the system used by showing that the data will be appropriately stored and protected during the period of storage.

Data stored in such systems shall be made readily available in legible form.

Production.

Article 25

Manufacturing processes for medicinal products shall be based on clear and well-established methods that are in accordance with good manufacturing practice. All processing instructions shall be written and formally validated.

In-process controls shall be carried out during production, as appropriate.

All new production processes shall be validated. Processes shall be re-validated in the case of any change liable to affect the quality of the product.

Quality control.

Article 26

Every holder of a manufacturing authorisation must operate a quality control department that is separate and independent from other departments of the company.

Quality control shall be an integral part of every production process and shall, in addition, consist of the testing of starting materials, packaging materials, intermediate products and finished products.

Article 27

Quality control analyses may be entrusted to independent contract laboratories and shall in that case be the subject of a written contract drawn up in accordance with relevant principles of good manufacturing practice, *cf.* Articles 32 and 33.

The Icelandic Medicines Agency shall have access, for monitoring purposes, to laboratories that have a contract with the holder of a manufacturing authorisation.

Final approval of a production batch.

Article 28

Companies shall establish written procedures for the final approval of a product at each manufacturing site.

The final approval of a product shall be performed by the qualified person. Prior to the final approval of each production batch, the qualified person shall certify that the batch has been manufactured in accordance with this Regulation and other applicable provisions. In the case of medicinal products for which a marketing authorisation has been issued, the qualified person shall also certify that the product fulfils the requirements on the basis of which the authorisation was granted.

A record shall be kept of the final approval of individual production batches and shall always contain up-to-date information. The record shall be retained for a period of at least six years and shall be made available to the Icelandic Medicines Agency.

Article 29

Each production batch of immunological medicinal products for veterinary use to be exported to another country within the European Economic Area shall be accompanied by a control report.

Article 30

Samples of each batch of a finished medicinal product shall be retained for at least one year after the expiry date.

Samples of starting materials (other than solvents, gases and water) shall be retained for at least two years after the final approval of a batch. This period may be shortened if the period of stability of the material is shorter.

Samples of the finished product and starting materials must be of sufficient size to allow all necessary analyses to be repeated.

Article 31

For the manufacture of officinal formulae where only one or a small number of units are produced, a reference sample of the finished product need not be taken, analysed or stored.

For other medicinal products which are produced in only one or a small number of units, and when special conditions make the storage of the product difficult, the Icelandic Medicines Agency may allow that special procedures are adopted for the sampling, analysis and storage of reference samples of the finished product.

Contract manufacture and analysis.

Article 32

For each project undertaken by a contractor for a buyer there must be a written contract between the parties.

The contractor must hold a manufacturing authorisation for the relevant manufacturing site.

The contract must clearly indicate the obligations of each party. It must state the way in which the qualified person performs his/her duties and where and how the final approval of the product takes place.

Article 33

The contractor must not sub-contract to a third party any of the work covered by the contract without the written approval of the contract originator.

This applies equally to written contracts for the manufacture and for the analysis of medicinal products.

Complaints and product recall.

Article 34

Companies shall have written procedures for how to respond to complaints concerning medicinal products. Records shall be kept of all complaints received.

Complaints shall be reviewed as soon as they are received and necessary action shall be taken.

The procedures shall indicate how a product recall can be carried out promptly and effectively whenever needed.

The Icelandic Medicines Agency shall be notified immediately of any complaint requiring specific action, for instance in the case of product defects, erroneous labelling or inadequate shelf life.

Self-inspection.

Article 35

Manufacturers shall establish a programme whereby individual departments are inspected at regular intervals in order to ensure that the principles of good manufacturing practice are strictly adhered to.

A manufacturer‘s self-inspections are part of the quality assurance of the operations.

Such inspections shall be recorded in reports detailing all observations made as well as proposals for corrective measures and any measures implemented.

4. Monitoring and sanctions.

Article 36

The Icelandic Medicines Agency is responsible for verifying that the provisions of this Regulation are complied with, *cf.* Article 47 of the Medicinal Products Act, No. 93/1994, as amended.

The Icelandic Medicines Agency shall monitor the activities of approved manufacturers and those quality control laboratories carrying out analyses for them. The manufacturers must provide the Icelandic Medicines Agency with any document or information which it considers necessary for its monitoring purposes. They must also allow the persons carrying out monitoring work access to premises and equipment used in relation to the activities, and provide samples of the products if so requested.

Should the Icelandic Medicines Agency identify shortcomings in the operations of a manufacturer, based on the provisions of this Regulation, it shall order the company to rectify this. The manufacturer must comply with such an order within the time limit set by the Icelandic Medicines Agency.

Article 37

[The Icelandic Medicines Agency may authorise companies to be exempted from specific provisions of this Regulation.][1)]

[1)] *Regulation No. 1100/2010, Article 5.*

Article 38

[The Icelandic Medicines Agency may refuse a manufacturing authorisation if the provisions of this Regulations are not fulfilled, stipulate the authorisation temporarily until the conditions are fulfilled, revoke the authorisation temporarily, wholly or partly, or deprive the holder of an authorisation of his/her authorisation if he/she infringes against the provisions of this Regulation. The Icelandic Medicines Agency shall for the purpose of any such decision respect the provisions of the Administrative Procedures Act, No. 37/1993, as amended, including those pertaining to proper justification an the right to be heard.][1)]

[1)] *Regulation No. 1100/2010, Article 6.*

Article 39

Infringements of the provisions of the present Regulation shall be dealt with according to Article 48 of the Medicinal Products Act, No. 93/1994, as amended.

5. Exemptions.

Article 40

The manufacture of medicinal products for specific patients on the prescription of a physician is exempted from the provisions of this Regulation.

6. Legal basis and entry into force.

Article 41

This Regulation is issued under the provisions of Article 49 of the Medicinal Products Act, No. 93/1994, as amended, and shall take effect on its publication. Regulation No. 700/1996, on the manufacture of medicinal products, shall be repealed as of the same date.

The provisions of this Regulation are in conformity with the provisions of the relevant European Union Directives listed in Annex 1.

Ministry for Health and Social Security, 3 November 2004.

Jón Kristjánsson.

Davíð Á. Gunnarsson.

ANNEX I

List of all European Union Directives which will be implemented partially or wholly through this regulation.

91/412/EEC: Commission Directive of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products.

2003/94/EC: Commission Directive 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 use.

2001/20/EC: Directive 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.

2001/82/EC: Directive of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

2001/83/EC: Directive of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

[2005/28/EC: Commission Directive 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 requirements for authorisation of the manufacturing or importation of such products.][1)]

[1)] *Regulation No. 1100/2010, Article 7.*

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The original Icelandic text is published in the Law Gazette.
In case of a possible discrepancy, the original Icelandic text applies.]