Ministry of Health

ORDER no. 775
of 20 May 2019
on registration of manufacturers, importers and distributors of active substances which shall be used as raw materials for medicinal products for human use

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On seeing Approval Report no. SP 6.271 of 16.05.2019 of the Medicinal Product and Medical Devices Policy Directorate of the Ministry of Health and Letter of the National Agency for Medicines and Medical Devices no. 49.081E of 26.02.2019, registered with the Ministry of Health under no. 49.092 of 26.02.2019, in line with Art. 771 and Art. 857 (3) of Law 95/2006 on healthcare reform, as further amended and supplemented,

taking into account the provisions of Art. 4 (2) a) of Government Decision no. 734/2010 on the organisation and operation of the National Agency for Medicines and Medical Devices, as further amended and supplemented,

pursuant to Article 7 (4) of Government Decision no. 144/2010 on the organisation and operation of the Ministry of Health, as further amended and supplemented,

the minister of health hereby issues the following order:

Art. 1 - (1) Manufacturers, importers and distributors of active substances established in Romania are required to register their activity with the National Agency for Medicines and Medical Devices (***NAMMD***), in accordance with the provisions of this Order.

(2) The obligation provided for in paragraph (1) applies only to manufacturers, importers and distributors of active substances used in the manufacture of medicinal products for human use.

Art. 2 - (1) In order to register the activity, manufacturers, importers or distributors of active substances must submit to the NAMMD, at least 60 days before the expected date of commencement of the activity, the registration form, according to the template provided in Annex 1.

(2) Manufacturers, importers and distributors of active substances who, at the date of adoption of this Order, are already carrying out this activity must submit

the registration form to the NAMMD within maximum 30 days from the date of entry into force of this Order, without ceasing the activity.

(3) The registration form must be submitted even if the manufacturer/importer holds, at the date of adoption of this Order, a certificate of good manufacturing practice issued by the NAMMD for the respective activity.

Art. 3 - (1) The registration form must be accompanied by a file containing administrative and technical documents.

(2) Administrative documents provided for in paragraph (1):

a) articles of incorporation of the company (article of incorporation, status, company contract, as the case may be), in a certified copy for compliance;

b) conclusion/resolution for authorisation and registration of the company, in a certified copy for compliance;

c) registration certificate issued by the National Trade Register Office, with its annexes, in a certified copy for compliance;

d) certificate of establishment issued no later than 30 days prior to submission of the application, in original;

e) proof of ownership of the company's premises, in a certified copy for compliance;

f) service agreement with a warehouse of active substances authorised for wholesale distribution, in the case of importers who do not have their own storage facilities, in a certified copy.

(3) Technical documents provided for in paragraph (1):

a) the list of active substances manufactured, imported, distributed; in the case of importers and distributors of active substances, the list shall include the identification data of the manufacturer of each active substance;

b) in the case of manufacturers and importers, the standard file, drawn up for each manufacturing/import site in accordance with the Guide for drawing up the standard file for the manufacturing site, which is an integral part of the Good Manufacturing Practice Guideline in force. Importers draw up the standard file for each import site, taking into account the specifics of the import activity;

c) in the case of active substance distributors, the standard file of the unit, according to Order of the Minister of Health no. 131 on approval of Rules on authorisation of human medicinal product wholesalers, Good Distribution Practice certification and registration of brokers of medicinal products for human use, the certification of good distribution practice and the registration of brokers of medicinal products for human use, as further amended and supplemented.

Art. 4 - (1) If the submitted documentation is not compliant with the provisions of Art. 3 paragraphs (2) and (3), within 15 days from registration of the form, the NAMMD requests the manufacturer, importer or distributor of

active substances to complete the documentation.

(2) If the file accompanying the registration form is complete, the NAMMD, based on a risk assessment, may decide to carry out an inspection before the applicant starts their activity; in this case, the applicant shall be notified within 60 days of receipt of the registration form of the date on which the inspection is to take place.

