Modifications of Commission Directive 91/356/EEC of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use

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Principles and guidelines of good manufacturing practice for medicinal products for human use.	**Principles and guidelines of good manufacturing practice for medicinal products for human use and investigational medicinal products for human use.**
CHAPTER I	**CHAPTER I**
General provisions	**General provisions**
Article 1	***Article 1***
This Directive lays down the principles and guidelines of good manufacturing practice for medicinal products for human use whose manufacture requires the authorisation referred to in Article 16 of Directive 75/319/EEC.	This Directive lays down the principles and guidelines of good manufacturing practice for medicinal products for human use whose manufacture or import requires the authorisation referred to in Article 40 of Directive 2001/83/EC and for investigational medicinal products for human use whose manufacture or import requires the authorisation referred to in Article 13 of Directive 2001/20/EC.
Article 2	***Article 2***
For the purposes of this Directive, the definition of medicinal products set out in Article 1 (2) of Council Directive 65/65/EEC ([3]), shall apply.	For the purposes of this Directive, the definition of medicinal products set out in Article 1 (2) of Directive 2001/83/EC, shall apply.
In addition, - manufacture shall mean any holder of the authorisation referred to in Article 16 of Directive 75/319/EEC.	In addition, - Manufacturer or importer shall mean any holder of the authorisation referred to in Article 40 of Directive

	2001/83/EC.
- qualified person shall mean the person referred to in Article 21 of Directive 75/319/EEC,	- In relation to a medicinal product, qualified person shall mean the person referred to in Article 48 of Directive 2001/83/EC,
- pharmaceutical quality assurance shall mean the sum total of the organised arrangements made with the object of ensuring that medicinal products are of the quality required for their intended use,	
- good manufacturing practice shall mean the part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use.	
	- Blinding, in relation to the labelling and packaging of an investigational medicinal product, shall mean the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor. Unblinding shall mean the disclosure of the identity of blinded products.
	- Investigational medicinal product shall mean a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form
	- Manufacturer or importer of an investigational medicinal product shall mean any holder of the authorisation referred to in Article 13.1 of Directive 2001/20/EC.
	- In relation to an investigational

	medicinal product, qualified person shall mean the person referred to in Article 13.2 of Directive 2001/20/EC.
Article 3	***Article 3***
By means of the repeated inspections referred to in Article 26 of Directive 75/.319/EEC, the Member States shall ensure that manufacturers respect the principles and guidelines of good manufacturing practice laid down by this Directive.	By means of the repeated inspections referred to in Article 111 of Directive 2001/83/EC and the inspections referred to in Article 15.1 of Directive 2001/20/EC, repeated as necessary, the Member States shall ensure that manufacturers and importers respect the principles and guidelines of good manufacturing practice laid down by this Directive.
For the interpretation of these principles and guidelines of good manufacturing practice, the manufacturers and the agents of the competent authorities shall refer to the detailed guidelines referred to in Article 19a of Directive 75/319/EEC.	For the interpretation of these principles and guidelines of good manufacturing practice, the manufacturers and importers and the agents of the competent authorities shall refer to the detailed guidelines referred to in Article 47 of Directive 2001/83/EC.
These detailed guidelines are published by the Commission in the 'Guide to good manufacturing practice for medicinal products' and in its Annexes (Office for Official Publications of the European Communities. The rules governing medicinal products in the European Community, Volume IV).	These detailed guidelines are published by the Commission in the 'Guide to good manufacturing practice for medicinal products' and in its Annexes, which include in particular an annex on the manufacture of investigational medicinal products.
Article 4	***Article 4***
The manufacturer shall ensure that the manufacturing operations are carried out in accordance with good manufacturing practice and with the manufacturing authorisation.	The manufacturer or importer shall ensure that the manufacturing operations are carried out in accordance with good manufacturing practice and with the manufacturing authorisation.
For medicinal products imported from third countries, the importer shall ensure that the medicinal products have been manufactured by manufacturers duly authorised and	For medicinal products and investigational medicinal products imported from third countries, the importer shall ensure that the medicinal products and investigational

