Draft Proposal for a

COMMISSION DIRECTIVE ../…/EC

amending Commission Directive 91/356/EEC , laying down the principles and guidelines of good manufacturing practice for medicinal products for human use

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the Council Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use[1],

Whereas:

(1) All medicinal products for human use manufactured or imported into the Community, including medicinal products intended for export, should be manufactured in accordance with the principles and guidelines of good manufacturing practice;

(2) Commission Directive 91/356/EEC lays down the principles and guidelines of good manufacturing practice for medicinal products for human use[2]

(3) Directive 2001/20/EC of the European Parliament and of the Council 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[3] requires that the principles and guidelines of good manufacturing practice should be applied to investigational medicinal products

(4) The detailed guidelines referred to in Article 47 of Directive 2001/83/EC which were published by the Commission after consultation with the pharmaceutical inspection services of the Member States in the form of a 'Guide to good manufacturing practice for medicinal products' are being revised to take investigational medicinal products into account

(5) It is necessary that all manufacturers of investigational medicinal products should operate an effective quality management of their manufacturing operations, and that this requires the implementation of a pharmaceutical quality assurance system;

(6) Officials representing the competent authorities should report on whether the manufacturer or importer of an investigational medicinal product complies with good

[1] OJ No L311 of 28.11.01 p 67
[2] OJ No L193 of 17.07.91 p 30
[3] OJ No L121 of 1.05.01 p 34

manufacturing practice and that these reports should be communicated upon reasoned request to the competent authorities of another Member State;

(7) The principles and guidelines of good manufacturing practice should primarily concern personnel, premises and equipment, documentation, production, quality control, contracting out, complaints and product recall, and self inspection;

(8) The principles and guidelines applied by this amending Directive are in accordance with the opinion of the Standing Committee on Medicinal Products for Human Use

(9) Commission Directive 91/356/EEC should be amended accordingly,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Directive 91/356/EEC is amended as follows:

1. Article 1 is amended as follows:

(a) The first paragraph is replaced by the following text:

"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."

2. Article 2 is amended as follows:

(a) In the first paragraph, the words "Article 1(2) of Council Directive 65/65/EEC" are replaced by the words "Article 1 (2) of Directive 2001/83/EC"

(b) The first indent is replaced by the following text:

"Manufacturer or importer shall mean any holder of the authorisation referred to in Article 40 of Directive 2001/83/EC."

(c) The second indent is replaced by the following text

"In relation to a medicinal product, qualified person shall mean the person referred to in Article 48 of Directive 2001/83/EC"

(d) A new fifth indent is added as follows:

– "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."

(e) A new sixth indent is added as follows:

– "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"

(f) A new seventh indent is added as follows:

– "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."

(g) A new eighth indent is added as follows:

– "In relation to an investigational medicinal product, qualified person shall mean the person referred to in Article 13.2 of Directive 2001/20/EC."

3. Article 3 is amended as follows:

(a) The first paragraph is replaced by the following text:

"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."

(b) The second paragraph is replaced by the following text:

"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, which include in particular an annex on the manufacture of investigational medicinal products."

4. Article 4 is amended as follows:

(a) In the first paragraph the words "or importer" are added after the words "The manufacturer".

(b) In the second paragraph the words "and investigational medicinal products" are added after the words " medicinal products"

5. Article 5 is amended as follows:

(a) The first paragraph is replaced by the following text:

"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."

(b) A new third paragraph is added as follows:

"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."

6. Article 6 is amended as follows:

(a) In the first paragraph, the words "or importer" are added after "The manufacturer".

7. Article 7 is amended as follows:

(a) The first paragraph is replaced with the following text:

"At each manufacturing site or site of importation, the manufacturer or importer shall have competent and appropriately qualified personnel at his disposal in sufficient number to achieve the pharmaceutical quality assurance objective."

(b) The second paragraph is amended as follows:

In the last sentence the words "or importer's" are added after the words "the manufacturer's".

(c) The fourth paragraph is amended as follows:

The words ",and, where appropriate, including the particular requirements for the manufacture of investigational medicinal products" are added after the words "good manufacturing practice".

8. Article 9 is amended as follows:

(a) The first paragraph is replaced with the following text:

"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 and, where appropriate, the changes introduced during the development of the investigational medicinal product. 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. 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."

(b) The second paragraph is replaced with the following text:

"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."

9. Article 10 is amended as follows:

(a) The second paragraph is amended as follows:

The words ", and in the case of investigational medicinal products with particular attention paid to the handling of products during and after any blinding operation." are added after the word "mix-ups".

(b) A new fourth paragraph is added as follows:

"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."

10. Article 11 is amended as follows:

(a) The first paragraph is amended as follows:

The words "of a medicinal product" are added after the words "The manufacturer".

(b) The second paragraph is replaced as follows:

"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."

(c) The third paragraph is replaced as follows:

"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."

(d) The fourth paragraph is replaced as follows:

"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)."

(e) A fifth paragraph is inserted as follows:

"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 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."

13. Article 12 is amended as follows:

(a) The first paragraph is amended as follows:

The words ", or for certifying each batch in the case of an investigational medicinal product," are added after the words "each batch".

(b) The fourth paragraph is amended as follows:

The words "Article 111 of Directive 2001/83/EC and by Article 15 of Directive 2001/20/EC" replace the words "Article 26 of Directive 75/319/EEC."

14. Article 13 is amended as follows:

(a) The title of the article is amended as follows:

"Complaints , emergency unblinding and product recall"

(b) In the last sentence of the first paragraph, the words "Article 33 of Directive 75/319/EEC" should be replaced by the words "Article 123 of Directive 2001/83/EC."

(c) A new second paragraph should be added as follows:

"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."

15. Article 14 is amended as follows:

The words "or importer" are added after the words "The manufacturer".

16. Article 15 is replaced by the following text:

"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."

17. Article 16 is replaced by the following text:

"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."

18. Article 17 is replaced by the following text:

"This Directive shall enter into force on the [….] day following that of its publication in the *Official Journal of the European Communities*.

19. Article 18 is replaced by the following text:

"This Directive is addressed to the Member States.

Done at Brussels _____."

For the Commission

[…]

Member of the Commission