(3) If the inspection report contains a favourable conclusion regarding compliance with good manufacturing/distribution practice, according to the template provided in Annex 2 to this Order, according to the European format approved by the European Commission, the NAMMD shall inform the applicant of its agreement to begin the activity.

(4) If the NAMMD does not notify the applicant, within 60 days of receiving the registration form and the complete file provided for in Article 3, that it will carry out an inspection, the applicant may begin the activity.

(5) After beginning the activity, the NAMMD may inspect the facilities of the manufacturer/importer/distributor of active substances, at any time.

Art. 5 - In order to carry out an inspection at the site of the manufacturer, importer or distributor of active substances, the NAMMD requests payment of the inspection fee, approved through Order of the Minister of Health No. 888/2014 on approval of fees payable to the National Agency for Medicines and Medical Devices for services related to medicinal products for human use, as further amended and supplemented.

Art. 6 - (1) The inspection is carried out in accordance with an inspection plan drawn up by the designated inspector(s) within the NAMMD, which is sent to the requesting unit at least 3 days before the inspection date.

(2) Except in justified situations, the inspection takes place within 10 days of confirmation of payment, on a date to be established in agreement with the manufacturer, importer or distributor of active substances.

Art. 7 - (1) In the case of active substance manufacturers, the inspection aims to ensure compliance with the Good Manufacturing Practice principles and guidelines for active substances adopted by the European Commission, as well as compliance with the Guide to Good Manufacturing Practice for Medicinal Products - Part II.

(2) In the case of importers and distributors of active substances, the inspection aims to ensure compliance with the Guide on the principles of Good Distribution Practice for active substances of medicinal products for human use, approved through Order of the Minister of Health No. 634/2017, and the specific chapters of the Guide to Good Manufacturing Practice for Medicinal Products - Part II.

Art. 8 - (1) Within maximum 20 days from the date of the inspection, the NAMMD shall send the unit the list of detected deficiencies or the inspection

report, as the case may be.

(2) In the case of a list of detected deficiencies, the inspected unit is obliged to send the proposed corrective and preventive measures plan within a maximum of 15 days.

(3) If the proposed corrective/preventive measures are not sufficient in order to correct the detected deficiencies, a single request to complete/re-create the plan may be sent to the inspected unit, before the final inspection report is drawn up.

(2) If the inspected unit does not submit the corrective/preventive measures plan within a maximum period of 15 days, this period may be extended once, for a similar period, at the request of the applicant. If the inspected unit does not submit the corrective/preventive measures plan within the established period, the inspector(s) who carried out the inspection shall draw up an unfavourable inspection report.

(3) In the event of an unfavourable inspection report stating non-compliance with Good Manufacturing/Distribution Practice for active substances, after resolution of the detected deficiencies by NAMMD inspectors, the inspected unit may request a new inspection.

Art. 9 - Manufacturers, importers and distributors of active pharmaceutical ingredients shall annually submit to the NAMMD a list of changes that have occurred with regard to the information provided in the registration form; any change which could have a potential impact on the quality/safety of manufactured, imported or distributed active ingredients must be notified immediately.

Art. 10 - The NAMMD enters information about importers, manufacturers and wholesale distributors of active pharmaceutical ingredients registered into the European Union database referred to in Art. 857 paragraphs (14) and (15) of Law 95/2006 on healthcare reform, as further amended and supplemented.

Art. 11 – Annexes 1 and 2 are integral parts of this Order.

Art. 12 - This Order shall be published in the Official Gazette of Romania, Part I.

Minister of health,

Sorina Pintea

Annex 1[1])

[1]) Annex 1 is reproduced in facsimile.

Application form for registration of the manufacturer, importer or distributor of active substances to be used as starting materials for medicinal products for human use

***)**

(Please fill in all relevant sections of this form in large, legible letters, using black ink.)

*) Please erase, as appropriate.

