

Guide to New applications and variations to Manufacturer's Authorisations



CONTENTS

CONTENTS	2
INTRODUCTION	3
ANNEXES OF THE EU FORMAT FOR A MANUFACTURER'S AUTHORISATION	4
TYPE OF AUTHORISATION REQUIRED	5
VARIATIONS TO A MANUFACTURER'S AUTHORISATION	5
APPLICANT DETAILS	6
ANNEX 1 AND 2 MANUFACTURING AND IMPORTATION OPERATIONS	8
ANNEX 3 CONTRACT MANUFACTURER(S)	20
ANNEX 4 CONTRACT LABORATORY	28
ANNEX 5 QUALIFIED PERSON(S)	31
ANNEX 6 PERSONNEL FOR PRODUCTION OPERATIONS AND QUALITY CONTROL	32
ANNEX 7 (OPTIONAL) – NOT USED BY THE HPRA	34
ANNEX 8 IMPORTATION OF PRODUCTS WHICH ARE CONTRACT MANUFACTURED AT A SITE OUTSIDE THE EEA	34
CONTACT DETAILS	36

INTRODUCTION

This document provides guidance on applying to the HPRA for a new manufacturer's authorisation^{1,2} or to vary an existing ~~manufacturing-manufacturer's~~ authorisation. This guide should be read in conjunction with the relevant application forms (AUT-F0200 Application for a manufacturer's or importer's authorisation, AUT-F0211 Application for variation to a manufacturer's authorisation, AUT-F0791 IMP expedited assessment of variations to Annex 3 and/or 4 application form or AUT-F0819 IMP immediate notification of variations to Annex 3 and/or 4 application form). The authorisation will be formatted into the agreed EU format included in the Compilation of Community Procedures on Inspections and Exchange of Information published by the European Medicines Agency on behalf of the European Commission.

The [Union Format for a Manufacturer's Authorisation](#) and guidance from the associated interpretation document on this format have been used as the general basis for this guidance.

The guidance applies to human and veterinary medicinal products (Annex 1) and also to IMPs (Annex 2). The headings in Annex 2 are not included in this document but any specific guidance which applies to investigational medicinal products (IMPs) only is identified where necessary. Clarifying remarks are often important in helping to define the scope of a manufacturer's authorisation and are cross-referenced to the numbered items within the manufacturer's authorisation format as applicable.

The sections of the manufacturer's authorisation which deal with the manufacturing and quality control activities conducted at the site are similar to the equivalent information presented in part 2 of the GMP certificates which the HPRA has issued for the site.

Please note that headings in green font relate to new applications and headings in blue font relate to variations.

¹ The authorisation referred to in paragraph 40(1) of Directive 2001/83/EC and 44(1) of Directive 2001/82/EC is also required for imports coming from third countries into a Member State.

² Guidance on the interpretation of this template can be found on www.hpra.ie and in the Help menu of [the](#) EudraGMP database.

ANNEXES OF THE EU FORMAT FOR A MANUFACTURER'S AUTHORISATION

Annex no.	Annex title	Notes
Annex 1	Scope of authorisation relating to medicinal products for human use or veterinary use	This describes manufacturing-/importation-/testing operations which are carried out directly under this authorisation only. Contracted manufacturing/storage or testing operations are described in Annexes 3 and 4 respectively.
Annex 2	Scope of authorisation relating to investigational medicinal products	This annex describes manufacturing-/importation-/testing operations which are carried out directly under this authorisation only. Contracted manufacturing/storage or testing activities are described in Annexes 3 and 4 respectively. (Annex 2 uses the same headings for manufacture, importation and testing activities and for this reason it is not reproduced as a separate section in this guidance document.)
Annex 3	Names and addresses of contract manufacturing site(s) and the activities carried out at those sites	This includes other activities related to manufacturing such as contract storage sites. This information is not published on the EudraGMDP database.
Annex 4	Names and addresses of contract laboratories and the testing activities carried out at those sites	This information is not published on the EudraGMDP database.
Annex 5	Name(s) of Qualified Person(s)	This information is not published on the EudraGMDP database.
Annex 6	Names of key personnel responsible for production operations and quality control	This information is not published on the EudraGMDP database.
Annex 7	Date of inspection on which authorisation granted, scope of last inspection	This optional a Annex within the EU format for a manufacturer's authorisation is not currently used by the HPRA. A description of the annex number/title is referenced here merely for completeness.
Annex 8	Importation of products which are contract manufactured at a site outside the EEA	This information is not published on the EudraGMDP database.

