MINISTRY OF HEALTH

ORDER

on approval of Regulations for manufacturing/importation authorisation of manufacturers and importers of medicinal products for human use, including investigational medicinal products and grant of the good manufacturing practice certificate to manufacturers of medicinal products for human use and/or active substances

On seeing the Approval report of the General Directorate for medicinal product strategies and policies No. I.B. 2.663/2009,

having regard to:

- provisions of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, as amended;
- Government Ordinance No. 125/1998 on the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law no. 594/2002, as amended,

based on Government Decision No. 1.718/2008 on the organisation and functioning of the Ministry of Health, as amended,

the minister of health hereby issues the following order:

Art. 1. – Regulations for manufacturing/importation authorisation of manufacturers and importers of medicinal products for human use, including investigational medicinal products and grant of the good manufacturing practice certificate to manufacturers of medicinal products for human use and/or active substances are approved as provided in the Annex which is integral part of this Order.

Art. 2. – On the date of this Order coming into force, Order of the Ministry of Public Health No. 918/2006 on approval of Regulations for manufacturing/importation authorisation of manufacturers and importers of medicinal products for human use, including investigational medicinal products, and of starting materials used in the manufacturing of medicinal products for human use, including investigational medicinal products, published in the Official Gazette of Romania, Part I, No. 719 of 22 august 2006, as amended, shall be repealed.

Art. 3. – The present order is to be published in the Official Gazette of Romania, Part I.

Minister of health,
Ion Bazac

Bucharest, 16 March 2009.
No. 312.

ANNEX

REGULATIONS
on approval of Regulations on manufacturing/importation authorisation of manufacturers and importers of medicinal products for human use, investigational medicinal products included, and granting of good manufacturing practice certificate for manufacturers of medicines and/or active substances

Article 1. – (1) In the context of these regulations, terms and notions in use shall mean the following:

a) the *European Medicines Agency* – European institution founded in 1995, based on Regulation 2.309/93, whose main attribution is "scientific evaluation of applications for European Union (EU) marketing authorisations for human and veterinary medicines in the centralised procedure", resulting in grant of a marketing authorisation for new medicinal products by European Commission Decision;

b) the *National Medicines Agency* – the Romanian competent authority in the field of medicinal products for human use, further referred to as *medicinal products*;

c) *Manufacturing/import authorisation* – document attesting compliance with good manufacturing practice rules concerning the manufacturing/import of medicinal products;

d) *Marketing authorisation* – document issued by the competent authority in the medicinal product field, based on evaluation and approval of documentation for authorisation submitted by the applicants to that specific authority, document allowing circulation of that medicinal product on the pharmaceutical market of the specific country;

e) *National marketing authorisation for medicinal products* – marketing authorisation for a medicinal product granted by the National Medicines Agency;

f) *Marketing authorisation valid in Romania* – national marketing authorisation on the national market or by European Commission Decision;

g) *Intra-community trade* – operations of introduction into Romania of medicinal products coming from member states of the European Economic Area; where these operations are concerned, the internal right of disposition is applied;

h) *European Commission Decision* – document granted by the European Commission concerning medicinal products authorised through centralised procedure in line with Regulation No. 726/2004, which allows the movement of the respective medicinal product throughout all member states of the European Economic Area;

i) *Import of medicinal products*: operation of introducing in Romania medicinal products coming from third countries;

j) M*edicinal product importer* – person who carries out, in accordance with legal dispositions, importing operations of medicinal products, including investigational products;

k) A*ctive substance* – Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body;

l) M*edicinal products coming from the European Economic Area* – medicinal products manufactured within the European Economic Area or which, although not manufactured within this area, have acquired the right of free circulation within the European Economic Area; medicinal products not coming from the European Economic Area are third country medicinal products;

m) C*entralised procedure* – marketing authorisation procedure stipulated by Regulation (CE) No. 726/2004 of the European Parliament and Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency ;

n) *National procedure* – marketing authorisation procedure, issued by the National Medicines Agency, based on national legislation in force;

o) *Mutual recognition procedure* – European marketing authorisation procedure, carried on in accordance with stipulations of section 5 "Mutual recognition procedure and decentralised procedure" from Chapter III "Marketing Authorisation" of Title XVII-Medicinal products from Law 95/2006 on healthcare reform, as amended;

p) *Decentralised procedure* – European marketing authorisation procedure, carried on in accordance with stipulations of section 5 "Mutual recognition procedure and decentralised procedure" from Chapter III "Marketing Authorisation" of Title XVII-Medicinal products from Law 95/2006 on healthcare reform, as amended;

q) *European Economic Area* – member states of the European Union including Norway, Iceland and Liechtenstein;

r) *third countries* – countries other than member states of the European Economic Area.

Chapter II
Manufacturing/import authorisation

Article 2. – (1) In compliance with Article 748 of Law No. 95/2006, in order to manufacture medicinal products inside Romania, investigational medicinal products included, applicants must own a manufacturing authorisation.

(2) According to the same legal provisions, in order to import medicinal products into Romania, applicants must own an import authorisation.

Article 3. – (1) The manufacturing/import authorisation is issued by the National Medicines Agency, in compliance with provisions of art. 748 of Law No. 95/2006.

(2) This authorisation is also necessary for medicinal products exclusively intended for export, in case of manufacturers of sterile active substances or excipients and in case of sterile biological raw materials manufacturers.

Article 4. – (1) The manufacturing/import authorisation for a manufacturing/import site is granted in consequence of applications submitted by the manufacturers and importers, respectively.

(2) The manufacturing/import authorisation is granted based on the favourable inspection report granted by the National Medicines Agency inspectors.

(3) In accordance with Article 750 (2) of Law No. 95/2006, the import authorisation can be issued conditionally, stipulating certain obligations to be met.

(4) To be granted a manufacturing/import authorisation, applicants submit an application to the NMA for schedule of an inspection, in accordance with the form stipulated in Annex I and the completed form as shown in Annexes III or IV, accompanied by the following documents:

a) administrative documents:

a1) constitutive acts of the company (status and social contract);

a2) irrevocable conclusion of the judge entrusted with authorisation and registration of the company or, as required, irrevocable court decision;

a3) copy of the Trade Register registration certificate, together with its annexes and, if needed, certificates of accompanying observations registration;

a4) title attesting ownership of site(s) in the company;

a5) in the case of importers who do not own their own storage areas, collaboration contract with a warehouse of medicinal products/starting materials authorised for wholesale distribution,.

b) technical documents:

b1) Site Master File for each site, filled in according to the Guideline in Annex V; importers will submit the Site Master file for each import site, taking into account the specificity of import activities;

b2) a commitment concerning submission of accurate status of each import (according to Annex IX), immediately upon accomplishment thereof, drawn in the format provided in Annex X – both on paper and in electronic format (requested from importers only).

Article 5. – 10 days as of the registration of the application, the National Medicines Agency provides a response to the applicant concerning the submitted documents for conduct of the inspections:

a) In case the documentation submitted is in line with Article 4 (4) provisions, the applicant is informed on acceptance of the respective application for inspection as well as on amount of the inspection fee, approved through Order of the Minister of Health; the inspection takes place 10 days as of fee payment confirmation, on an agreed date, except otherwise justified;

b) In case the documentation submitted is not comprehensive, the applicant is notified as to the information to be submitted to the National Medicines Agency; in such cases, implementation of deadlines as provided in Article 751 and 752 of Law No. 95/2006 are suspended until submission of the comprehensive documentation.

Article 6. – The inspection is carried out in line with an inspection plan established by an inspector/inspectors nominated by the National Medicines Agency; the respective plan is forwarded to the applicant unit at least 3 days prior to the date of inspection.

Article 7. – (1) The inspection for manufacturing/import authorisation assesses compliance with the principles and guidelines for medicinal products good manufacturing practice, investigational medicinal products included, approved through Order of the Minister of Health and compliance with the Guideline for Good Manufacturing Practice for medicinal products, approved through Scientific Council decision of the National Medicines Agency.

(2) Manufacturing authorisation is required both for total and partial manufacture and for different operations concerning medicinal products division, packaging or change of presentation form (repackaging, relabeling), investigational medicinal products included.

Article 8. – Within 20 days as of the inspection date, a preliminary/final report is sent to the applicant, as appropriate; in case of a preliminary report, the applicant is required to submit a proposed corrective action plan within 15 days.

a) In case of an unfavourable inspection report (critical deficiencies), following the resolution of deficiencies found by the inspectors, the inspected unit may apply for a new inspection

b) In case of a favourable inspection report, the manufacturing/import authorisation is granted by the National Medicines Agency within 90 days as of the registration date of the full documentation submitted by the applicant;

c) Follow-up of the resolution of potential deficiencies found (major or other) is performed following the issue of the manufacturing/import authorisation, in accordance with

provisions of Article 750 (2) of Law No. 95/2006, based on documentation submitted by the applicant or via another inspection;

Article 9. – The manufacturing/import authorisation is issued in the format provided in Annex VI, in two original copies, one of which is handed to the applicant unit, while the other remains with the National Medicines Agency – the Pharmaceutical Inspection Department.

Article 10. – (1) As appropriate, a follow-up inspection at medicinal products manufacturers/importers is established, according to an annual inspection plan, set up based on risk assessment, in agreement with NMA Scientific Council Decision no. 11/23.05.2008 on approval of the Guide for elaboration of the inspection plan at medicinal products manufacturers, based on risk assessment; for this purpose, 90 days prior to the scheduled date, the National Medicines Agency requires payment of the inspection fee by the legal authorisation holder, as approved by Order of the Minister of Health.

(2) The inspection is performed within 10 days after inspection fee payment confirmation; the inspection is performed in agreement with articles 6-8 stipulations.

Article 11. – (1) The inspection for manufacturing/import authorisation renewal is performed according to the annual inspection plan; for this purpose, 90 days prior to the 3 years expiry term stipulated in art. 750 of Law 95/2006 as validity of manufacture/import authorisation, the National Medicines Agency requires the legal authorisation holder to submit an application for inspection (according to Annex I), accompanied by the Site Master File (according to Annex V);

(2) Renewal of manufacture/import authorisation is made according to art. 5-8.

Article 12. – Any change subsequent to grant of the manufacturing/import authorisation is notified to the National Medicines Agency in advance, in accordance with Article 754 c) of Law No. 95/2006, at the same time with an application for a new authorisation or change of one/several annexes of the authorisation; depending on the nature of the change (administrative and/or technical), the manufacturing/importation authorisation is granted based on an updated dossier submitted or based on a new favourable inspection report.

Article 13. – According to Law No. 339/2005, for import of medicinal products, psychotropic substances and drugs, after grant of manufacturing/importation authorisation, applicants must apply to the Ministry of Public Health – the General Directorate for Strategies and Medicines Policy, for grant of authorisations required in order to hold and import this type of medicinal products.

Article 14. – Loss of the manufacturing/importation authorisation requires cancellation thereof; grant of a new manufacturing/importation authorisation is done based on the following documents:

- an application written in the format mentioned in Annex VIII;
- proof of publication of the loss in a widely circulated daily paper;
- copies of the documents attached to the initial MA dossier;
- statutory declaration that no changes have been made other than referred to in the information allowing for initial manufacturing/importation marketing authorisation.

Article 15. – (1) Should one or several conditions for conditional authorisation found that had not been met, the National Medicines Agency suspends or withdraws the previously granted manufacturing/importation authorisation or the good manufacturing certificate(s), respectively.

(2) If the company ceases its activity, the authorisation and good manufacturing practice certificate(s) is/are withdrawn and returned to the National Medicines Agency.

CHAPTER III
Good manufacturing practice certificate

Article 16. (1) Pursuant to art. 823(5) of Law 95/2006 for healthcare reform, in case of inspections concerning authorisation of medicinal product manufacturers, authorisation renewal or follow-up, the National Medicines Agency grants a good manufacturing certificate within 90 days as of the inspection date.