conforming to good manufacturing practice standards, at least equivalent to those laid down by the Community.	medicinal products have been manufactured by manufacturers duly authorised and conforming to good manufacturing practice standards, at least equivalent to those laid down by the Community.
Article 5	***Article 5***
The manufacturer shall ensure that all manufacturing operations subject to an authorisation for marketing are carried out in accordance with the information given in the application for marketing authorisation as accepted by the competent authorities.	The manufacturer or importer shall ensure that all manufacturing operations subject to an authorisation for marketing are carried out in accordance with the information given in the application for marketing authorisation as accepted by the competent authorities or in accordance with the information given by the sponsor pursuant to Article 9.2 of Directive 2001/20/EC as accepted by the competent authorities. .
The manufacture shall regularly review their manufacturing methods in the light of scientific and technical progress. When a modification to the marketing authorisation dossier is necessary, the application for modification must be submitted to the competent authorities.	For an investigational medicinal product, the manufacturer or importer shall regularly review their manufacturing methods in the light of scientific and technical progress and the development of the investigational medicinal product. When a modification to the information given pursuant to Article 9.2 of directive 2001/20/EC concerning the manufacturer and/or importer is necessary, the amendment shall be notified to the competent authorities.
Article 6	***Article 6***
Quality management	*Quality management*
The manufacturer shall establish and implement an effective pharmaceutical	The manufacturer or importer shall establish and implement an effective pharmaceutical

quality assurance system, involving the active participation of the management and personnel of the different services involved.	quality assurance system, involving the active participation of the management and personnel of the different services involved.
Article 7	***Article 7***
Personnel	*Personnel*
1. At each manufacturing site, the manufacturer shall have competent and appropriately qualified personnel at his disposal in sufficient number to achieve the pharmaceutical quality assurance objective.	
2. The duties of managerial and supervisory staff, including the qualified person(s), responsible for implementing and operating good manufacturing practice shall be defined in job descriptions. Their hierarchical relationships shall be defined in an organisation chart. Organisation charts and job descriptions shall be approved in accordance with the manufacturer's internal procedures.	2 The duties of managerial and supervisory staff, including the qualified person(s), responsible for implementing and operating good manufacturing practice shall be defined in job descriptions. Their hierarchical relationships shall be defined in an organisation chart. Organisation charts and job descriptions shall be approved in accordance with the manufacturer's or importer's internal procedures.
3. Staff referred to in paragraph 2 shall be given sufficient authority to discharge their responsibility correctly.	
4. Personnel shall receive initial and continuing training including the theory and application of the concept of quality assurance and good manufacturing practice.	4 Personnel shall receive initial and continuing training including the theory and application of the concept of quality assurance and good manufacturing practice, and, where appropriate, including the particular requirements for manufacture of investigational medicinal products.
5. Hygiene programmes adapted to the activities to be carried out shall be established and observed. These programmes include procedures relating to health, hygiene and clothing of personnel.	

Article 8	***Article 8***
Premises and equipment	*Premises and equipment*
1. Premises and manufacturing equipment shall be located, designed, constructed, adapted and maintained to suit the intended operations.	Unchanged
2. Lay out, design and operation must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid contamination, cross contamination and, in general, any adverse effect on the quality of the product.	
3. Premises and equipment intended to be used for manufacturing operations which are critical for the quality of the products shall be subjected to appropriate qualification.	
Article 9	***Article 9***
Documentation	*Documentation*
1. The manufacturer shall have a system of documentation based upon specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the various manufacturing operations that they perform. Documents shall be clear, free from errors and kept up to date. Pre-established procedures for general manufacturing operations and conditions shall be available, together with specific documents for the manufacture of each batch. This set of documents shall make it possible to trace the history of the manufacture of each batch.	1. The manufacturer or importer shall have a system of documentation based upon specifications, manufacturing formulae and processing and packaging instructions, procedures and records covering the various manufacturing operations that they perform. Documents shall be clear, free from errors and kept up to date. Pre-established procedures for general manufacturing operations and conditions shall be available, together with specific documents for the manufacture of each batch. This set of documents shall make it possible to trace the history of the manufacture of each batch <u>and, where appropriate, the changes introduced during the development of the investigational medicinal product.</u>