TYPE OF AUTHORISATION REQUIRED

There are three types of authorisation:

- Manufacturer's authorisation for medicinal products for human use
- Manufacturer's authorisation for investigational medicinal products for human use
- Manufacturer's authorisation for medicinal products for veterinary use

A separate application is required for each type of authorisation.

VARIATIONS TO A MANUFACTURER'S AUTHORISATION

There are three processes that can be used to vary a manufacturer's authorisation. Details of the variation type, timeline and scope of each process is provided in the table below. In order to vary a manufacturer's authorisation applicants must submit a completed application form, the required supporting documentation as detailed in this guide, and the appropriate fee.

Variation type	Timeline	Scope	Application form reference
Standard variation process	30- 90 days ³	Applies to all variation types for human medicines, veterinary medicines and IMP manufacturer's authorisations. -Timeline is dependent on the type of variation and is specified throughout the guide.	AUT-F0211
IMP expedited assessment of variations to Annex 3 and/or 4	7 working days	Applicable to third country based contract manufacturing sites and contract laboratories (Annex 3 and 4) of IMP authorisations. Assessment timeline is 7 working days; however, the timeline is contingent on the appropriate supporting documentation. Note that this is an optional process as the standard variation process can be applied if an expedited assessment is not required.	AUT-F0791
IMP immediate notification of	n/a	Applicable to EU/EEA based contract manufacturing sites and contract laboratories (Annex 3 and 4) of IMP authorisations only. Manufacturer's	AUT-F0819

³ The timeline for technical variations can vary from 30 to 90 days depending on whether additional information is requested by the HPRA and if an inspection is required.

Variation type	Timeline	Scope	Application form reference
variations to Annex 3 and/or 4		authorisation holders can commence proposed activities immediately after submission of the variation application. Additionally, all variations are subject to administrative variation fees. Note that this is an optional process as the standard variation process can be applied if required.	

APPLICANT DETAILS

The manufacturer should provide appropriate documentation as evidence of the authorisation holder's legally registered address (e.g. Certificate of Incorporation from the Companies Registration Office). This address may differ from the address where manufacturing activities take place.

A business name (also known as a trading style) is where the name used to carry on business by any individual, body corporate or partnership (whether of individuals and/or bodies corporate), at a place of business in the Republic of Ireland is not the same as their company registered name(s). Evidence of registration of the business name with the Companies Registration Office should also be provided.

Guidance on addresses

- If the manufacturing site consists of a number of separate units located in an industrial estate which are managed under the same pharmaceutical quality system and under the responsibility of the same key personnel named on this application, then include the main contact address for the manufacturing site.
 - o Provide details of other 'units' which will operate under the scope of this authorisation below the main contact address.
 - o In the event that this application is successful then a single manufacturer's authorisation and one GMP certificate referencing all the units will be issued on the EudraGMDP database.
- If the manufacturing activities are carried out at addresses which are not adjacent or in close proximity, then a separate 'Scope of authorisation' section must be completed for each address.
 - o All of the manufacturing activities must be under the same pharmaceutical quality system and under the responsibility of the same key personnel for these separate addresses to be considered under a single manufacturer's authorisation application. In the event that this application is successful then a single manufacturer's authorisation, which includes details of the activities at each separate address, will be issued on EudraGMDP and a separate GMP certificate will be issued on EudraGMDP for each manufacturing address.

- The Eircode is required on all new applications for a manufacturer's authorisation and on completion of a successful application will be included on the GMP certificate.
 - o The addition of the Eircode on existing manufacturer's authorisations does not, in itself, represent a change in the physical location of the manufacturing site regulated by the HPRA. The HPRA is happy to clarify address details for manufacturers located in Ireland directly with other regulatory authorities outside the European Union as necessary.