(2) In cases not related to inspections, when applicants require a novel good manufacturing practice certificate, (e.g. issue of a copy of a valid GMP certificate), this is granted by the National Medicines Agency after confirmation of the fee payment as approved through Order of the Minister of Health.

(3) In cases when Annex 8 is not issued (as included in Annex VI to the present regulation) concerning the list of medicinal products authorised for manufacturing, issuance of GMP certificates is only done after conduct of a follow-up inspection to prove GMP compliance during manufacture of products to be included in Annex 8.

Article 17. – (1) Active substances manufacturers notify the National Medicines Agency in writing concerning their intent to manufacture active substances for medicinal products for human use, for clinical investigation included; subsequent to notification, the active substance manufacturer is inspected, on request, by the National Medicines Agency for assessment of their good manufacturing practice compliance, in accordance with art. 823(1) of Law 95/2006; in case of favourable final inspection report, the NMA issues a good manufacturing practice certificate.

(2) In order to assess compliance with good manufacturing practice rules, third country manufacturers (or their representatives in Romania) may require the National Medicines Agency to conduct an inspection in relation to their applications(s) for marketing authorisation of a medicinal product in Romania, in accordance with art. 823 (4) of Law 95/2006.

Article 18. – (1) For grant of a good manufacturing practice certificate, the applicant (active substances manufacturer or third country manufacturer) submits to the National Medicines Agency an application according to Annex II, accompanied by the Site Master File (in case of third country manufacturers, the documentation is submitted in English).

(2) The application for inspection must clearly specify the product/products for which it application for marketing authorisation in Romania is sought.

Article 19 – Within 20 days as of receipt of the application, the National Medicines Agency provides the applicant a response in relation with the documents submitted for inspection:

a) In case the documentation submitted is comprehensive, the applicant is informed on acceptance of their application for inspection and amount of the inspection fee, as approved through Order of the Minister of Health; the inspection takes place within 30 days as of the confirmation of fee payment, on an agreed date, except otherwise justified;

b) In case the documentation submitted is not comprehensive, the applicant is notified on the information to be submitted to the National Medicines Agency.

Article 20 - The inspection is carried out in line with an inspection plan established by an inspector/inspectors nominated by the National Medicines Agency; the plan is forwarded to the applicant at least 3 days prior to inspection date.

Article 21. – (1) The inspection for grant of good manufacturing practice certificate pursues compliance with the principles and guidelines for the good manufacturing practice

of medicinal products, investigational medicinal products included, approved through Order of the Minister of Health and compliance with the Guideline for Good Manufacturing Practice for medicinal products, approved through Scientific Council decision of the National Medicines Agency.

Article 22. - The inspection is finalised with a preliminary inspection report, sent to the applicant within 30 days as of the inspection date.

a) In case of an unfavourable inspection report (critical deficiencies), following the resolution of deficiencies found by the inspectors, the inspected unit may apply for a new inspection;

b) in case of a favourable inspection report, the good manufacturing practice certificate is issued by the National Medicines Agency in maximum 90 days from the date of inspection;

c) follow-up of resolution of potential deficiencies found (major or other) is done after grant of the good manufacturing practice certificate, based on documentation submitted by the applicant or, in case of Romanian manufacturers of active substances, via another inspection;

Article 23. – The good manufacturing practice certificate is issued in the format provided in Annex VI, in two original copies, one of which is handed to the applicant unit, while the other remains with the National Medicines Agency – the Pharmaceutical Inspection Department.

Article 24. – (1) Within 90 days prior to the expiry date stipulated in the good manufacturing practice certificate, the active substance manufacturer/third country manufacturer or their Romanian representative submits an application for inspection (according to Annex II), accompanied by Site Master File (according to Annex V);

(2) Good manufacturing practice certificate renewal is done in accordance with stipulations of articles 19, 20, 21, 22 and 23.

Article 25. – Non-compliance of the applicant with the terms stipulated in the present regulations, entails suspension or cancellation of the manufacturing/import authorisation process or of the good manufacturing practice certificate granting and enforcement of adequate measures.

CHAPTER IV
General provisions relating to introduction of medicinal products into Romania

Article 27. – (1) Customs authority allow performance of customs operations which consist of introducing medicinal products from third countries in Romania based on the following documents:

a) medicinal products authorised in Romania through national procedure – based on import authorisation and marketing authorisation granted by the National Medicines Agency;

b) medicinal products authorised in Romania through national procedure, introduced into Romania for use in the promotion process – based on the import authorisation, of the marketing authorisation issued by the National Medicines Agency or, as required, on the confirmation letter attesting that the medicinal product is under renewal procedure and invoice declaring the non-commercial value of the respective samples;

c) medicinal products authorised in Romania through national procedure, introduced into Romania for use in quality control performed by the National Medicines Agency or a control laboratory agreed by the National Medicines Agency – based on importation

authorisation and marketing authorisation granted by the National Medicines Agency (or, as required, on confirmation letter attesting that the medicinal product is under renewal) and on the invoice declaring the non-commercial value of the respective samples;

d) medicinal products without valid marketing authorisation in Romania, introduced into Romania in view of clinical testing – based on the import authorisation and approvals granted by the National Medicines Agency and the Ethics Committee;

e) medicinal products without marketing authorisation valid in Romania, intended for special needs purposes – based on authorisation for supply of medicinal products for special needs purposes issued by the Ministry of Health.

f) medicinal products introduced into Romania as donations or medical aid – based on acceptance letter issued by the Interdepartmental Commission of the Ministry of Health in accordance with legal provisions in force and attached list of medicinal products as approved, signed and stamped by a Pharmacist-Inspector with the General Directorate for Strategies and Medicines Policy within the Ministry of Health;

h) medicinal products without marketing authorisation valid in Romania, introduced into Romania for partial manufacture (e.g. primary, secondary packaging, labelling) for intra-community trade and/or export – based on the manufacturing/import authorisation issued by the National Medicines Agency.

(2) – The following categories of medicinal products from the European Economic Area are introduced into Romania based on the following documents:

a) medicinal products authorised in the European Union through centralised procedure – based on wholesale distribution authorisation, issued in compliance with Article 788 (1) of Title XVII – The medicinal product of Law No. 95/2006 and the European Commission Decision;

b) medicinal products authorised in the European Union through centralised procedure, authorised in Romania through the CADREAC simplified procedure, manufactured prior to Accession – based on wholesale distribution authorisation issued by the Ministry of Health, of the marketing authorisation issued through simplified procedure by the National Medicines Agency (withdrawn by the National Medicines Agency on Accession) and by European Commission Decision (even without express reference within its content to validity inside Romania) – only for a 2 year period as of Accession date.

c) medicinal products authorised in Romania through national procedure, whose period of validity of the marketing authorisation issued by the National Medicines Agency has expired, undergoing marketing authorisation renewal with the National Medicines Agency – based on a valid distribution authorisation or confirmation letter issued by the National Medicines Agency, for the medicinal products concerned;

d) medicinal products authorised in the European Union through centralised procedure, whose period of validity as per European Commission Decision has expired, undergoing marketing authorisation renewal with the European Medicines Agency – based on the valid wholesale distribution authorisation and confirmation letter issued by the European Medicines Agency, for the medicinal products concerned;

e) medicinal products authorised in the European Union through centralised procedure, introduced into Romania for use in the promotion process – based on European Commission Decision or, as required, of the confirmation letter that the medicinal products undergo renewal and of the invoice declaring the non-commercial value of samples in question;

f) medicinal products authorised in the European Union through centralised procedure, introduced into Romania for use in the quality control by the National Medicines

Agency or a control laboratory agreed by the National Medicines Agency – based on European Commission Decision or, as required, of the confirmation letter that the medicinal product undergoes a renewal and of the invoice declaring the non-commercial value of samples in question;

g) medicinal products without marketing authorisation valid in Romania, introduced into Romania for investigational purposes – based on approvals granted by the National Medicines Agency and the Ethics Committee;

h) medicinal products without marketing authorisation valid in Romania, introduced into Romania for use in the marketing authorisation procedure – based on the confirmation received from the National Medicines Agency, concerning submission of the marketing authorisation dossier;

i) medicinal products introduced into Romania as donations or medical aid – based on agreement issued by the Interdepartmental Commission of the Ministry of Health in accordance with legal provisions in force and with the attached list of medicinal products as approved, signed and stamped by a Pharmacist Inspector from the Pharmaceutical General Directorate for Strategies and Medicines Policy within the Ministry of Health;

j) medicinal products without marketing authorisation valid in Romania, intended for special needs purposes – based on authorisation for supply of medicinal products for special needs purposes issued by the Ministry of Health.

k) medicinal products without marketing authorisation valid in Romania, introduced into Romania for partial manufacture (e.g. primary, secondary packaging, labelling) for intra-community trade and/or export – based on the manufacturing/import authorisation issued by the National Medicines Agency.

Article 27. – Introduction of medicinal products for human use in customs warehouses, storage in free zone or customs warehouse may be performed only after previous authorisation by the National Medicines Agency of the premises and activities performed by the person holding proprietary and/or usage rights of the premises, in agreement with legal norms regarding authorisation of importers for medicines for human use

Article 18. – Annexes I- X are integral part of the present regulations.

ANNEX I
to Regulations

To

NATIONAL MEDICINES AGENCY
The Pharmaceutical Inspection Department

I, the undersigned, ..., representative of …....,
(Name and Surname)
hereby apply for schedule of an inspection at the unit site in view of manufacturing/import authorisation.

Attached to the present application is documentation required under Art. 4 (4) of Order of Minister of Health on approval of Regulations regarding manufacturing / import authorisation of medicinal products for human use, investigational medicinal products included and good manufacturing practice certification for manufacturers of medicines/active substances.

Signature, stamp
.....

ANNEX II
to Regulations

To

NATIONAL MEDICINES AGENCY
The Pharmaceutical Inspection Department

I, the undersigned, ..., representative of …....,
(Name and Surname)
hereby apply for schedule of an inspection at the unit site in view of granting the good manufacturing practice certificate for the following medicine/medicines* ……., currently undergoing authorisation/reauthorisation by the National Medicines Agency/ for the following active substances**:…….. .

Attached to the present application is documentation required under Art. 4 (4) of Order of Minister of Health on approval of Regulations regarding manufacturing / import authorisation of medicinal products for human use, investigational medicinal products included and good manufacturing practice certification for manufacturers of medicines/active substances.

Signature, stamp
.....