	The batch documentation shall be retained for at least one year after the expiry date of the batches to which it relates or at least five years after the certification referred to in Article 22(2) of Directive 75/319/EEC whichever is the longer.		For a medicinal product, the batch documentation shall be retained for at least one year after the expiry date of the batches to which it relates or at least five years after the certification referred to in Article 51(3) of Directive 2001/83/EC whichever is the longer.
		2	For an investigational medicinal product, the batch documentation shall be retained for at least five years after the completion or formal discontinuation of the trial. The sponsor or marketing authorisation holder, if different, is responsible for ensuring records are retained as required for marketing authorisation in accordance with the annex to Directive 2001/83/EC.
2.	When electronic, photographic or other data processing systems are used instead of written documents, the manufacturer shall have validated the systems by proving that the data will be appropriately stored during the anticipated period of storage. Data stored by these systems shall be made readily available in legible form.	3.	When electronic, photographic or other data processing systems are used instead of written documents, the manufacturer or importer shall have validated the systems by proving that the data will be appropriately stored during the anticipated period of storage. Data stored by these systems shall be made readily available in legible form and shall be provided on demand to the competent authorities. For an investigational medicinal product when electronic, photographic or other data processing systems are used instead of written documents the manufacturer or importer shall have validated the systems to maintain the data during the required period of storage. Data stored by these systems shall be readily available in legible form and shall be provided on demand to the competent authorities.

3. The electronically stored data shall be protected against loss or damage of data (e.g. by duplication or back-up and transfer onto another storage system).	4. The electronically stored data shall be protected against loss or damage of data (e.g. by duplication or back-up and transfer onto another storage system).
Article 10	***Article 10***
Production	*Production*
The different production operations shall be carried out according to pre-established instructions and procedures and in accordance with good manufacturing practice. Adequate and sufficient resources shall be made available for the in-process controls.	
Appropriate technical and/or organisational measures shall be taken to avoid cross contamination and mix-ups.	Appropriate technical and/or organisational measures shall be taken to avoid cross contamination and mix-ups, and in the case of investigational medicinal products with particular attention paid to the handling of products during and after any blinding operation.
Any new manufacture or important modification of a manufacturing process shall be validated. Critical phases of manufacturing processes shall be regularly revalidated.	For investigational medicinal products, standard manufacturing processes, including in particular any sterilisation process, and any important modifications to these processes, shall be validated. In all cases measures shall be taken to ensure and demonstrate that the process has achieved what it is intended to achieve.
Article 11	***Article 11***
Quality Control	*Quality Control*
1. The manufacturer shall establish and	1 The manufacturer of a medicinal

	maintain a quality control department. This department shall be placed under the authority of a person having the required qualifications and shall be independent of the other departments.		product shall establish and maintain a quality control department. This department shall be placed under the authority of a person having the required qualifications and shall be independent of the other departments.
		2	For investigational medicinal products, the function of quality control shall be established and maintained distinct from other functions. It shall be placed under the authority of a person having the required qualifications and who is independent of production.
2.	The quality control department shall have at its disposal one or more quality control laboratories appropriately staffed and equipped to carry out the necessary examination and testing of starting materials, packaging materials and intermediate and finished products testing. Resorting to outside laboratories may be authorised in accordance with Article 12 of this Directive after the authorisation referred to in Article 5b of Directive 75/319/EEC has been granted.	3	The quality control department or function shall have at its disposal one or more quality control laboratories appropriately staffed and equipped to carry out the necessary examination and testing of starting materials, packaging materials and intermediate and finished products testing in accordance with good manufacturing practice. Resorting to outside laboratories may be authorised in accordance with Article 12 after the authorisation referred to in Article 20b of Directive 2001/83/EC has been granted. For investigational medicinal products, the laboratory shall be authorised under the authorisation referred to in Article 13.1 of Directive 2001/20/EC.
3.	During the final control of finished products before their release for sale or distribution, in addition to analytical results, the quality control department shall take into account essential information such as the production conditions, the results of in-process controls, the examination of the manufacturing documents and the conformity of the products to their specifications (including the final finished pack).	4	During the final control of finished products before their release for sale or distribution or for use in clinical trials, in addition to analytical results, the quality control department shall take into account essential information such as the production conditions, the results of in-process controls, the examination of the manufacturing documents and the conformity of the products to their specifications (including the

	final finished pack).
4. Samples of each batch of finished products shall be retained for at least one year after the expiry date.	5 Samples of each batch of finished products shall be retained for at least one year after the expiry date. For investigational medicinal products, sufficient samples of each batch of bulk formulated products and of the packaging components used for each finished product batch shall be retained by the manufacturer or importer for at least two years after completion or formal discontinuation of the clinical trial, whichever is the longer.
For certain medicinal products manufactured individually or in small quantities, or when their storage could raise special problems, other sampling and retaining conditions may be defined in agreement with the competent authority.	For certain medicinal products and investigational medicinal products manufactured individually or in small quantities, or when their storage could raise special problems, other sampling and retaining conditions may be defined in agreement with the competent authority.
5. Unless in the Member States of manufacture a longer period is required, samples of starting materials (other than solvents, gases and water) used shall be retained for at lest two years after the release of the product. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter. All these samples shall be maintained at the disposal of the competent authorities.	
Article 12	***Article 12***
Work contracted out	*Work contracted out*