Variations to applicant details

Variation	Variation type and timeline	Supporting documentation
Minor corrections of typographical errors to authorisation	Admin timeline: 30 days	Submit a signed variation application form outlining the nature of the typographical error. State the endorsement number and variation reference number where this error occurred.
Change in the name of authorisation holder ⁴	Admin timeline: 30 days	Submit a Certificate of Incorporation. Submit a statement from a Qualified Person (QP) named on the authorisation outlining any implications that this change may have on the quality management system or its operation at the site. The HPRA reserves the right to perform an inspection at the site if considered necessary.
Change in the legally registered address of the authorisation holder	Admin timeline: 30 days	Submit a Certificate of Incorporation.
Change in the main address of the manufacturing site Or Addition of new manufacturing site to a manufacturer's authorisation	Technical timeline: 90 days	Submit an updated revision of the site master file including the new manufacturing address. Notes: If the company is not relocating to a different premises and the address of the current site is being updated, the QP must submit a declaration. An inspection may also take place as part of the assessment of such a variation.

ANNEX 1 AND 2 MANUFACTURING AND IMPORTATION OPERATIONS

⁴ When a change to the name of the authorisation holder (MAH) is a result of a proposed transfer to another MAH please refer to 'Guide to Transfers of Marketing Authorisations, Parallel Import Licences and Dual Pack Import Registrations for Human Medicines' available on www.hpra.ie.

The information in this section of the form is relevant to Annex 1 or Annex 2 and will be designated in the final authorisation document depending on the type of authorisation selected in the previous step.

Part 1 Manufacturing operations

The scope of manufacturing operations which are authorised at the site is defined using the unit operations listed below. Each of the individual operations carried out by the authorisation holder is identified on the manufacturer's authorisation, as appropriate.

Processing operations ¹	This includes any or all processing steps in the manufacture of a dosage form.
Primary packing ¹	Refers to placing and sealing of the medicinal product within the finished product packaging material which is in direct contact with the product.
Secondary packing ¹	Refers to placing the medicinal product, which is already sealed within its primary packaging material, within an outer packaging material. This also includes labelling operations or the assembly of other components which are specified in the marketing authorisation (or product specification file in the case of an IMP) to form the finished product pack.
Batch certification ¹	Refers to the certification of a finished product batch of medicinal product by a QP before its release into the market place or before a batch is exported. For an IMP , this refers to the QP certification of the batch of IMP before release to the clinical trial sponsor or before export.
Quality control ¹	Refers to types of laboratory testing which the manufacturer's authorisation holder is authorised to perform.
Storage	Any site which holds a manufacturer's authorisation and carries out processing operations or packaging of medicinal products is also understood to be authorised for storage. If a site is carrying out other manufacturing operations where storage is not automatically understood to be included, as described above, then use section 1.4.3 <Other> to identify storage activity.
Distribution ²	Any site which holds a manufacturer's authorisation and which carries out manufacturing operations on batches of medicinal products is also authorised to distribute those batches of medicinal products unless there is a comment to the contrary in the clarifying remarks. Distribution activities related to post QP batch certification by another

	manufacturing authorisation holder require a wholesale distribution authorisation (WDA) .
Real time release testing	If a manufacturer is authorised to carry out real time release testing instead of one or more finished product tests, then identify this as a clarifying remark in relation to the processing operations for the particular dosage form. The type of real time release testing (e.g. parametric release) which is authorised is also to be identified in the clarifying remarks. The use of real time release testing should reflect any relevant requirements described in a marketing authorisation or clinical trial application.

Notes:

¹Using the guidance described in chapters 3 and 5 of the GMP Guide, manufacturers should evaluate materials which are handled at the site with regard to the risk posed in terms of their potency, toxicity or potential for sensitisation.