* to be filled in by third country manufacturers or their representatives in Romania

** to be filled in by active substances manufacturers

Application form

ANNEX II
to Regulations

Authorisation for total or partial manufacturing of medicinal products for human use

(Please fill in all relevant sections in this form in readable capitals, in black ink)

1. Application Form: administrative data

1.1. Applicant details

Authorisation number (if previously authorised):			
Name of the company:			
Name of the applicant:			
Address:			
Postal code:		Telephone No.:	
Mobile phone No.:		Fax No.:	
E-mail address:			

The application is submitted on behalf of the proposed authorisation holder (e.g. if a consultant or representative). If YES, please fill in section 1.2 ☐ *yes* ☐ *no*

1.2 Contact person information (if different from the above)

Contact name:			
Name of the company:			
Address:			
Postal code:		Tel. No.:	
Mobile phone		Fax No.:	
E-mail address:			

1.3 Information on invoicing address (if other than that of the authorisation holder)

Contact name:			
Company:			
Address:			
Postal code:		Telephone No.:	
Mobile phone No.:		Fax No.:	
E-mail address:			

Section 2: Information regarding the manufacturing/import site

2.1 Information on manufacturing/import site

Sections 2 and 3 have to be filled in for <u>each</u> total, partial manufacturing or import site to be included in the authorisation

Name of the manufacturing site:			
Address:			
Postal code:			
Contact name			
Telephone No.:		Fax No.:	
Mobile phone No.:			
E-mail address:			

2.2 Types of medicinal products manufactured/imported

Medicinal products for human use ☐ *yes* ☐ *no*

Medicinal products for veterinary use ☐ *yes* ☐ *no*

2.3 Types of activities conducted at the manufacturing/import site

☐ Manufacturing ☐ Dividing up and packaging ☐ Storage and handling

☐ Distribution ☐ Analytic testing ☐ Contract laboratory

☐ Batch release ☐ Vivarium ☐ Preservation of animal origin material

☐ Biological products ☐ Non-biologial products ☐ Import

☐ Export ☐ Other, please specify:

Name of manufacturing site [ ] Postal Code [ ]

2.4 Types of operations

Part 1 MANUFACTURING OPERATIONS

- authorised manufacturing operations include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, importation, storage and distribution of specified dosage forms unless informed to the contrary;
- quality control testing and/or release and batch certification activities without manufacturing operations should be specified under the relevant items;
- if the company is engaged in manufacture of products with special requirements e.g. radiopharmaceuticals or products containing penicillin, sulphonamides, cytotoxics, cephalosporins, substances with hormonal activity or other or potentially hazardous active ingredients this should be stated under the relevant product type and dosage form (applicable to all sections of Part 1 apart from sections 1.5.2 and 1.6)

1.1	**Sterile products**	**Manufacture (please tick)**
1.1.1	*Aseptically prepared (list of dosage forms)*	
	1.1.1.1 Large volume liquids	
	1.1.1.2 Lyophilisates	
	1.1.1.3 Semi-solids	
	1.1.1.4 Small volume liquids	
	1.1.1.5 Solids and implants	
	1.1.1.6. Other aseptically prepared products <free text>	
1.1.2	*Terminally sterilised (list of dosage forms)*	
	1.1.2.1. Large volume liquids	
	1.1.1.6 Semi-solids	
	1.1.1.7 Small volume liquids	
	1.1.1.8 Solids and implants	
	1.1.1.6. Other aseptically prepared products <free text>	
1.1.3	**Batch certification only**	

1.2	**Non-sterile products**	**Manufacture (please tick)**
1.2.1	**Non-sterile products (list of dosage forms)**	
	1.2.1.1. Capsules, hard shell	
	1.2.1.2 Capsules, soft shell	
	1.2.1.3. Chewing gums	
	1.2.1.4 Impregnated matrices	
	1.2.1.5. Liquids for external use	
	1.2.1.6. Liquids for internal use	
	1.2.1.7 Medicinal gases	
	1.2.1.8 Other solid dosage forms	
	1.2.1.9. Pressurised preparations	
	1.2.1.10 Radionuclide generators	
	1.2.1.11 Semi-solids	
	1.2.1.12 Suppositories	
	1.2.1.13. Tablets	
	1.2.1.14 Transdermal patches	
	1.2.1.15 Other non-sterile medicinal product <free text >	
1.2.2	**Batch certification only**	

1.3	**Biological medicinal products**	**Manufacture (please tick)**
1.3.1	**Biological medicinal products**	
	1.3.1.1 Blood products	
	1.3.1.2 Immunological products	
	1.3.1.3 Cell therapy products	
	1.3.1.4 Gene therapy products	
	1.3.1.5 Biotechnology products	
	1.3.1.6. Human or animal extracted products	
	1.3.1.7 Other biological medicinal products <free text >	
1.3.2	**Batch certification only**	
	1.3.2.1 Blood products	
	1.3.2.2 Immunological products	
	1.3.2.3 Cell therapy products	
	1.3.2.4 Gene therapy products	
	1.3.2.5 Biotechnology products	
	1.3.2.6. Human or animal extracted products	
	1.3.2.7 Other biological medicinal products <free text >	

1.4	**Other products or manufacturing activity** (any other relevant manufacturing activity/product type that is not covered above e.g. sterilisation of active substances, manufacture of biological active starting materials, herbal or homeopathic products, bulk or total manufacturing etc).	**Manufacture (please tick)**
1.4.1	**Manufacture of:**	
	1.4.1.1 Herbal products	
	1.4.1.2 Homoeopathic products	
	1.4.1.3 Biological active starting materials	
	1.4.1.4 Other <free text >	
1.4.2	**Sterilisation of active substances/excipients/finished product:**	
	1.4.2.1 Filtration	
	1.4.2.2 Dry heat	
	1.4.2.3 Moist heat	
	1.4.2.4 Chemical	
	1.4.2.5 Gamma irradiation	
	1.4.2.6 Electron beam	
1.4.3	**Others (please specify)**	

1.5	**Packaging only**	**Packaging (please tick)**
1.5.1	**Primary packing**	
	1.5.1.1 Capsules, hard shell	
	1.5.1.2 Capsules, soft shell	
	1.5.1.3 Chewing gums	
	1.5.1.4 Impregnated matrices	
	1.5.1.5 Liquids for external use	
	1.5.1.6 Liquids for internal use	
	1.5.1.7 Medicinal gases	
	1.5.1.8 Other solid dosage forms	
	1.5.1.9 Pressurised preparations	
	1.5.1.10 Radionuclide generators	
	1.5.1.11 Semi-solids	
	1.5.1.12 Suppositories	
	1.5.1.13 Tablets	
	1.5.1.14 Transdermal patches	
	1.5.1.15 Other non-sterile medicinal products <free text >	
1.5.2	**Secondary packing**	

1.6	**Quality control testing**	**Activities related to manufacture (please tick)**
	1.6.1 Microbiological: sterility	
	1.6.2 Microbiological: non-sterility	
	1.6.3 Chemical/Physical	
	1.6.4 Biological	

Part 2 - IMPORTATION OF MEDICINAL PRODUCTS

- authorised importation activities without manufacturing activity
- authorised importation activities include storage and distribution unless informed to the contrary

2.1	**Quality control testing of imported medicinal products**	**Import (please tick)**
	2.1.1 Microbiological: sterility	
	2.1.2 Microbiological: non-sterility	
	2.1.3 Chemical/Physical	
	2.1.4 Biological	
2.2	**Batch certification of imported medicinal products**	
2.2.1	**Sterile Products**	
	2.2.1.1. Aseptically prepared	
	2.2.1.2. Terminally sterilised	
2.2.2	**Non-sterile products**	
2.2.3	**Biological medicinal products**	
	2.2.3.1. Blood products	
	2.2.3.2. Immunological products	
	2.2.3.3. Cell therapy products	
	2.2.3.4. Gene therapy products	
	2.2.3.5. Biotechnology products	
	2.2.3.6. Human or animal extracted products	
	2.2.3.7 Other biological medicinal products <free text >	
2.2.4	***Other importation activities*** **(any other relevant importation activity that is not covered above e.g. importation of radiopharmaceuticals, medicinal gases, herbal or homeopathic products etc.)**	
	2.2.4.1. Radiopharmaceuticals/Radionuclide generators	
	2.2.4.2. Medicinal gases	
	2.2.4.3 Herbal products	
	2.2.4.4. Homoeopathic products	
	2.2.4.5. Biological active starting materials	
	2.2.4.6 Other <free text >	

2.5 Imported products

Please answer to the question below for import activities performed

Are there authorised medicines from outside European Economic Area (AEE) imported at this site? ☐ *yes* ☐ *no*

If Yes, please indicate below all authorised products, imported from outside AEE, including products authorised in EU.

MA number	Product name	Country of origin

2.6 Other information

The following information is required by the Inspectorate to be included in the authorisation

Manufacture of bulk product or partial manufacture ☐ *yes* ☐ *no*

Parallel imported products assembly ☐ *yes* ☐ *no*

Total and partial manufacturing for export ☐ *yes* ☐ *no*

Partial manufacturing for export ☐ *yes* ☐ *no*

Are present at the manufacturing/import site materials or products of animal origin? ☐ *yes* ☐ *no*

CONTRACT GIVING AND/OR ACCEPTING

Applicants to be contract acceptors (e.g. providing partial/total manufacturing to other parties) ☐ *yes* ☐ *no*

Applicants to be contract givers (e.g. use external manufacturers for certain products) ☐ *yes* ☐ *no*

Applicants to be contract acceptors (e.g. providing partial/total testing to other parties) ☐ *yes* ☐ *no*

Applicants to be contract givers (e.g. use external testing units for certain/all tests) ☐ *yes* ☐ *no*

ADDITIONAL INFORMATION RELATING TO TESTING IN THIS MANUFACTURING SITE

Stability testing? ☐ *yes* ☐ *no*

Is the manufacturing site involved in finished products testing? ☐ *yes* ☐ *no*

Is the manufacturing site involved in microbiological Testing of finished products and/or raw materials? ☐ *yes* ☐ *no*

If answer NO at the above questions, please explain the activities:

Other information

Do you possess stocks of products requiring freezing or low temperature storage? ☐ *yes* ☐ *no*

Do you import intermediate products for further processing? ☐ *yes* ☐ *no*

Are the premises ready to be inspected? ☐ *yes* ☐ *no*

Are you familiar with good manufacturing practice rules Principles and with good manufacturing practice rules Guide and are available relevant procedures and records? ☐ *yes* ☐ *no*

If applicable, your contracts are available for inspection? ☐ *yes* ☐ *no*

2.4 Additional information required

Have you submitted a Site Master File of your unit containing your initial application? ☐ *yes* ☐ *no*

Notice: All Unit Standard Dossiers have to be submitted on paper or CD format.

If not, will the Site Master File be available during inspection? ☐ *yes* ☐ *no*

MANUFACTURING SITES FACILITIES

Details must be included in the Site Master File

MANUFACTURING AND CONTROL EQUIPMENT

Details must be included in the Site Master File

Section 3. Assigned persons

Please indicate below staff categories working at the manufacturing site

Staff	**Number**
Qualified person (QP)	
Manufacture responsible person	
Quality control responsible person (QC)	

Please ensure you have included copies of the required documentation.

3.1 Qualified person

1. Please fill in a separate page for each QP
2. QP assignation should be signed by the person assigned and the applicant
3. QP applications should include a relevant CV and a copy of the PQ Certificate issued by NMA.

Family name:			
Name:			
Office address:			
Postal code:		Telephone No.:	
Fax No.:		Mobile telephone No.:	
E-mail address:			

Please indicate your status

Permanent employee ☐ Consultant ☐ Temporary employee ☐

If a consultant, please give details on your availability. How often do you visit the site?

Qualifications (relevant for authorisation purposes)

Experience (brief outline of jobs and responsibilities relevant for authorisation purposes)

Professional Bodies:

I hereby confirm that all above details are accurate and true according to my knowledge and opinions. I agree with my assignment as Qualified Person

Signature (of the assigned person): _____Date:_____
Name in full: _____
Signature (of the applicant): _____Date:_____
Name in full: _____

3.2 Manufacture responsible person

Please fill in an individual sheet for each Manufacture responsible person.What is your position as signatory? Please specify below.

Manufacture manager ☐ Section manager (manufacturing flow) ☐

Family name:			
Name:			
Office address:			
Postal code:		Telephone No.:	
Fax No.:		Mobile phone No.:	
E-mail address:			

Qualifications (relevant for authorisation purposes)

Experience (brief outline of jobs and responsibilities relevant for authorisation purposes)

Name and position of seniors:

Responsibility scope

I hereby confirm that all above details are accurate and true according to my knowledge and opinions. I agree with my assignment as Manufacture responsible person

Signature (of the assigned person of the applicant): _____Date:_____
Name in full: _____
Signature (of the applicant): _____Date:_____
Name in full: _____

3.3 Quality control responsible person

Please fill in the following details of the person(s) in charge with quality control. When the responsibility is shared among several persons, please fill in an individual sheet for each person and give details on each person's responsibility scope.