1.	Any manufacturing operation or operation linked with the manufacture which is carried out under contract, shall be the subject of a written contract between the contract giver and the contract acceptor.	
2.	The contract shall clearly define the responsibilities of each party and in particular the observance of good manufacturing practice by the contract acceptor and the manner in which the qualified person responsible for releasing each batch shall undertake his full responsibilities.	2 The contract shall clearly define the responsibilities of each party and in particular the observance of good manufacturing practice by the contract acceptor and the manner in which the qualified person responsible for releasing each batch, or for certifying each batch in the case of an investigational medicinal product, shall undertake his full responsibilities.
3.	The contract acceptor shall not subcontract any of the work entrusted to him by the contract giver without the written authorisation of the contract giver.	3 The contract acceptor shall not subcontract any of the work entrusted to him by the contract giver without the written authorisation of the contract giver.
4.	The contract acceptor shall respect the principles and guidelines of good manufacturing practice and shall submit to inspections carried out by the competent authorities as provided for by Article 26 of Directive 75/319/EEC.	4 The contract acceptor shall respect the principles and guidelines of good manufacturing practice and shall submit to inspections carried out by the competent authorities as provided for by Article 111 of Directive 2001/83/EC and by Article 15 of Directive 2001/20/EC.
Article 13		***Article 13***
Complaints and product recall		*Complaints, emergency un-blinding and product recall*
The manufacture shall implement a system for recording and reviewing complaints together with an effective system for recalling promptly and at any time the medicinal products in the distribution network. Any complaint concerning a		

defect shall be recorded and investigated by the manufacturer. The competent authority shall be informed by the manufacturer of any defect that could result in a recall or abnormal restriction on the supply. In so far as possible, the countries of destination shall also be indicated.	
Any recall shall be made in accordance with the requirements referred to in Article 33 of Directive 75/319/EEC.	Any recall shall be made in accordance with the requirements referred to in Article 123 of Directive 2001/83/EC. For an investigational medicinal product, the manufacturer or importer, in collaboration with the sponsor when different, shall implement a system for recording and reviewing complaints together with an effective system for recalling promptly and at any time the investigational medicinal products distributed for use in a clinical trial. Any complaint concerning a defect shall be recorded and investigated by the manufacturer or importer. The competent authority shall be informed by the manufacturer or importer of any defect that could result in a recall. The centres and countries of destination shall also be indicated. This system shall include comparator products and in the case of comparator products with a marketing authorisation the marketing authorisation holder shall also be notified The sponsor shall maintain and, when necessary, implement a procedure for the rapid identification of blinded products in an emergency. The procedure shall not permit undetectable breaks of the blinding.
Article 14	***Article 14***
Self-inspection	*Self-inspection*
The manufacturer shall conduct repeated self-inspections as part of the quality assurance system in order to monitor the	The manufacturer or importer shall conduct repeated self-inspections as part of the quality assurance system in order to monitor

implementation and respect of good manufacturing practice and to propose any necessary corrective measures. Records of such self-inspections and any subsequent corrective action shall be maintained.	the implementation and respect of good manufacturing practice and to propose any necessary corrective measures. Records of such self-inspections and any subsequent corrective action shall be maintained.
	Article 15
	In the case of an investigational medicinal product, labelling must ensure protection of the subject and traceability, allow identification of the product and trial, and facilitate proper use of the investigational medicinal product.
	The Commission shall publish detailed guidance on the content of labels and leaflets, or other explanatory documents, for the trial subject or other user in the relevant annex to its Guide to good manufacturing practice referred to in Article 3.
CHAPTER III	**CHAPTER III**
Final Provisions	**Final Provisions**
Article 15	***Article 16***
Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive not later than 1 January 1992. They shall forthwith inform the Commission thereof.	Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive not later than …….They shall forthwith inform the Commission thereof.
When Member States adopt these provisions, these shall contain a reference to this Directive or shall be accompanied by such reference at the time of their official publication. The procedure for such reference shall be adopted by Member States.	When Member States adopt these provisions, these shall contain a reference to this Directive or shall be accompanied by such reference at the time of their official publication. The procedure for such reference shall be adopted by Member States.

Article 16	***Article 17***
This Directive is addressed to the Member States.	This Directive is addressed to the Member States.
Done at Brussels, 13 June 1991.	Done at Brussels _____.