- If a site is authorised to carry out processing operations or primary packing activities on substances or products which are considered to be highly sensitising, highly potent or highly toxic or have a specific hazard (e.g. radiopharmaceuticals) then this is identified in relation to the particular dosage form using the relevant items from the list below.
- Any restrictions that may apply in relation to these products (e.g. if product is to be manufactured in a dedicated facility) should be included in the clarifying remarks with reference to the relevant dosage form.
- List of specific hazards for a dosage form (as per drop down menu items from EudraGMDP):
 - o β-Lactam antibiotics
 - o Other highly sensitising materials
 - o Live cells
 - o Pathogenic Organisms (Biosafety 3 or 4)
 - o Radiopharmaceuticals
 - o Ectoparasiticides
 - o Others (Free text entry)

Examples of products to be included under 'Other' category include:

- o Highly potent products
- o Highly toxic products

² If a manufacturer has not carried out a manufacturing operation on a batch of medicinal product which it intends to distribute (including manufacture of the dosage form, packaging, or batch certification) then the site is required to hold a separate wholesale distribution authorisation (WDA) for distribution activities in relation to those batches or products.

1.1 Sterile Products

1.1.1 Aseptically prepared (processing operations for the following 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>

An example of an activity captured under 1.1.1.6 'Other':
'Manufacture of sterile active substance'.

1.1.2 Terminally sterilised (processing operations for the following dosage forms)

Where terminal sterilisation of a product is not carried out on site by the manufacturer's authorisation holder but is contracted out to another site, enter a comment such as 'terminal sterilisation by gamma irradiation is outsourced to another site' in relation to that dosage form in the clarifying remarks section.

- 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

This is understood to apply to all sterile dosage forms unless restrictions are stated in the clarifying remarks.

1.2 Non-sterile products

1.2.1 Non-sterile products (processing operations for the following 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

1.2.1.9 'Pressurised preparations' are defined as preparations presented in special containers under pressure of a gas. If, for example, a liquid aerosol is generated by mechanical pumping action rather than a propellant then such dosage forms are categorised as 'Liquids for external use' or 'Liquids for internal use', as appropriate.

A metered dose inhaler which uses a propellant to deliver the required dose is listed as a 'Pressurised preparation'. If the dose is delivered by other means e.g. breath activation, then enter processing operations relating to this dosage form under Other (1.2.1.17) 'Breath activated metered dose inhaler'.

- 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 Intraruminal devices
- 1.2.1.16 Veterinary premixes
- 1.2.1.17 Other non-sterile medicinal product <free text>

Examples of activities captured under 1.2.1.17 'Other':

- 'Manufacture of intermediates' (e.g. powders for further processing)-
- 'Overencapsulation' (this activity is usually applicable to IMPs and controls may differ from those used in filling a standard hard shell capsule product)
- 'Breath activated metered dose inhaler'

1.2.2 Batch certification

This is understood to apply to all non-sterile dosage forms unless restrictions are stated in the clarifying remarks.

1.3 Biological medicinal products

A biological medicinal product is a medicinal product, the active substance of which is a biological substance.

A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

There may be substances which are obtained from a biological source (e.g. extracted from a plant or animal source) which do not require a biological test to determine appropriate quality of the substance. Products manufactured using such substances are not generally

classified as biological medicinal products and therefore not listed under this section of the manufacturer's authorisation.

1.3.1 *Biological medicinal products*

Categorisation of biological products:

The following product categories are used to identify if a site is carrying out any processing steps relating to the manufacture of a biological product. The manufacture of the biological substance may be part of the continuum of processing steps in the manufacture of the finished biological product and these operations are captured under this section, where appropriate.

- Where the authorised operations also include manufacture of the finished dosage form for the biological product then the relevant dosage form is also selected on the manufacturer's authorisation.
 - o Example: for a company manufacturing a lyophilised finished dosage form of a biotechnology derived product the following operations are stated on the manufacturing authorisation:
 - 1.1.1.2 Lyophilisates
 - 1.3.1.5 Biotechnology products
 - Example of clarifying remark: 1.3.1.5 relates to the manufacture of a biological active substance using mammalian cell culture, its isolation/purification, formulation of a low bioburden bulk intermediate and manufacture of the finished dosage form.