Family name:			
Name:			
Office address:			
Postal code:		Telephone No.:	
Fax No.:		Mobile phone No.:	
E-mail address::			

Qualifications (relevant for authorisation purposes)

Experience (brief outline of jobs and responsibilities relevant for authorisation purposes)

Name and position of seniors:

Responsibility scope

I hereby confirm that all above details are accurate and true according to my knowledge and opinions. I agree with my assignment as quality control responsible person.

Signature (of the assigned person): _____Date:_____
Name in full: _____
Signature (of the applicant): _____Date:_____
Name in full: _____

Section 4: Contract Laboratories

Please complete a copy of section 4 for <u>each</u> contract laboratory you wish to name on this authorisation

Laboratory Name:	
Address:	
Postcode:	
Site Contact Name:	
Telephone:	Fax:
Mobile:	
Email:	

Please indicate the type of testing carried out by ticking the relevant box(es) below.

Quality Control Testing

Microbiological: sterility		Yes		No
Microbiological: non-sterility		Yes		No
Chemical/Physical		Yes		No
Biological		Yes		No
Stability testing?		Yes		No
Is this site involved in doing finished product testing?		Yes		No
Is this site involved in microbiological testing of finished products and/or raw materials?		Yes		No
If answer No to above, explain activities:				

Section 5: Storage & Handling Sites

Please complete a copy of section 5 for <u>each</u> storage and handling site that you wish to include on the licence.

Site Name:			
Address:			
Postcode:			
Site Contact Name:			
Telephone:		Fax:	
Mobile:			
Email:			

Section 6: Comments

Please provide any other information that may support your application. You can also detail any changes to addresses, person names etc.

Section 7: Declaration

I/We apply for the grant of a Manufacturer's/Importer's Authorisation(MIA) to the proposed holder named in this application form in respect of the activities to which the application refers.

7.1 The activities are to be only in accordance with the information set out in the application or furnished in connection with it.

7.2 To the best of my knowledge and belief the particulars I have given in this form are correct, truthful and complete.

Signed (Applicant): _____ **Date:** _____

Print Name: _____

State capacity in which signed:

ANNEX IV
to Regulations

Application form
Manufacturing/import authorisation for investigational medicinal products for human use

(Please fill in all relevant sections in this form in readable capitals, in black ink)

Section 1: Administrative Data

1.1 Applicant's Details

Authorisation Number (if known):	
Company Name:	
Applicant's Name:	
Address:	

Postcode:		Telephone:	
Mobile:		Fax:	
Email:			

Are you applying on behalf of the Proposed Authorisation Holder? (e.g. if you are a consultant/representative) if YES please fill out section 1.2

☐ Yes ☐ No

1.2 Contact Details for Communication (if different from the applicant address)

Contact Name	

Company Name:

Address:

Postcode: Telephone:

Mobile: Fax:

Email:

1.3 Invoicing Address Details (if different from Authorisation Holder Address)

Contact Name:

Company:

Address:

Postcode: Telephone:

Mobile: Fax:

Email:

Section 2: Site Information

2.1 Site Details

You will need to complete one copy of Sections 2 & 3 for <u>each</u> manufacturing site that you wish to include on the Authorisation.

Site ID: (Variation only)	
Site Name:	
Address:	
Postcode:	
Contact Name:	
Telephone:	Fax:
Mobile:	
Email:	

2.2 Use of Products at Site

Are the products for administration to human beings? ☐ Yes ☐ No

2.3 Site Types

Manufacture	☐	Assembly and Packaging	☐
Batch Certification	☐	QC Testing	☐
Biological	☐	Non-biological	☐

Export	☐	Import	☐
Storage and Handling	☐	Other, please specify	☐

Site name:		Postal code:	

2.4 Site Functions

Part 1 – MANUFACTURING OPERATIONS

- manufacturing operations include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch certification, importation, storage and distribution of specified dosage forms unless informed to the contrary;

- batch certification activities and/or quality control testing without other manufacturing operations should be specified under the relevant items/or section 4;

- if the company is engaged in manufacture of products with special requirements e.g. radiopharmaceuticals or products containing penicillin, sulphonamides, cytotoxics, cephalosporins, substances with hormonal activity or other or potentially hazardous active ingredients this should be stated under the relevant product type and dosage form (applicable to all sections of Part 1 apart from sections 1.5.2 and 1.6)

Please tick each of the site functions proposed to be conducted.

1.1	**Sterile Products**	**Manufacture (Please Tick)**
1.1.1	**Aseptically Prepared (list of dosage forms)**	
	1.1.1.1 Large volume liquids	
	1.1.1.2 Lyophilisates	
	1.1.1.3 Semi-solids	
	1.1.1.4 Small volume liquids	
	1.1.1.5 Solids and implants	
	1.1.1.6 Other aseptically prepared products (please specify)	

Site name:		**Postal code:**	

1.1.2	**Terminally Sterilised**	**Manufacture (Please Tick)**
	1.1.2.1 Large volume liquids	
	1.1.2.2 Semi-solids	
	1.1.2.3 Small volume liquids	
	1.1.2.4 Solids and implants	
	1.1.2.5 Other terminally sterilised prepared products (please specify)	
1.1.3	**Batch certification only**	

1.2	Non-sterile products	Manufacture (Please Tick)
1.2.1	**Non-sterile products (list of dosage forms)**	
	1.2.1.1 Capsules, hard shell	
	1.2.1.2 Capsules, soft shell	
	1.2.1.3 Chewing gums	
	1.2.1.4 Impregnated matrices	
	1.2.1.5 Liquids for external use	
	1.2.1.6 Liquids for internal use	
	1.2.1.7 Medicinal gases	
	1.2.1.8 Other solid dosage forms	

Site name: | **Postal code:**

	Non-sterile products	**Manufacture (Please Tick)**
	1.2.1.9 Pressurised preparations	
	1.2.1.10 Radionuclide generators	
	1.2.1.11Semi-solids	
	1.2.1.12 Suppositories	
	1.2.1.13 Tablets	
	1.2.1.14 Transdermal patches	
	1.2.1.15 Other non-sterile medicinal products (please specify)	
1.2.2	**Batch certification only**	

Site ID: (Variation only)		**Site Name:**	

1.3	**Biological Investigational Medicinal Products**	**Manufacture (Please Tick)**
1.3.1	**Biological Investigational Medicinal Products**	
	1.3.1.1 Blood products	
	1.3.1.2 Immunological products	
	1.3.1.3 Cell therapy products	
	1.3.1.4 Gene therapy products	
	1.3.1.5 Biotechnology products	
	1.3.1.6 Human or animal extracted products	
	1.3.1.7 Other biological medicinal products (please specify)	
1.3.2	**Batch certification only**	
	1.3.2.1 Blood products	
	1.3.2.2 Immunological products	
	1.3.2.3 Cell therapy products	
	1.3.2.4 Gene therapy products	
	1.3.2.5 Biotechnology products	
	1.3.2.6 Human or animal extracted products	
	1.3.2.7 Other biological medicinal products (please specify)	

Site name:		**Postal code:**	

1.4	**Other products or manufacturing activity (any other relevant manufacturing activity/product type that is not covered above e.g. sterilisation of active substances, manufacture of biological active starting materials (when required by national legislation), herbal or homeopathic products).**	**Manufacture (Please Tick)**
1.4.1	**Manufacture of:**	
	1.4.1.1 Herbal products	
	1.4.1.2 Homoeopathic products	
	1.4.1.3 Biological active starting materials	
	1.4.1.4 Other (please specify)	
1.4.2	**Sterilisation of active substances/excipients/finished product:**	
	1.4.2.1 Filtration	
	1.4.2.2 Dry Heat	
	1.4.2.3 Moist Heat	
	1.4.2.4 Chemical	
	1.4.2.5 Gamma irradiation	
	1.4.2.6 Electron beam	
1.4.3	Others (please specify)	

Site name: | **Postal code:**

1.5	Packaging only	Packaging (Please Tick)
1.5.1	**Primary packing**	
	1.5.1.1 Capsules, hard shell	
	1.5.1.2 Capsules, soft shell	
	1.5.1.3 Chewing gums	
	1.5.1.4 Impregnated matrices	
	1.5.1.5 Liquids for external use	
	1.5.1.6 Liquids for internal use	
	1.5.1.7 Medicinal gases	
	1.5.1.8 Other solid dosage forms	
	1.5.1.9 Pressurised preparations	
	1.5.1.10 Radionuclide generators	
	1.5.1.11 Semi-solids	
	1.5.1.12 Suppositories	
	1.5.1.13 Tablets	
	1.5.1.14 Transdermal patches	
	1.5.1.15 Other non-sterile medicinal products (please specify)	
1.5.2	**Secondary packing**	

Site name:		**Postal code:**	

1.6	**Quality control testing**	**Manufacture related (Please Tick)**
	1.6.1 Microbiological: sterility	
	1.6.2 Microbiological: non-sterility	
	1.6.3 Chemical/Physical	
	1.6.4 Biological	

Site name:		**Postal code:**	

<u>Part 2</u> *– **<u>IMPORTATION OF INVESTIGATIONAL MEDICINAL PRODUCTS</u>***

- authorised importation activities without manufacturing activity
- authorised importation activities include storage and distribution unless informed to the contrary

2.1	**Quality control testing of imported Investigational Medicinal Products**	**Import (Please tick)**
	2.1.1 Microbiological: sterility	
	2.1.2 Microbiological: non-sterility	
	2.1.3 Chemical/Physical	
	2.1.4 Biological	
2.2	**Batch certification of imported Investigational Medicinal Products**	
2.2.1	**Sterile Products**	
	2.2.1.1 Aseptically Prepared	
	2.2.1.2 Terminally Sterilised	
2.2.2	**Non-Sterile Investigational Medicinal Products**	
2.2.3	**Biological Investigational Medicinal Products**	
	2.2.3.1 Blood products	
	2.2.3.2 Immunological products	
	2.2.3.3 Cell therapy products	
	2.2.3.4 Gene therapy products	
	2.2.3.5 Biotechnology products	
	2.2.3.6 Human or animal extracted products	
	2.2.3.7 Other biological medicinal products (please specify)	

Site name: | **Postal code:**

2.2.4	**Other importation activities (any other relevant importation activity that is not covered above e.g. importation of radiopharmaceuticals, medicinal gases, herbal or homeopathic products etc.)**	**Import (Please Tick)**
	2.2.4.1 Radiopharmaceuticals/Radionuclide generators	
	2.2.4.2 Medicinal gases	
	2.2.4.3 Herbal products	
	2.2.4.4 Homoeopathic products	
	2.2.4.5 Biological active starting materials	
	2.2.4.6 Other (please specify)	

Site name:		**Postal code:**	

2.6 Other Information

The following information is required for inspectorate action but will not appear on your authorisation.