Section 1: Administrative data	
1.1 Applicant details	
Company name:	
Applicant name:	
Address:	
Postal code:	Telephone number:
Mobile phone number:	Fax number:
E-mail address	

Is the request made on behalf of the applicant? (e.g. if you are a consultant/representative). If YES, please fill in Section 1.2

|¯| Yes |¯| No

1.2 Contact information (if different from above)

Contact name:

Company name:

Address:

Postal code:

Telephone number:

Mobile phone number:

Fax number:

E-mail address

1.3 Information regarding the invoice sending address (if different from the applicant's)

Contact name:

Company name:

Address:

Postal code: Telephone number:

Mobile phone number: Fax number:

E-mail address

Name of the manufacturing/import/distribution site

Postal code:

Section 2: Information on the manufacturing/import/distribution site*)

2.1 Details on the manufacturing/import/distribution site*)

Sections 2 and 3 must be filled in for each full/partial manufacturing, import or distribution site you wish to register.

Name of the manufacturing/import/distribution site*):

Address:

Postal code:

Contact name

Telephone number: Fax number:

Mobile phone number:

E-mail address

*) Please erase, as appropriate.

2.2 Types of activities carried out at the manufacturing/import/distribution site	
Manufacture of active substances through chemical synthesis	☐
Extraction of active substances from natural sources	☐
Manufacture of active substances through biological processes	☐
Manufacture of sterile active substances	☐
General steps for manufacturing active substances (physical processing, Primary packaging, secondary packaging)	☐
Quality control tests for active substances	☐
Import of active substances	☐
Distribution of active substances	☐
Others, please specify:	☐

Name of manufacturing/import/distribution site		Postal code:	

Section 3: Activities performed

Part 1 MANUFACTURING ACTIVITIES

- Manufacturing operations include total and partial manufacturing (including various division, packaging or presentation processes)
- Please fill in separately for each category of active substances

1. MANUFACTURING ACTIVITIES Active substance(s):	Manufacturing activities, please check
Manufacture of active substances through chemical synthesis	
1. Manufacture of active substance intermediates ***2. Manufacture of raw active substances*** ***3. Salt formation / Purification steps: <free text> (e.g. crystallisation)***	

4. Other <please fill in>	
Extraction of active substances from natural sources	
1. Extraction of substances from plant sources *2. Extraction of substances from animal sources* *3. Extraction of substances from human sources* *4. Extraction of substances from mineral sources* *5. Modification of extracted substances <please specify source 1, 2, 3 or 4>* *6. Modification of purified substances <please specify source 1, 2, 3 or 4>* *7. Other <please fill in>*	
Manufacture of active substances using biological processes	
1. Fermentation *2. Cell Culture <specify cell type> (e.g. mammalian/bacterial)* *3. Isolation/purification*	

4. Modification ***5. Other <please fill in>***	
Manufacture of sterile active substances	
1. Aseptically prepared ***2. Terminally sterilised***	
General finishing steps	
1. Physical processing steps < specify > (e.g. drying, milling / micronisation, sieving) ***2. Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)*** ***3. Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)*** ***4. Other (for activities which are not described above)***	
Quality control testing ***This section should only be filled in if any part of the sections has been***	
1. Physical / Chemical testing ***2. Microbiological testing (excluding sterility testing)*** ***3. Microbiological testing (including sterility testing)*** ***4. Biological testing***	

Name of the manufacturing/import/distribution site

Postal code:

Part 2 - IMPORT OR DISTRIBUTION OF ACTIVE SUBSTANCES

- Import or distribution activities which do not involve the manufacturing activity.
- Import activities include storage and distribution, unless otherwise stated.

2. IMPORT AND DISTRIBUTION ACTIVITIES	
A	**Import**

	(all imported active substances shall be listed, together with relevant details of manufacturers and, where applicable, distributors)		
	Active substance	***Manufacturer from the third country***	***Distributor (name and address)***
B	**Distribution**		
	Active substance(s) ***(Please list all active substances subject to distribution)***		

OTHER INFORMATION

Are the sites ready for inspection? |¯| ***yes*** |¯| ***no***

Are you familiar with the Principles of Good Manufacturing Practice/Good Wholesale Distribution and the Guideline on Good Manufacturing Practice/Good Wholesale Distribution Practice and do you have the relevant procedures and records available?