1.3.1.1 Blood products

Blood products:

Select this category where there are processing operations performed in relation to biological products containing an active substance isolated from blood. Examples of such products include albumin, plasma Factor VIII or immunoglobulins which are isolated from blood. The processing of Factor VIII which is manufactured using a biotechnology method is not included in this category. For a human medicine, the steps in the manufacture of a blood product which come under a manufacturer's authorisation are those processing steps which are not covered under Directive 2002/98/EC.

1.3.1.2. Immunological products

Immunological products:

Select this category where there are processing operations carried out in relation to manufacture of biological products which have an immunological mode of action (e.g. vaccines).

1.3.1.3 Cell therapy products

Cell therapy products:

Select this category where there are processing operations carried out in relation to the manufacture of cell therapy products. The steps in the manufacture of cell therapy product which come under a manufacturer's authorisation are those steps which are not covered under Directive 2004/23/EC.

1.3.1.4 Gene therapy products

Gene therapy products:

Select this category where there are processing operations carried out in relation to the manufacture of gene therapy products. The steps in the manufacture of a gene therapy product which come under a manufacturer's authorisation are those steps which are not covered under Directive 2004/23/EC.

1.3.1.5 Biotechnology products

Biotechnology products:

Biotechnology includes the use of genetically modified mammalian cells or micro-organisms, (e.g. bacteria or yeasts), or biological substances (e.g. enzymes), in the manufacture of biological products. This category is selected where there are processing operations carried out in relation to the manufacture of biological products using biotechnology.

For steps involving the manufacture of a biological product manufactured via a biotechnology route, insert a clarifying remark relating to activities under 1.3.1.5 to specify which of the following activities apply:

- fermentation
- cell culture (specify whether mammalian/bacterial, etc.)
- isolation/purification
- modification (e.g. pegylation)
- other (specify)
- manufacture of finished dosage form

1.3.1.6 Human or animal extracted products

Human or animal extracted products:

Select this category where processing steps are carried out in relation to the manufacture of a biological product containing active substances derived from human or animal sources (cells, tissues, fluids), with the exception of blood. The steps in the manufacture of human extracted product which come under a manufacturer's authorisation are those steps which are not covered under Directive 2004/23/EC.

1.3.1.7 Tissue engineered products

Tissue engineered products:

Select this category where processing steps are carried out in relation to the manufacture of a product that contains or consists of engineered cells or tissues, and is presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue. The steps in the manufacture of tissue engineered product derived from human tissue which come under a manufacturer's authorisation are those steps which are not covered under Directive 2004/23/EC.

1.3.1.8 Other biological medicinal products <free text>

Other biological medicinal products (specify):

Select this category where processing steps are carried out in relation to manufacture of a biological product, including a biological active substance which does not fit into the previously named categories. An example would be allergen products which are derived from non-animal sources such as grass-pollen.

1.3.2 *Batch certification (list of product types)*

Complete this section with regard to final QP certification of the finished dosage form of a biological product. Entries can also be made under 1.1.3 or 1.2.2, as appropriate, to reflect the type of dosage form being certified.

- 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 Tissue engineered products
- 1.3.2.8 Other biological medicinal products <free text>

1.4 Other products or manufacturing activity

Note: where a manufacturer carries out processing steps in relation to herbal or homoeopathic dosage forms (e.g. tablets) then there will be an entry for the relevant dosage form (sections 1.1 to 1.2) in addition to the entry in this section. Where the facility is only authorised for manufacturing operations in relation to herbal or homoeopathic products then include a clarifying remark ('herbal products only' or 'homoeopathic products only') in relation to the dosage forms-/manufacturing operation authorised on the manufacturer's authorisation.

1.4.1 *Manufacture of other products*

- 1.4.1.1 Herbal products
- 1.4.1.2 Homoeopathic products

1.4.1.3 Other <free text>

1.4.2 *Sterilisation of active substances/excipients/finished product*

Complete this section where these sterilisation activities are not carried out as part of the manufacture of a dosage form, for example, where the manufacturer's authorisation holder is a contract sterilisation facility performing gamma irradiation of products on behalf of other manufacturers.