OTHER SPECIFIC PROCESSES/ACTIVITIES

Bulk or partial manufacturing		**Yes**		**No**
Manufacture and assembly for export		**Yes**		**No**
Assembly for export		**Yes**		**No**
Are materials or products of Animal Human Origin (AHO) present at this site?		**Yes**		**No**

LETTING AND/OR ACCEPTING CONTRACTS

Applicants intends to be contract acceptor (i.e. manufactures partially/wholly for others)		**Yes**		**No**
Applicant intends to be contract giver (i.e. uses external manufacturers for total or partial manufacture)		**Yes**		**No**
Applicant intends to be contract acceptor (i.e. carries out testing partially/wholly for others)		**Yes**		**No**
Applicants intends to be contract giver (i.e. uses external test houses for some/all testing)		**Yes**		**No**

SUPPLEMENTARY QC TESTING INFORMATION AT THIS SITE

Stability testing?	☐ **Yes**	☐ **No**
Is this site involved in doing finished product testing?	☐ **Yes**	☐ **No**
Is this site involved in microbiological testing of finished products and/or raw materials?	☐ **Yes**	☐ **No**
If answer No to above, explain activities:		

Site name:		**Postal code:**	

OTHER INFORMATION

Do you handle medicines which require refrigeration or low temperature storage?	**Yes**	**No**
Do you import intermediate products for further processing?	**Yes**	**No**
Is this site ready for inspection?	**Yes**	**No**
Are you conversant with the Rules and Guidance for Pharmaceutical Manufacturer's and Distributors and do you have available the relevant procedures and records.	**Yes**	**No**
Are signed technical agreements available for inspection where applicable?	**Yes**	**No**

2.7 Further information which should be attached

Have you submitted a Site Master File with your initial application? ☐ **Yes** ☐ **No**

NOTE: All Site Master Files should be submitted either as a hard copy or as a CD ROM.

If No will a Site Master File be available on site during an inspection? ☐ **Yes** ☐ **No**

FACILITIES ON SITE

Details should be included in your Site Master File

EQUIPMENT ON SITE

Details should be included in your Site Master File.

Site name:		**Postal code:**	

Section 3: Named Persons

Please indicate below how many of the following types of personnel you have working at this site.

Personnel	Number
Qualified Person (QP)	
Production Manager/Supervisor (PM)	
Person responsible for Quality Control (QC)	

Please ensure you have included copies of the required documentation.

Site name:		**Postal code:**	

3.1. Qualified Person

1. **Please complete a separate page for each QP.**
2. **Each QP nomination must be signed by both the nominee and the applicant.**
3. **All applications by a QP must include a relevant CV and a copy of the nominee's certificate of eligibility from RPSGB, IOB or RSC.**

Title:		Person ID: (if known)	
First name(s):			
Surname:			
Business Address:			
Postcode:		Telephone:	
Fax:		Mobile:	
Email:			

Please indicate your status

Permanent Employee	☐	Consultant	☐	Transitional	☐

If you are a consultant, please give details of your availability. How frequently will you visit?

Site name:		**Postal code:**	

Qualifications (relevant to this authorisation)

Experience (brief details of employment and responsibilities relevant to this authorisation)

Professional Association(s):

Site name:		**Postal code:**	

I confirm that the above particulars are accurate and true to the best of my knowledge and belief. I agree to be nominated as a Qualified Person.

Signed (Nominee): _____ **Date:** _____

Print Name: _____

Signed (Applicant): _____ **Date:** _____

Print Name: _____

Site name:		**Postal code:**	

3.2. Person Responsible for Production

Please complete a separate sheet for each person responsible for production.

In what capacity are you signing this? Please indicate in the box below.

Manager of Production ☐ Supervisor of Production ☐

Title:		Person ID: (if known)	
First name(s):			
Surname:			
Business Address:			
Postcode:		Telephone:	
Fax:		Mobile:	
Email:			

Qualifications (relevant to this authorisation)

Experience (brief details of employment and responsibilities relevant to this authorisation)

Site name: **Postal code:**

Name and function of the person(s) to whom he/she reports:

Area of responsibility

I confirm that the above particulars are accurate and true to the best of my knowledge and belief. I agree to be nominated as the person responsible for production.

Signed (Nominee): _____ **Date:** _____

Print Name: _____

Signed (Applicant): _____ **Date:** _____

Print Name: _____

Site name:		**Postal code:**	

3.3. Person Responsible for Quality Control

Please give the following details of the person(s) with overall responsibility for Quality Control. Where this responsibility is shared between more than one person, please complete a separate page for <u>each</u> person, and give details of each person's areas of responsibility.

Title:		Person ID: (if known)	
First name(s):			
Surname:			
Business Address:			

Postcode:		Telephone:	
Fax:		Mobile:	
Email:			

Qualifications (relevant to this authorisation)

Experience (brief details of employment and responsibilities relevant to this authorisation)

Site ID: (Variations only)		**Site Name:**	

Name and function of the person(s) to whom he/she reports:

Area of responsibility

I confirm that the above particulars are accurate and true to the best of my knowledge and belief. I agree to be nominated as the person responsible for Quality Control.

Signed (Nominee): _____ **Date:** _____

Print Name: _____

Signed (Applicant): _____ **Date:** _____

Print Name: _____

Section 4: Contract Laboratories

Please complete a copy of section 4 for <u>each</u> contract laboratory you wish to name on this authorisation

Site ID: (Variation only)	
Site Name:	
Address:	
Postcode:	
Site Contact Name:	
Telephone:	Fax:
Mobile:	
Email:	

Please indicate the type of testing carried out by ticking the relevant box(es) below.

Quality Control Testing

Microbiological: sterility		Yes		No
Microbiological: non-sterility		Yes		No
Chemical/Physical		Yes		No
Biological		Yes		No
Stability testing?		Yes		No
Is this site involved in doing finished product testing?		Yes		No

Is this site involved in microbiological testing of finished products and/or raw materials?		Yes		No
If answer No to above, explain activities:				

Section 5: Storage & Handling Sites

Please complete a copy of section 5 for <u>each</u> storage and handling site that you wish to include on the authorisation.

Site ID: (Variation only)			
Site Name:			
Address:			
Postcode:			
Site Contact Name:			
Telephone:		Fax:	
Mobile:			
Email:			

Section 6: Comments

Please provide any other information that may support your application. You can also detail any changes to addresses, person names etc.

Section 7: Declaration

I/We apply for grant of a Manufacturer's Authorisation for Investigational Medicinal Products (MIAIMP) to the proposed holder named in this application form in respect of the activities to which the application refers.

7.1 The activities are to be only in accordance with the information set out in the application or furnished in connection with it.

7.2 To the best of my knowledge and belief, the particulars I have given in this form are correct, truthful and complete.

Signed (Applicant): _____ **Date:** _____

Print Name: _____

State capacity in which signed:

ANNEX V
to Regulations

GUIDE FOR PREPARATION OF THE SITE MASTER FILE

Summary

I. Introduction

2.1 The Site Master File is prepared by the pharmaceutical manufacturer and should contain specific information about the quality system policies and quality assurance activities of the company, the production and/or quality control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a pharmaceutical operation is carried out on the site, a Site Master File need only describe those operations, e.g. analysis, packaging etc.

2.2 When submitted to a regulatory authority, the Site Master File should provide clear information on the manufacturer's GMP related activities that can be useful in general supervision and in the efficient planning and undertaking of a GMP inspection.

2.3 A Site Master File should be detailed enough but, as far as possible, not exceed approximately twenty-five to thirty A4 pages plus appendixes.

2.4 The Site Master File should be a part of official documentation system of the manufacturer and kept updated accordingly. The Site Master File should have an

edition number and effective and expired dates. The format and headings should follow these guidance notes.

2.5 Wherever possible, simple plans, outline drawings or schematic layouts should be used instead of narrative. These plans etc should fit on A4 sheets of paper.

2.6 These Explanatory Notes apply to the preparation and content of the Site Master File. Refer to national regulatory requirements to establish whether it is mandatory for manufacturers of medicinal products to prepare a Site Master File and supply it regularly to the Supervisory Authority.

II. Purpose

The aim of these Explanatory Notes is to guide the manufacturer of medicinal products in the preparation of a Site Master File that can be useful to the regulatory authority in planning and conducting GMP inspections.

III. CONTENT OF SITE MASTER FILE

1. GENERAL INFORMATION ON THE COMPANY

1.1 Contact information on the firm

- Name and official address of the company;
- Names and street addresses of the site, buildings and production units;
- Contact information of the company including 24 hrs telephone number of the contact person in the case of product defects or recalls.

1.2 Pharmaceutical manufacturing activities as licensed by the Competent Authorities.

- **Brief description of manufacture, import, export, distribution and other activities as licensed by the Competent Authorities including foreign authorities with authorised dosage forms/activities, respectively;**
- **Copy of the valid manufacturing authorisation in Appendix 1;**
- Type of actual products manufactured on-site (list in Appendix 2);
- Information about toxic or hazardous substances handled on the site.

1.3 Any other manufacturing activities carried out on the site

- Description of non-pharmaceutical activities on-site, if any.

2. QUALITY MANAGEMENT SYSTEM OF THE COMPANY

2.1 Description of the quality system of the company

- Information of the quality systems run by the company and refers to the relevant standards;
- Owner of the quality system;
- Information of accredited and certified activities of the company contents of accreditations, dates and names of notified bodies;

- Information of supervision of competent authorities, dates of latest GMP-inspections.

2.2 Quality policy of the company

- Brief description of elements of the QA system e.g. organisational structure, responsibilities, procedures, processes;
- Description of system of product quality reviews, internal audit and management review programme;
- Brief description of validation and change control policies of the company.

2.3. Release procedure of finished products

- Name(s) of responsible person(s) / Qualified Person(s) responsible for releasing procedures
- General description of releasing procedure

2.4 Qualification policy of contractors, API manufacturers and other critical material suppliers

2.5 Quality Risk Management Policy of the company

- Brief description of QRM policy of the company;
- Scope and focus of QRM including brief description what activities are performed corporately and what locally; is the system operated across site or limited in scope; does the QRM system assess continuity of supply;
- Responsibilities within QRM system and integration of QRM system with the overall quality system;
- Description how the system assesses, controls, communicates and reviews risks.

3. PERSONNEL

- Organisation chart showing the arrangements for quality assurance, production and quality control in Appendix 3;
- Number of employees engaged in the quality assurance, production, quality control, storage and distribution;
- Key personnel; qualifications and experience requirements and responsibilities;
- Short description of training policy of the company; initial and in-service training programmes, qualification procedure of personnel;
- Health requirements for personnel engaged in production and in special activities.

4. PREMISES AND EQUIPMENT

4.1 Premises

- Short description of plant; size of the site, type and age of buildings;
- Simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings are not required);

- Lay out of the production area with the room classification and pressure differentials between adjoining areas and indicating the production activities of the rooms in Appendix 4;
- Description of special areas for the handling of highly toxic, hazardous and sensitising materials.

4.1.1 Brief description of ventilation systems

- Design criteria of the system e.g. Specification of the air supply, temperature, humidity, pressure differentials and air change rates, policy of recirculation (%);
- Filter designs and efficiency; alarming system, limits for testing and changing;
- Policy of requalification and maintenance of the system.

4.1.2 Brief description of water systems (schematic drawings of the systems in Appendix 5) including sanitation

- Specifications of the water produced;
- Monitoring system, sampling policy and frequency of testing;
- Method and frequency for sanitation.

4.2 Equipment

- Brief description of major production and control laboratory equipment.; list in Appendix 6.

4.3 Maintenance and calibration

- Description of preventative maintenance system, responsibilities and recording system.

4.4 Qualification, validation and calibration

- Brief description of the company's general policy for qualifications, validation and calibration

4.5 Cleaning and sanitation

- Cleaning validation policy of the company and method of evaluation the effectiveness of cleaning;
- Cleaning agents and quality of water used for cleaning;
- Brief description of cleaning methods and frequency for the water supply system, air handling system and dust extraction system.

4.6 GMP critical computerised systems

- Description of GMP critical computerised systems;
- Validation policy of the computerized systems.

5. DOCUMENTATION

- Description of documentation system of the company;
- Brief description of preparing, revision, releasing, distribution, controlling and archiving systems of documents.