|¯| ***yes*** |¯| ***no***

If applicable, are the contracts you own available for inspection?

|¯| ***yes*** |¯| ***no***

Section 4. Assigned persons

Please state below the categories of staff working at the manufacturing site

Staff	**Name**	**Qualification**
Person responsible for the release of active substance batches		
Person responsible for the manufacturing process		
Person responsible for quality control		

Please state below the categories of staff working at the import/distribution site

Staff	**Name**	**Qualification**
Responsible person		

Section 5. Comments

Please provide any other information which may support your request. You may also detail any changes to addresses, assigned persons, etc.

Section 6. Declaration

I hereby request the registration of the manufacturer/importer/wholesale distributor named in the application form, for the activities to which the request refers.

6.1 The activities shall comply with the information in the application or submitted in connection with it.

6.2 To the best of my knowledge and belief, the details in the application are correct and complete.

Signature (of the applicant):

_____ Date: _____

Name in clear script: _____

Please specify your status as signatory:

Annex 2

Template of the agreement on registration of manufacturers, importers and distributors of active substances which shall be used as raw materials for medicinal products for human use

AGREEMENT
registration of manufacturers, importers and distributors of active substances which shall be used as raw materials for medicinal products for human use

1. Registration number
2. Name of registered unit
3. Permanent or legal address of the registered unit
4. Address(es) of the site(s) where the registered activities are carried out (All authorised places must be listed, unless subject to a separate registration.)
5. Legal basis for registration
6. Name of the responsible person of the National Agency for Medicines and Medical Devices (the competent authority of Romania which validates the registration)
7. Signature
8. Date

This registration agreement is only valid if all its pages are presented. The authenticity of this registration agreement can be verified in the European Union database or with the authority who validated it.

The registered entity referred to in Section 2 must communicate on a yearly basis to the National Agency for Medicines and Medical Devices a list of all changes which have occurred regarding the information provided in the registration form. Any changes which may have an impact on the quality or safety of the listed active substances must be notified immediately.

Scope of registration

Name and address of the site:

1.MANUFACTURING OPERATIONS Active substance(s):	
A	Manufacture of active substances through chemical synthesis
	1. Manufacture of active substance intermediates 2. Manufacture of raw active substances 3. Salt formation / Purification steps: <free text> (e.g. crystallisation) 4. Other <please fill in>
B	Extraction of active substances from natural sources
	1. Extraction of substances from plant sources 2. Extraction of substances from animal sources 3. Extraction of substances from human sources 4. Extraction of substances from mineral sources 5. Modification of extracted substances <please specify source 1, 2, 3 or 4> 6. Modification of purified substances < please specify source 1, 2, 3 or 4> 7. Other <please fill in>
C	Manufacture of active substances through biological processes
	1. Fermentation 2. Cell Culture <specify cell type> (e.g. mammalian/bacterial) 3. Isolation/Purification 4. Modification 5. Other <please fill in>
D	Manufacture of sterile active substances (sections A, B & C to be completed as appropriate)
	1. Preparate aseptic 2. Terminally sterilised
E	General finishing steps
	1. Physical processing steps (e.g. drying, milling / micronisation, sieving) 2. Primary packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance) 3. Secondary packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance) 4. Other (for activities which are not described above)
F	Quality control tests
	This section should only be filled in if any part of sections A, B, C, D, E has been filled

	in 1. Physical / Chemical testing 2. Microbiological testing (excluding sterility testing) 3. Microbiological testing (including sterility testing) 4. Biological testing		
2. Import and distribution activities			
A	Import (All imported active substances shall be listed, together with relevant details of manufacturers and, where applicable, distributors.)		
	Active substance	Manufacturer from the third country (name and address)	Distributor (name and address)
B	Distribution		
	Active substance(s) (Please list all active substances subject to distribution.)		

Any restrictions or observations clarifying the scope of these registered operations:

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Name of the responsible person from the National Agency for Medicines and Medical Devices who validates the registration .....

Signature

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