- 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 Other <free text>

Example of activities to be listed under 1.4.3: 'Storage': where a site only carries out batch certification and storage of medicinal products.

1.5 **Packaging**

1.5.1 *Primary packing*

Primary packing of a sterile product is taken as being included as part of the processing operations covered under section 1.1 in relation to sterile products unless a comment to the contrary is entered in the clarifying remarks in relation to the particular dosage form.

- 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 Intraruminal devices
- 1.5.1.16 Veterinary premixes
- 1.5.1.17 Other non-sterile medicinal products <free text>

Example of activities to be captured under 1.5.1.17 'Other non-sterile medicinal products': if the manufacturer's authorisation holder carries out primary packing but not the actual manufacture of a dosage form (e.g. implants) which subsequently undergoes terminal sterilisation, enter a statement under 'Other non-sterile medicinal products' 1.5.1.17, as follows: 'Primary packing of *(name of dosage form)* which undergoes terminal sterilisation'.

1.5.2 *Secondary packing*

Where secondary packaging is authorised it is understood to apply to all dosage forms unless otherwise specified in the clarifying remarks.

1.6 Quality control testing

Where quality control testing is carried out at the site authorised categories of testing should be identified below.

- 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:

Unless a clarifying remark is intended as a general comment relating to activities at the site, a numerical reference, as per the item listing on the manufacturer's authorisation format, is included wherever a clarifying remark or restriction is applied.

Remarks may be entered as confidential or public remarks on EudraGMDP, as determined by the HPRA. Confidential remarks may only be viewed by competent authorities (registered users on EudraGMDP) whereas public remarks can be viewed by anyone.

Variations to part 1 manufacturing operations of Annex 1/2

Variation	Variation type and timeline	Supporting documentation
Addition to the currently approved manufacturing operations (this refers to operations which are managed directly by the authorisation holder)-	Technical	Specify the proposed manufacturing operation(s), using the guidance provided in Part 1 manufacturing operations and the address(es) where each operation is carried out.

<p>or</p> <p>Addition of new manufacturing site to authorisation-</p>	<p>timeline: 30/90 days⁵</p>	<p>Submit a revision of the site master file including the proposed additional manufacturing operations. Submit a summary of training provided to QPs responsible for batch certification, where the proposed general product class/dosage form is new to the manufacturing site. Note: an inspection may also take place as part of the assessment of such a variation.</p>
<p>Deletion of currently approved manufacturing operations-</p>	<p>Admin timeline: 30 days</p>	<p>None required.</p>

Part 2 Importation of medicinal products

- For requirements regarding listing of contract manufacturing sites in Annex 3 and imported products in Annex 8 on manufacturer's authorisations refer to guidance provided in Annex 3 and 8 of this document.
- No entries are required in Annex 3 and 8 where physical importation is the only activity carried out in relation to the imported product. However, all relevant information regarding contract manufacturers and listing of imported products must be available in the site master file.

2.1 Quality control testing of imported medicinal products

Where quality control testing is carried out at the site in relation to imported medicinal products, identify the authorised categories of testing. Complete this section where applicable, even if entries have been made under section 1.6 relating to the same testing operations on products manufactured in the EEA.

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

⁵ The timeline for technical variations can vary from 30 to 90 days depending on whether additional information is requested by the HPRA and if an inspection is required.

2.2 Batch certification of imported medicinal products

Complete this section where the site performs certification of either an imported finished product or a bulk dosage form which undergoes packing after importation. If the manufacturer's authorisation holder is also the site of physical importation, then an entry is made under 2.3.1.

For **IMP** manufacturers (Annex 2), identify authorisation to carry out certification of imported comparator products by a clarifying remark in relation to the relevant product category.

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*

Identify the relevant dosage form under 2.2.1 or 2.2.2 in addition to the category of biological product.

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 Tissue engineered products

2.2.3.8 Other biological medicinal products <free text>

2.3 Other importation activities (any other relevant importation activity that is not covered above)

2.3.1 Site of physical importation

An entry here means that the site is authorised to receive and store imported product which is awaiting QP certification. Certification is identified separately in relation to the relevant product categories under section 2.2.