6. PRODUCTION

- Type of products manufactured including
    - description if both human and veterinary products are prepared on the site
    - description if investigational medicinal products are produced including the detailed information of production areas and personnel responsible of IMP if different than commercial manufacturing processes
- Note any toxic or hazardous substances handled e.g. antibiotics, hormones, cytostatics;
- Note whether the products are manufactured in a dedicated facility or on a campaign basis;
- Flow charts of production operations for each product type/ dosage forms and department/ process line types including the steps for sampling and information related the open/closed phased or isolators used;
- Brief description of general policy for process validation;
- Policy for reprocessing or rework;
- Description of the arrangements for ensuring GMP compliance of API-manufacturers.

7. QUALITY CONTROL

- Description of the Quality Control activities carried out on the site describing the elements of the QC system e.g. specifications, test methods, and other quality related data collection;
- Brief description of Quality Control Department's activities in the release of finished products e.g. if the review of batch documentation and release of final documentation takes place in this department;
- Role of Authorised Person/ Qualified Person in quarantine and release of finished products and compliance with the Marketing Authorisation.– with QP activities specified, including arrangements when several QPs are involved in;
- Arrangements for the handling of rejected materials and products.

8. CONTRACT MANUFACTURING

- Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;
- List of contractors including the addresses and contact information in Appendix 7;
- Comprehensive flow charts of supply-chains for both incoming and out-going materials and activities, including but not limited to APIs, excipients, packaging materials, bulk products, finished products, samples for QC testing – if outsourced;
- Brief description of the details of the technical contract between the contract giver and acceptor and the way in which the GMP compliance is assessed to ensure product compliance with the Marketing Authorisation.

9. DISTRIBUTION, COMPLAINTS AND PRODUCT RECALL

- Names and locations of the companies to which products are shipped;
- Arrangements, recording and traceability system for distribution.

9.1 Complains and product recalls

- Brief description of complains, product defect and recalls handling system

10. SELF INSPECTIONS

- Short description of the self inspection system with focuses, practical arrangements and follow-up activities

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Appendix 1	Copy of valid manufacturing authorisation
Appendix 2	List of products manufactured including INN-names of APIs used
Appendix 3	Organisational charts
Appendix 4	Lay-outs of production areas
Appendix 5	Schematic drawings of water systems
Appendix 6	Lists of major production and laboratory equipment used indicating the latest qualification date of the equipment
Appendix 7	List of contractors including addresses and contact information

.....

ANNEX VI
on Regulations

MANUFACTURING/IMPORT AUTHORISATION FORMAT

1. Authorisation number

2. Name of authorisation holder

3. Address(es) of manufacturing site(s)
(All authorised sites should be listed if not covered by separate authorisations)

4. Legally registered address of
authorisation holder

5. Scope of authorisation and dosage[1] ANNEX 1 and/ or ANNEX 2

6. Legal basis of authorisation

7. Name of responsible officer of the
competent authority of the member state
granting the manufacturing authorisation

8. Signature

9. Date

10. Annexes attached Annex 1 and/or Annex 2
Annex 3
Annex 4
Annex 5
Annex 6
Annex 7
Annex 8

[1] The National Medicines Agency is responsible for appropriate linking of the authorisation with the manufacturer's application [art. 750 (3) from Title XVII –Medicinal Product of Law 95/2006 regarding healthcare reform/]

ANNEX 1 of Authorisation No.

SCOPE OF AUTHORISATION (delete the sections that do not apply)
Name and address of the site:

☐ Human Medicinal Products

AUTHORISED OPERATIONS
☐ Manufacturing Operations (according to part 1)
☐ Importation of Medicinal Products (according to part 2)

Part 1 - MANUFACTURING OPERATIONS
- authorised manufacturing operations include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, importation, storage and distribution of specified dosage forms unless informed to the contrary;
- quality control testing and/or release and batch certification activities without manufacturing operations should be specified under the relevant items;
- if the company is engaged in manufacture of products with special requirements e.g. radiopharmaceuticals or products containing penicillin, sulphonamides, cytotoxics, cephalosporins, substances with hormonal activity or other or potentially hazardous active ingredients this should be stated under the relevant product type and dosage form (applicable to all sections of Part 1 apart from sections 1.5.2 and 1.6)

1.1 Sterile Products
1.1.1 Aseptically prepared (list of dosage forms)
1.1.1.1 Large volume liquids
1.1.1.2 Lyophilisates
1.1.1.3 Semi-solids
1.1.1.4 Small volume liquids
1.1.1.5 Solids and implants
1.1.1.6 Other aseptically prepared products <free text>
1.1.2 Terminally sterilised (list of dosage forms)
1.1.2.1 Large volume liquids
1.1.2.2 Semi-solids
1.1.2.3 Small volume liquids
1.1.2.4 Solids and implants
1.1.2.5 Other terminally sterilised prepared products <free text>
1.1.3 Batch certification only

1.2 Non-sterile products
1.2.1 Non-sterile products (list of dosage forms)
1.2.1.1 Capsules, hard shell
1.2.1.2 Capsules, soft shell
1.2.1.3 Chewing gums
1.2.1.4 Impregnated matrices
1.2.1.5 Liquids for external use
1.2.1.6 Liquids for internal use
1.2.1.7 Medicinal gases
1.2.1.8 Other solid dosage forms

1.2.1.9 Pressurised preparations
1.2.1.10 Radionuclide generators
1.2.1.11 Semi-solids
1.2.1.12 Suppositories
1.2.1.13 Tablets
1.2.1.14 Transdermal patches
1.2.1.15 Other non-sterile medicinal product <free text >
1.2.2 Batch certification only
1.3 Biological medicinal products
1.3.1 *Biological medicinal products*
1.3.1.1 Blood products
1.3.1.2 Immunological products
1.3.1.3 Cell therapy products
1.3.1.4 Gene therapy products
1.3.1.5 Biotechnology products
1.3.1.6 Human or animal extracted products
1.3.1.7 Other biological medicinal products <free text >
1.3.2 Batch certification only (list of product types)
1.3.2.1 Blood products
1.3.2.2 Immunological products
1.3.2.3 Cell therapy products
1.3.2.4 Gene therapy products
1.3.2.5 Biotechnology products
1.3.2.6 Human or animal extracted products
1.3.2.7 Other biological medicinal products <free text >
1.4 Other products or manufacturing activity (any other relevant manufacturing activity/product type that is not covered above e.g. sterilisation of active substances, manufacture of biological active starting materials (when required by national legislation), herbal or homeopathic products, bulk or total manufacturing etc).
1.4.1 Manufacture of:
1.4.1.1 Herbal products
1.4.1.2 Homoeopathic products
1.4.1.3 Biological active starting materials
1.4.1.4 Other <free text >
1.4.2 Sterilisation of active substances/excipients/finished product:
1.4.2.1 Filtration
1.4.2.2 Dry heat
1.4.2.3 Moist heat
1.4.2.4 Chemical
1.4.2.5 Gamma irradiation
1.4.2.6 Electron beam
1.4.3 Others <free text>
1.5 Packaging only
1.5.1 Primary packing
1.5.1.1 Capsules, hard shell
1.5.1.2 Capsules, soft shell
1.5.1.3 Chewing gums
1.5.1.4 Impregnated matrices

1.5.1.5 Liquids for external use
1.5.1.6 Liquids for internal use
1.5.1.7 Medicinal gases
1.5.1.8 Other solid dosage forms
1.5.1.9 Pressurised preparations
1.5.1.10 Radionuclide generators
1.5.1.11 Semi-solids
1.5.1.12 Suppositories
1.5.1.13 Tablets
1.5.1.14 Transdermal patches
1.5.1.15 Other non-sterile medicinal products <free text >
1.5.2 Secondary packing

1.6 Quality control testing

1.6.1 Microbiological: sterility
1.6.2 Microbiological: non-sterility
1.6.3 Chemical/Physical
1.6.4 Biological

Any restrictions or clarifying remarks related to the scope of these Manufacturing operations

.....
.....
.....

Part 2 - IMPORTATION OF MEDICINAL PRODUCTS

- authorised importation activities without manufacturing activity
- authorised importation activities include storage and distribution unless informed to the contrary

2.1 Quality control testing of imported medicinal products

2.1.1 Microbiological: sterility
2.1.2 Microbiological: non-sterility
2.1.3 Chemical/Physical
2.1.4 Biological

2.2 Batch certification of imported medicinal products

2.2.1 Sterile Products
2.2.1.1 Aseptically prepared
2.2.1.2 Terminally sterilised
2.2.2 Non-sterile products
2.2.3 Biological medicinal products
2.2.3.1 Blood products
2.2.3.2 Immunological products
2.2.3.3 Cell therapy products
2.2.3.4 Gene therapy products
2.2.3.5 Biotechnology products
2.2.3.6 Human or animal extracted products
2.2.3.7 Other biological medicinal products <free text >
2.2.4 *Other importation activities* (any other relevant importation activity that is not covered above e.g. importation of radiopharmaceuticals, medicinal gases, herbal or homeopathic products etc.)
2.2.4.1 Radiopharmaceuticals/Radionuclide generators

2.2.4.2 Medicinal gases
2.2.4.3 Herbal products
2.2.4.4 Homoeopathic products
2.2.4.5 Biological active starting materials
2.2.4.6 Other <free text >
Any restrictions or clarifying remarks related to the scope of these Importing operations
.....
.....
.....

ANNEX 2 of Authorisation No.

SCOPE OF AUTHORISATION (delete the sections that do not apply or use yes/no)
Name and address of the site:

☐ Human Investigational Medicinal Products for phase I, II, III clinical trials

AUTHORISED OPERATIONS

☐Manufacturing Operations of Investigational Medicinal Products (according to part 1)
☐Importation of Investigational Medicinal Products (according to part 2)

Part 1 - MANUFACTURING OPERATIONS OF INVESTIGATIONAL MEDICINAL PRODUCTS

- authorised manufacturing operations include total and partial manufacturing (including various processes of dividing up, packagingor presentation), batch release and certification, importation, storage and distribution of specified dosage forms unless informed to the contrary;
- quality control testing and/or release and batch certification activities without manufacturing operations should be specified under the relevant items;
- if the company is engaged in manufacture of products with special requirements e.g. radiopharmaceuticals or products containing penicillin, sulphonamides, cytotoxics, cephalosporins, substances with hormonal activity or other potentially hazardous active ingredients this should be stated under the relevant product type and dosage form (applicable to all sections of Part 1 apart from sections 1.5.2 and 1.6)

1.1 Sterile investigational medicinal products

1.1.1 Aseptically prepared (list of dosage forms)
1.1.1.1 Large volume liquids
1.1.1.2 Lyophilisates
1.1.1.3 Semi-solids
1.1.1.4 Small volume liquids
1.1.1.5 Solids and implants
1.1.1.6 Other aseptically prepared products <free text>
1.1.2 Terminally sterilised (list of dosage forms)
1.1.2.1 Large volume liquids
1.1.2.2 Semi-solids
1.1.2.3 Small volume liquids
1.1.2.4 Solids and implants
1.1.2.5 Other terminally sterilised prepared products <free text>
1.1.3 Batch certification only

1.2 Non-sterile investigational medicinal products

1.2.1 Non-sterile products (list of dosage forms)
1.2.1.1 Capsules, hard shell
1.2.1.2 Capsules, soft shell
1.2.1.3 Chewing gums
1.2.1.4 Impregnated matrices
1.2.1.5 Liquids for external use
1.2.1.6 Liquids for internal use
1.2.1.7 Medicinal gases
1.2.1.8 Other solid dosage forms
1.2.1.9 Pressurised preparations
1.2.1.10 Radionuclide generators

