Regulation Amending the Regulation on Manufacturing Sites of Medicinal Products for Human Use

ARTICLE 1 — The second sentence in the first paragraph of Article 5 of the Regulation on Manufacturing Sites of Medicinal Products, published on the Official Gazette dated 23/10/2003, no. 25268 and the last sentence of the third paragraph of the same article have been amended as follows.

"In sites where medicinal products for human use are manufactured , no manufacture shall take place except for the products classified as intermediate products with manufacturing permission and veterinary medicinal products registered by the Ministry of Agriculture and Rural Affairs and considered suitable for the product classification."

"In case of continuation of manufacture, this document shall be renewed before the expiry date."

ARTICLE 2 — The statement “within 90 working days”, specified in the first paragraph of Article 6 in the same Regulation, has been amended as "within ninety days" and the statement “may be granted”, specified at the end of the second paragraph of the same article has been amended as “shall be granted”.

ARTICLE 3 — The statement “within 90 working days”, specified at the end of Article 7 of the same Regulation, has been amended as "within ninety days”.

ARTICLE 4 — The statement “of 90 working days”, specified in the second sentence of Article 8 of the same Regulation, has been amended as “of ninety days”.

ARTICLE 5 — Article 9 of the same Regulation has been amended as follows.

"**Article 9 —** Holder of manufacturing site permission shall be obliged to;

a) Employ adequate personnel as required by this Regulation and the guidelines, to provide for the control, storage and distribution transactions,

b) Provide for the destruction in accordance with the relevant legislation of the products which may no longer be used or have lost such characteristic to be used,

c) Inform the Ministry in advance, in cases when changes have to be made in the information and documents submitted during application in order to obtain the manufacturing site permission,

d) Forthwith inform the Ministry in the failure of the responsible manager to continue his functions for any reason or in case he quits his job,

e) Allow inspectors to enter into areas they require to be necessary and conduct inspections, within the framework of their certificates of authority,

f) Provide all necessary opportunities to the responsible manager to fulfill his duties,

g) Fulfill the requirements brought by the good clinical practices guideline to be prepared by taking as basis this regulation."

ARTICLE 6 — The second paragraph of Article 10 of the same Regulation has been amended as follows.

"The manufacturer shall pursue the manufacturing methods, scientific and technical advancements and review his own practices on a regular basis. Within this scope, in case of a change in the marketing authorisation, the relevant dossier of the manufacturing site, these shall be submitted to the Ministry and become approved if regarded as suitable."

ARTICLE 7 — The first paragraph of Article 11 of the same Regulation has been amended as follows.

"The holder of the manufacturing site permission shall employ as the responsible manager on a full-time basis, a person who has obtained a graduate degree upon completion of a pharmaceutical or medical education or upon graduation from a chemical sciences branch providing a graduate education of at least four years, in accordance with the first paragraph of Article 5 of the Law no. 1262 on Pharmaceutical and Medicinal Preparations. In manufacturing sites of biotechnological products, a biologist may be employed as product responsible. Furthermore, in case veterinary medicinal products are manufacture in the manufacturing sites of medicinal products for human use, the holder of the manufacturing site permission may employ a veterinary physician only for veterinary medicinal products."

ARTICLE 8 — The second paragraph of Article 12 of the same Regulation has been omitted from the text.

ARTICLE 9 — The second sentence of the first paragraph of Article 13 of the same Regulation has been amended as follows.

"Inspectors shall be authorised to inspect all manufacturing, quality control, quality assurance documents and other records within the scope of the inspection and to get samples where deemed necessary."

ARTICLE 10 — Item (b) of Article 15 of the same Regulation and the last paragraph of the same article have been amended as follows.

"b) The duties of administrative and supervisory staff and the qualified persons responsible for implementing and operating good manufacturing practice shall be defined in the job descriptions. The hierarchical relationships between these persons shall be defined in an organisational chart. The organisational chart and the job descriptions shall be approved in accordance with the manufacturers's internal procedures."

"The responsible manager and the quality control officer shall be obliged to be present at the manufacturing site during manufacture and fulfill the responsibilities defined in this Regulation. In cases of absence of the responsible manager, quality assurance and quality control officers for a period longer than ten days, persons with the same qualities to act as their proxies during their absence shall be appointed by the holder of the manufacturing site permission and the local healthcare authorities shall be duly informed."

ARTICLE 11 — Item (b) of Article 16 of the same Regulation has been amended as follows.

"b) The manufacturing process shall be designed and arranged in accordance with good manufacturing practice guidelines, in order to prevent contamination, cross-contamination and any negative impact that may affect the quality of the product in general, minimise the risk of errors and provide an effective cleaning and maintenance."

ARTICLE 12 — The second paragraph of item (a) in Article 17 of the same Regulation has been amended as follows.

"The documents pertaining to batches shall be retained for at last five years and for at least one year after the expiry date of the batches. The documents first submitted to the relevant Ministry and then updated, shall be retained until the annulment of the registration."

ARTICLE 13 — The last sentence of Article 18 of the same Regulation has been amended as follows.

"The critical phases of the manufacture process shall be regularly revalidated."

ARTICLE 14 — Items (b) and (d) of Article 19 of the same Regulation have been amended as follows.

"b) 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 materialsi intermediate and finished products testing. In order to allow manufacturers and importers to resort to laboratories outside the manufacturing site, the Ministry shall permit manufacturers and importers by condition of a toll agreement explicitly specifying mutual responsibilities and the responsibilities towards the Ministry."

"d) Samples of each finished products shall be retained for at least one year after the expiry date. Samples of starting materials used, other than solvents, gasses and water, shall be retained for at least two years after the release of the product. This period may be shortened if their stability as mentioned in the relevant specification is shorter. The products manufactured in small amounts or in individual units and the products the storage of which gives rise to special problems shall be sampled and retained separately, upon the approval of the Ministry."

ARTICLE 15 — Item (b) of Article 20 of the same Regulation has been amended as follows.

"b) The contract shall clearly define the responsibilities of the toll contract giver and acceptor and in particular the observance of good manufacturing practice by the contract acceptor and specify which qualified person shall be responsible for releasing each batch on both parties."

ARTICLE 16 — The first paragraph of Article 21 of the same Regulation has been amended as follows.

"The manufacturer shall implement a system for recording and reviewing complaints together with an effective distribution network system for recalling promptly and at any time the medicinal products from the market. Any complaint concerning a defect shall be recorded and investigated by the manufacturer. In case of the need to recall the product in consequence to the transactions conducted, the Ministry shall be promptly notified about this condition. If the product has been exported to other countries, notification shall be made to the countries of destination and the World Health Organisation."

ARTICLE 17 — The first paragraph of Article 24 of the same Regulation has been amended as follows and the following sentences have been added at the end of the second paragraph.

"In cases of manufacturing sites determined to function in disagreement with the provision of this Regulation, the Ministry, at the end of the inspections, may suspend the permission of manufacturing sites entirely or partially until the discrepancies are corrected, or may suspend it for certain pharmaceutical forms or annul it entirely."

"In case of annulment of the authority of the responsible manager, a new responsible manager shall be forthwith appointed. In case of suspension of the authority of responsible manager, a new responsible manager shall be forthwith appointed to serve during the period of suspension."

ARTICLE 18 — Items 5 and 7 in ATTACHMENT I of the same Regulation have been omitted from the attachment and the other items have been sequenced accordingly.

Enforcement

ARTICLE 19 — This Regulation shall be enforced on 30/6/2004.

Execution

ARTICLE 20 — This Regulation shall be executed by the Minister of Health.