2.3.2 Importation of intermediate which undergoes further processing

The type of intermediate is specified, e.g. granulate, sterile active substance, partially manufactured biological product.

2.3.4 Other <free text>

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

Unless a clarifying remark is intended as a general comment relating to activities at the site, include a numerical reference, as per the item listing on the manufacturer's authorisation format, wherever a clarifying remark or restriction is applied.

Remarks may be entered as confidential or public remarks on EudraGMDP, as determined by the HPRA. Confidential remarks may only be viewed by competent authorities (registered users on EudraGMDP) whereas public remarks can be viewed by anyone.

Variations to Part 2 Importation of medicinal products of Annex 1/2

Variation	Variation type and timeline	Supporting documentation
Addition to the manufacturing operations in relation to imported medicinal products	Technical timeline: 90 days	Specify the proposed addition as per the guidance for Part 2 Importation of Medicinal Products. Note: an inspection may also take place as part of the assessment of such a variation.
Deletion to the manufacturing operations in relation to imported medicinal products	Admin timeline: 30 days	None required

ANNEX 3 CONTRACT MANUFACTURER(S)

Please complete a separate Annex 3 for **each** contract manufacturer.

- Contract manufacturing sites should be named in Annex 3 in the following scenarios:
 - When a manufacturer's authorisation holder performs batch certification, all sites (including those in third countries) involved in the manufacture of the product are required to be listed on the manufacturer's authorisation.
 - For contract manufacturers located in a third country: refer to guidance in Annex 8 regarding requirements for naming of imported products.
 - For **IMP** authorisations no entries are required in Annex 8.

- All sites involved in the manufacture of a biological medicinal product, including the biological active substance, are required to be named on the manufacturer's authorisation.
- When a manufacturer's authorisation holder outsources manufacturing activities for which it is responsible through technical agreements, all sites where outsourced activities occur are required to be listed.
- Contract manufacturing sites are not required to be named in Annex 3 when:
 - ~~Where~~ Site of physical importation is the only activity carried out by the holder of the manufacturer's authorisation.
 - In the case of an **IMP** authorisation: Manufacturers which carry out manufacturing steps for a product which are in accordance with an EU approved marketing authorisation for that product and where a QP has provided confirmation that the steps have been carried out in accordance with the marketing authorisation.
 - The product supplied is to be used as a comparator product in an operational clinical trial.
 - Sites where Master or Working Cell Banks are generated and/or stored.
- Please refer to the guidance provided in Annex 1/2 Part 1 manufacturing operation section which is also applicable for operations carried out at a contract manufacturer (with the exception of batch certification).
- Guidance regarding listing of contract storage sites in Annex 3:
 - Only contract storage sites which store the following product types should be listed on the manufacturer's authorisation:
 - Raw materials that have been approved for use by the MIA holder.
 - Intermediates/partially manufactured medicinal products.
 - Products in quarantine/-products awaiting QP certification.
 - Storage location of reference/retention samples.
- There is no requirement to list contract storage sites on manufacturer's authorisation which store:
 - QP certified finished product.
 - Master Cell Banks or Working Cell Banks.
 - Storage sites for IMP finished product or intermediate product located in a third country.
- For sites which are engaged in storage or secondary packing it is not necessary to specify the particular product types to which these activities apply.

Applicants **must** submit the following details relating to contract manufacturing facilities used:

- Name and address of facility (as it appears on a GMP certificate for the site, if one exists).
- Manufacturing operations performed and quality control testing, where the testing is performed at the same site (as per guidance for Annex 1/2).
- Evidence of satisfactory inspection, e.g. copy of GMP certificate or reference to certificate on EudraGMDP.