1.2.1.11 Semi-solids
1.2.1.12 Suppositories
1.2.1.13 Tablets
1.2.1.14 Transdermal patches
1.2.1.15 Other non-sterile medicinal product <free text >
1.2.2 Batch certification only
1.3 Biological investigational medicinal products
1.3.1 Biological medicinal products (list of product types)
1.3.1.1 Blood products
1.3.1.2 Immunological products
1.3.1.3 Cell therapy products
1.3.1.4 Gene therapy products
1.3.1.5 Biotechnology products
1.3.1.6 Human or animal extracted products
1.3.1.7 Other biological medicinal products <free text >
1.3.2 Batch certification only (list of product types)
1.3.2.1 Blood products
1.3.2.2 Immunological products
1.3.2.3 Cell therapy products
1.3.2.4 Gene therapy products
1.3.2.5 Biotechnology products
1.3.2.6 Human or animal extracted products
1.3.2.7 Other biological medicinal products <free text >
1.4 Other investigational medicinal products or manufacturing activity (any other relevant manufacturing activity/product type that is not covered above e.g. sterilisation of active substances, manufacture of biological active starting materials (when required by national legislation), herbal or homeopathic products, bulk or total manufacturing etc).
1.4.1 Manufacture of:
1.4.1.1 Herbal products
1.4.1.2 Homoeopathic products
1.4.1.3 Biological active starting materials
1.4.1.4 Other <free text>
1.4.2 Sterilisation of active substances/excipients/finished product:
1.4.2.1 Filtration
1.4.2.2 Dry heat
1.4.2.3 Moist heat
1.4.2.4 Chemical
1.4.2.5 Gamma irradiation
1.4.2.6 Electron beam
1.4.3 Others <free text>
1.5 Packaging only
1.5.1 Primary packing
1.5.1.1 Capsules, hard shell
1.5.1.2 Capsules, soft shell
1.5.1.3 Chewing gums
1.5.1.4 Impregnated matrices
1.5.1.5 Liquids for external use
1.5.1.6 Liquids for internal use

1.5.1.7 Medicinal gases
1.5.1.8 Other solid dosage forms
1.5.1.9 Pressurised preparations
1.5.1.10 Radionuclide generators
1.5.1.11 Semi-solids
1.5.1.12 Suppositories
1.5.1.13 Tablets
1.5.1.14 Transdermal patches
1.5.1.15 Other non-sterile medicinal products <free text >
1.5.2 Secondary packing

1.6 Quality control testing

1.6.1 Microbiological: sterility
1.6.2 Microbiological: non-sterility
1.6.3 Chemical/Physical
1.6.4 Biological

Any restrictions or clarifying remarks related to the scope of these Manufacturing operations

.....
.....
.....

Part 2 - IMPORTATION OF INVESTIGATIONAL MEDICINAL PRODUCTS

- authorised importation activities without manufacturing activity
- authorised importation activities include storage and distribution unless indicated to the contrary

2.1 Quality control testing of imported investigational medicinal products

2.1.1 Microbiological: sterility
2.1.2 Microbiological: non-sterility
2.1.3 Chemical/Physical
2.1.4 Biological

2.2 Batch certification of imported investigational medicinal products

2.2.1 Sterile Products
2.2.1.1 Aseptically prepared
2.2.1.2 Terminally sterilised
2.2.2 Non-sterile products
2.2.3 Biological products
2.2.3.1 Blood products
2.2.3.2 Immunological products
2.2.3.3 Cell therapy products
2.2.3.4 Gene therapy products
2.2.3.5 Biotechnology products
2.2.3.6 Human or animal extracted products
2.2.3.7 Other biological medicinal products <free text >
2.2.4 *Other importation activities* (any other relevant importation activity that is not covered above e.g. importation of radiopharmaceuticals, medicinal gases, herbal or homeopathic products etc.)
2.2.4.1 Radiopharmaceuticals/Radionuclide generators
2.2.4.2 Medicinal gases

2.2.4.3 Herbal products
2.2.4.4 Homoeopathic products
2.2.4.5 Biological active starting materials
2.2.4.6 Other <free text >
Any restrictions or clarifying remarks related to the scope of these Importing operations
.....
.....
.....

ANNEX 3
Address(es) of Contract
Manufacturing Sites
.....
.....

ANNEX 4
Address(es) of Contract
Laboratories
.....
.....
.....

ANNEX 5
Name(s) of Qualified
Person(s)
.....

ANNEX 6
Name(s) of person(s)
responsible for quality control
.....
Name(s) of person(s)
responsible for production
.....

ANNEX 7
Date of Inspection on which authorisation was granted: dd/mm/yyyy
Scope of last Inspection
.....

ANNEX 8
Products authorised to be manufactured/imported (in accordance with Article 749 and 750 of Title XVII-Medicinal Product from Law 95/2006, as amended).
.....

ANNEX VII
on Regulations

GOOD MANUFACTURING PRACTICE CERTIFICATE FORMAT

(NATIONAL MEDICINES AGENCY HEADING)

Certificat Nr.: ___/___/___
Certificate No:____/____/____

CERTIFICAT PRIVIND CONFORMITATEA CU BUNA PRACTICĂ DE FABRICAŢIE
CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Partea 1
Part 1

Emis în urma unei inspecţii în acord cu art. 111(5) al Directivei 2001/83/EC sau art. 15 al Directivei 2001/20/EC*)

*Issued following an inspection in accordance with Art. 111(5) of Directive 2001/83/EC or Art. 15 of Directive 2001/20/EC**

sau
or

Emis în baza prevederilor Acordului de Recunoaştere Mutuală între Comunitatea Europeană şi [*Partenerul ARM*].*

*Issued under the provisions of the Mutual Recognition Agreement between the European Community and [MRA Partner].**

Autoritatea competentă AGENŢIA NAŢIONALĂ A MEDICAMENTULUI din ROMÂNIA confirmă următoarele:

The competent authority NATIONAL MEDICINES AGENCY from ROMANIA confirms the following:

Fabricantul
The manufacturer
.....

Adresa locului de fabricaţie
Site address
.....……..

A fost inspectat în cadrul programului naţional de inspecţie referitor la autorizaţia de fabricaţie nr. ..... în acord cu art. 40 al Directivei 2001/83/CE consolidată/art. 13 al Directivei 2001/20/EC*) transpuse în legislaţia naţională prin art. 748 din Legea nr. 95/2006 privind reforma în domeniul sănătăţii, Titlul XVII, Medicamentul/art. 48 din Ordinul ministrului sănătăţii publice nr. 904/2006 pentru aprobarea Reglementărilor privind implementarea regulilor de bună practică în desfăşurarea studiilor clinice efectuate cu medicamente de uz uman*

Has been inspected under the national inspection programme in connection with manufacturing authorisation no. ..... in accordance with Art. 40 of Directive 2001/83/EC/Art. 44 of Directive 2001/82/EC/Art. 13 of Directive 2001/20/EC transposed in the following national legislation: art. 748 from Law no. 95/2006 regarding the reform in the field of health, Title XVII, Medicinal product/art. 48 from Minister of Public Health Order*) no. 904/2006 for approval of Regulations relating the implementation of Good clinical practice in the conduct of clinical trials on medicinal products of human use**

sau
or

A fost inspectat în legătură cu autorizaţia(iile) de punere pe piaţă care se referă la fabricanţi situaţi în afara Spaţiului Economic European în acord cu art. 111(4) al Directivei 2001/83/CE transpusă în legislaţia naţională prin art. 823 alin. 1 din Legea nr. 95/2006 privind reforma în domeniul sănătăţii, Titlul XVII, Medicamentul*

*Has been inspected in connection with marketing authorisation(s) listing manufacturers located outside of the European Economic Area in accordance with Art. 111(4) of Directive 2001/83/EC transposed in the following national legislation: art. 823 (4) from Law no. 95/2006 regarding the reform in the field of health, Title XVII, Medicinal product**

şi/sau)*
*and/or**

Este un fabricant de substanţe active care a fost inspectat în acord cu art. 111(1) al Directivei 2001/83/CE transpusă în legislaţia naţională prin art. 823 alin. 1 din Legea nr. 95/2006 privind reforma în domeniul sănătăţii, Titlul XVII, Medicamentul*

*Is an active substance manufacturer that has been inspected in accordance with Art. 111(1) of Directive 2001/83/EC transposed in the following national legislation: art. 823 (1) from Law no. 95/2006 regarding the reform in the field of health, Title XVII, Medicinal product**

sau*
*or**

Altele (specificaţi):.....
Other (please specify): .....

Din informaţiile acumulate în timpul inspecţiei la acest fabricant, ultima fiind efectuată în ...../...../..... [data], se apreciază că acesta respectă cerinţele[1] de Bună Practică de fabricaţie la care se face referire în Acordul de Recunoaştere Mutuală între Comunitatea Europeană şi *[Partenerul ARM]/* Principiile şi ghidurile pentru Buna Practică de Fabricaţie stabilite în Directiva 2003/94/CE[2]/Principiile BPF pentru substanţe active[2] la care se face referire în art. 47 al Directivei 2001/83/EC.*

*From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ...../...../..... [date], it is considered that it complies with the Good Manufacturing Practice requirements[1] referred to in the Agreement of Mutual Recognition between the European Community and [MRA partner]/The principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC[2]/The principles of GMP for active substances[2] referred to in Article 47 of Directive 2001/83/EC.**

Acest certificat reflectă statutul locului de fabricaţie la data inspecţiei menţionată mai sus şi nu mai poate fi luat în consideraţie dacă de la data acestei inspecţii au trecut mai mult de trei ani; după această perioadă trebuie consultată autoritatea emitentă.

Autenticitatea acestui certificat poate fi verificată la autoritatea emitentă.

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection, after which time the issuing authority should be consulted.

The authenticity of this certificate may be verified with the issuing authority.

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[1] Certificatul la care se face referire în paragraful 111(5) la Directivei 2001/83/EC consolidată, este de asemenea necesar şi pentru importurile din ţări terţe într-un Stat Membru.

[1] *The certificate referred to in paragraph 111(5) of Directive 2001/83/EC and 80(5) of Directive 2001/82/EC, as amended, shall also be required for imports coming from third countries into a Member State.*

[2] Aceste cerinţe îndeplinesc recomandările de bună practică de fabricaţie ale Organizaţiei Mondiale a Sănătăţii.

[2] *These requirements meet the GMP recommendations of WHO.*

Partea a 2-a
Part 2

□ Medicamente de uz uman* *Human Medicinal Products*)* □ Medicamente de uz uman pentru investigaţie clinică* pentru studii clinice faza I, II, III* *Human Investigational Medicinal Products*) for phase I, II, III clinical trials*)*
1. OPERAŢII DE FABRICAŢIE*) ***1. MANUFACTURING OPERATIONS*)*** - operaţiile de fabricaţie autorizate includ fabricaţia totală şi parţială (inclusiv diferite procese de divizare, ambalare sau prezentare), eliberarea şi certificarea seriei, importul, depozitarea şi distribuţia formelor dozate menţionate; *- authorised manufacturing operations include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, storage and distribution of specified dosage forms unless informed to the contrary;* - testele pentru controlul calităţii şi/sau activităţile de eliberare şi certificare a seriei, atunci când nu există operaţii de fabricaţie, trebuie menţionate la articolele respective; *- quality control testing and/or release and batch certification activities without manufacturing operations should be specified under the relevant items;* - în cazul în care compania este implicată în fabricaţia produselor pentru care există cerinţe speciale (de ex. produse radiofarmaceutice sau medicamente conţinând peniciline, sulfonamide, citotoxice, cefalosporine, substanţe cu acţiune hormonală sau ingrediente active potenţial periculoase), aceasta trebuie menţionată la tipul de produs şi forma dozată respective. *- if the company is engaged in manufacture of products with special requirements e.g. radiopharmaceuticals or products containing penicillin, sulphonamides, cytotoxics, cephalosporins, substances with hormonal activity or other or potentially hazardous active ingredients this should be stated under the relevant product type and dosage form.*

1.1	**Produse sterile** ***Sterile Products***
	1.1.1. *Preparate aseptic (lista formelor dozate*) *Aseptically prepared (list of dosage forms)* 1.1.1.1. Lichide volume mari *Large volume liquids* 1.1.1.2. Liofilizate *Lyophilisates* 1.1.1.3. Semisolide *Semi-solids* 1.1.1.4. Lichide volume mici *Small volume liquids* 1.1.1.5. Solide şi implanturi *Solids and implants* 1.1.1.6. Alte produse preparate aseptic <se va completa>

	Other aseptically prepared products <free text>
	1.1.2. *Sterilizate final (lista formelor dozate*) *Terminally sterilised (list of dosage forms)* 1.1.2.1. Lichide volume mari *Large volume liquids* 1.1.2.2. Semisolide *Semi-solids* 1.1.2.3. Lichide volume mici *Small volume liquids* 1.1.2.4. Solide şi implanturi *Solids and implants* 1.1.2.5. Alte produse sterilizate final <se va completa> *Other terminally sterilised prepared products <free text>*
	1.1.3. Numai certificarea seriei *Batch certification only*
1.2	**Produse nesterile** ***Non-sterile products***
	1.2.1. Produse nesterile (lista formelor dozate) *Non-sterile products (list of dosage forms)* 1.2.1.1. Capsule *Capsules, hard shell* 1.2.1.2. Capsule moi *Capsules, soft shell* 1.2.1.3. Gume masticabile *Chewing gums* 1.2.1.4. Matrici impregnate *Impregnated matrices* 1.2.1.5. Lichide pentru uz extern *Liquids for external use* 1.2.1.6. Lichide pentru uz intern *Liquids for internal use* 1.2.1.7. Gaze medicinale *Medicinal gases* 1.2.1.8. Alte forme solide dozate *Other solid dosage forms* 1.2.1.9. Preparate presurizate *Pressurised preparations* 1.2.1.10. Generatoare de radionuclizi *Radionuclide generators* 1.2.1.11. Semisolide *Semi-solids* 1.2.1.12. Supozitoare *Suppositories* 1.2.1.13. Comprimate *Tablets* 1.2.1.14. Sisteme terapeutice transdermice *Transdermal patches*

	1.2.1.15. Alte medicamente nesterile, neincluse în altă parte <se va completa> *1.2.1.15. Other non-sterile medicinal product <free text>*
	1.2.2. Numai certificarea seriei *Batch certification only*
1.3	**Medicamente biologice** ***Biological medicinal products***
	1.3.1. Medicamente biologice *Biological medicinal products* 1.3.1.1. Produse din sânge *Blood products* 1.3.1.2. Produse imunologice *Immunological products* 1.3.1.3. Produse pentru terapia celulară *Cell therapy products* 1.3.1.4. Produse pentru terapia genică *Gene therapy products* 1.3.1.5. Produse obţinute prin biotehnologie *Biotechnology products* 1.3.1.6. Produse extrase din ţesuturi umane sau animale *Human or animal extracted products* 1.3.1.7. Alte medicamente biologice <se va completa> *Other biological medicinal products <free text>*
	1.3.2. Numai certificarea seriei (lista tipurilor de produse) *Batch certification only (list of product types*) 1.3.2.1. Produse din sânge *Blood products* 1.3.2.2. Produse imunologice *Immunological products* 1.3.2.3. Produse pentru terapia celulară *Cell therapy products* 1.3.2.4. Produse pentru terapia genică *Gene therapy products* 1.3.2.5. Produse obţinute prin biotehnologie *Biotechnology products* 1.3.2.6. Produse extrase din ţesuturi umane sau animale *Human or animal extracted products* 1.3.2.7. Alte medicamente biologice <se va completa> *Other biological medicinal products <free text>*
1.4	**Alte produse sau activităţi de fabricaţie** (orice altă activitate de fabricaţie/tip de produs relevante care nu sunt incluse mai sus, de ex. sterilizarea substanţelor active, fabricaţia materiilor prime biologice active, gaze medicinale, produse din plante sau homeopate, fabricaţie totală sau parţială etc.) ***Other products or manufacturing activity*** *(any other relevant manufacturing activity/product type that is not covered above e.g. sterilisation of active substances, manufacture of biological active starting*

	materials (when required by national legislation), medicinal gases, herbal or homeopathic products, bulk or total manufacturing etc).
	1.4.1. Fabricaţie: *Manufacture of*: 1.4.1.1. Produse din plante *Herbal products* 1.4.1.2. Produse homeopate *Homoeopathic products* 1.4.1.3. Materii prime biologice active *Biological active starting materials* 1.4.1.4. Altele <se va completa> *Other <free text>* *1.4.2. Sterilizarea substanţelor active/excipienţilor/produselor finite* *Sterilisation of active substances/excipients/finished product:* 1.4.2.1. prin filtrare *Filtration* 1.4.2.2. cu căldură uscată *Dry heat* 1.4.2.3. cu căldură umedă *Moist heat* 1.4.2.4. chimică *Chemical* 1.4.2.5. cu radiaţii Gamma *Gamma irradiation* 1.4.2.6. prin bombardare cu electroni *Electron beam* *1.4.3. Altele <se va completa>* *Other <free text>*
1.5	**Numai ambalare** ***Packaging only***
	1.5.1. Ambalare primară *Primary packing* 1.5.1.1. Capsule *Capsules, hard shell* 1.5.1.2. Capsule moi *Capsules, soft shell* 1.5.1.3. Gume masticabile *Chewing gums* 1.5.1.4. Matrici impregnate *Impregnated matrices* 1.5.1.5. Lichide pentru uz extern *Liquids for external use* 1.5.1.6. Lichide pentru uz intern *Liquids for internal use* 1.5.1.7. Gaze medicinale *Medicinal gases* 1.5.1.8. Alte forme solide dozate *Other solid dosage forms*

	1.5.1.9. Preparate presurizate *Pressurised preparations* 1.5.1.10. Generatoare de radionuclizi *Radionuclide generators* 1.5.1.11. Semisolide *Semi-solids* 1.5.1.12. Supozitoare *Suppositories* 1.5.1.13. Comprimate *Tablets* 1.5.1.14. Sisteme terapeutice transdermice *Transdermal patches* 1.5.1.15. Alte medicamente nesterile <se va completa> *Other non-sterile medicinal products <free text>*
	1.5.2. Ambalare secundară *Secondary packing*
1.6	**Teste pentru controlul calităţii** ***Quality control testing***
	1.6.1. Microbiologice: sterilitate *Microbiological: sterility* 1.6.2. Microbiologice: fără testul de sterilitate *Microbiological: non-sterility* 1.6.3. Fizico-chimice *Chemical/Physical* 1.6.4. Biologice *Biological*
2. IMPORTUL MEDICAMENTELOR*) ***IMPORTATION OF MEDICINAL PRODUCTS*)*** - activităţi de import fără activitate de fabricaţie - *importation activities without manufacturing activity* - activităţile de import includ depozitarea şi distribuţia cu excepţia situaţiei în care sunt informaţii contrare - *importation activities include storage and distribution unless informed to the contrary*	
2.1	**Teste pentru controlul calităţii medicamentelor importate** ***Quality control testing of imported medicinal products***
	2.1.1. Microbiologice: sterilitate *Microbiological: sterility* 2.1.2. Microbiologice: fără testul de sterilitate *Microbiological: non-sterility* 2.1.3. Fizico-chimice *Chemical/Physical* 2.1.4. Biologice *Biological*
2.2	**Certificarea seriei medicamentelor importate** ***Batch certification of imported medicinal products***
	2.2.1. Produse sterile *Sterile Products*

	2.2.1.1. preparate aseptic *Aseptically prepared* 2.2.1.2. sterilizate final *Terminally sterilised* *2.2.2. Produse nesterile* *Non-sterile products*
	2.2.3. Medicamente biologice *Biological medicinal products* 2.2.3.1. Produse din sânge *Blood products* 2.2.3.2. Produse imunologice *Immunological products* 2.2.3.3. Produse pentru terapia celulară *Cell therapy products* 2.2.3.4. Produse pentru terapia genică *Gene therapy products* 2.2.3.5. Produse obţinute prin biotehnologie . *Biotechnology products* *2.2.3.6. Produse extrase din ţesuturi umane sau animale* *Human or animal extracted products* 2.2.3.7. Alte medicamente biologice <se va completa> *Other biological medicinal products <free text >*
	2.2.4. Alte activităţi de import (orice altă activitate de import relevantă care nu este inclusă mai sus, de ex. importul produselor radiofarmaceutice, gazelor medicinale, produselor din plante sau homeopate etc.) *Other importation activities (any other relevant importation activity that is not covered above e.g. importation of radiopharmaceuticals, medicinal gases, herbal or homeopathic products etc.)* 2.2.4.1. Radiofarmaceutice *Radiopharmaceuticals* 2.2.4.2. Gaze medicinale *Medicinal gases* 2.2.4.3. Produse din plante *Herbal products* 2.2.4.4. Produse homeopate *Homoeopathic products* 2.2.4.5. Materii prime biologice active *Biological active starting materials* 2.2.4.6. Altele <se va completa> *Other <free text>*

Fabricaţia substanţelor active. Numele substanţelor care au făcut obiectul inspecţiei*):
Manufacture of active substance. Names of substances subject to inspection:*

.....
.....

Orice restricţii sau observaţii care să clarifice domeniul acoperit de acest certificat*):
Any restrictions or clarifying remarks related to the scope of this certificate:*

.....
….....

....../..../.... [*data*]
[*date*]

Numele, titlul şi semnătura persoanei autorizate din Agenţia Naţională a Medicamentului din România[3]
Name and signature of the authorised person of the National Medicines Agency from Romania[3]

.....
[*autoritatea naţională, numerele de telefon şi fax*]
[*name, title, national authority,phone & fax numbers*]

(*): se va şterge ceea ce nu este aplicabil.
(*): delete that which does not apply.

Notă: versiunea în limba engleză este versiunea de referinţă.

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[3] Semnătura, data şi detaliile de contact trebuie să apară pe fiecare pagină a certificatului.
[3] The signature, date and contact details should appear on each page of the certificate.

ANNEX VIII
on Regulations

To

NATIONAL MEDICINES AGENCY

Pharmaceutical Inspection Department

The ....., established in …....., Address …....., Telephone/Fax number ....., registered with the Registry of Commerce under....., fiscal code....., represented by ....., position …….

(name and surname)

....., in line with Article 14 of Order of the Minister of Health for approval of Regulations on manufacturing/importation authorisation of manufacturers and importers of medicinal products for human use, investigational medicinal products included, and granting of good manufacturing certificate for manufacturers of medicinal products/active substances, hereby applies for grant of a new manufacturing / import authorisation.

We hereby attach the proof of notification on loss of independent control unit authorisation in .....

(name of the newspaper)

Signature, stamp

…….

ANNEX IX
on Regulations

COMMITMENT

The …….....…, established in ……, Address
…….....,
represented by …….....…, position …… ……..., hereby commits itself to submit information required under Annex X to Regulations for each import.

Signature, stamp
.....

ANNEX X
on Regulations

INFORMATION ON IMPORT

NOTICE: Information required in this Annex is to be submitted to the National Medicines Agency – The Pharmaceutical Inspection Department, by importers only. The data should be sent as a table, immediately upon each import.

The table obligatorily consists of 14 columns, filled in as follows:

1. No.
2. Product
3. INN
4. Pharmaceutical form
5. Strength
6. Package type
7. On prescription/Over the counter
8. Marketing authorisation holder
9. Manufacturer
10. Country of origin
11. Batch(es)
12. Importing data
13. Imported amount
14. Notes