- The GMP certificate should be issued by a relevant competent authority in the EEA (preferably within the last ~~3~~-three years).
- The scope of the certificate should include the proposed manufacturing operations for the relevant dosage which will be manufactured at the site.
 - For example, a GMP certificate related to investigational medicinal products would not support the addition of a contract site to an authorised human medicines manufacturer's authorisation.
- Alternatively, the equivalent document as specified in a relevant MRA (e.g. Canada – Establishment Licence) issued by an MRA partner where the manufacturer is located in an MRA territory and the product type concerned is within the scope of that MRA.
- For sites located in the United States, the date of the last FDA inspection and the FDA Establishment Identification (FEI) number must be provided.
- For addition of contract manufacturing sites located in a third country to **IMP** authorisations: In the absence of an EU GMP certificate or equivalent MRA document, submit a declaration by a QP named on the authorisation regarding GMP compliance of the contracted site in relation to the activities concerned at the new address.
- Applicants are encouraged to utilise the European Commission's QP declaration template.
 - The basis of the QP declaration should be clearly stated and encompass the proposed activities of the contract site.
- For contract storage sites:
 - In the absence of GMP certification a declaration by a QP named on the authorisation stating that he/she is satisfied that the contracted site operates in accordance with EU GMP in relation to the activities concerned is acceptable.
 - The HPRA reserves the right to perform its own inspection of the contracted site.
 - A wholesale distribution authorisation (WDA) can be used to support the addition of a storage site for products awaiting batch certification by a QP.
 - The WDA must include authorisation for holding of medicinal products.
- ~~○ Appropriate active substance registrations may be acceptable to support the addition of a storage site.~~
- ~~○ For the addition of contract manufacturers regarding contract sterilisation sites involved in sterilisation of primary packaging for sterile medicinal products, and where the site performing sterilisation of the packaging materials may not have undergone inspection by an EU authority and consequently may not hold an EU GMP certificate in relation to this activity:~~

~~When GMP certification is not available, certification that the sterilisation has been conducted and validated in accordance with the following ISO standards would be considered to provide an acceptable level of sterility assurance for the empty primary container:~~

 - ~~I.S. EN ISO 20857~~
 - ~~I.S. EN ISO 11135~~
 - ~~I.S. EN ISO 17665~~
 - ~~I.S. EN ISO 11137~~

~~In the absence of GMP certification or confirmation that the component is a CE marked Class I medical device, certification that the sterilisation process has been conducted and validated in accordance with the relevant ISO standards should be provided in support of the application.~~

- ~~○ A declaration by a QP named on the authorisation stating that he/she is satisfied that the contracted site operates in accordance with EU GMP in relation to the activities concerned.~~

1.4.3 Other <free text>

For a contract storage site which is also acting as site of physical importation, include the following text 'storage / site of physical importation' here.

Enter clarifying remarks in relation to the contract manufacturing operations following the same guidance as applied in Annex 1.

Variations to Annex 3 Contract manufacturers⁶

Variation	Standard process: variation type, timeline	Expedited process (IMP only): variation type, timeline	Immediate notification (IMP only): variation type, timeline
Addition of contract manufacturing site	Technical, 30/90 days ⁷	Technical, 7 working days	Administrative, n/a

Supporting documentation:
As per guidance in Annex 3 contract manufacturers.

Variation	Standard process: variation type, timeline	Expedited process (IMP only): variation type, timeline	Immediate notification (IMP only): variation type, timeline
Change in the name of a contract manufacturing site	Administrative, 30 days	Administrative, 7 working days	Administrative, n/a

Supporting documentation:

- Submit a formal document from a relevant official body (e.g. Companies Registration Office or Chamber of Commerce or equivalent) in which the new name is mentioned.
- Submit a statement from a QP named on the manufacturer's authorisation regarding any implications that this change may have on the quality management system or its operation at the contracted site.
- Alternatively, a revised GMP certificate which includes the new name may be provided.

Variation	Standard process: variation type, timeline	Expedited process (IMP only): variation type, timeline	Immediate notification (IMP only): variation type, timeline
Change in the address of a contract manufacturing site	Technical, 30/90 days	Technical, 7 working days	Administrative, n/a

⁶ Refer to the table in the variation section of this guide for full detail regarding scope of standard, expedited and immediate notification variation processes.

Supporting documentation:

- Submit a formal document from a relevant official body (e.g. Companies Registration Office or Chamber of Commerce or equivalent) in which the new address is mentioned, **or**
- Supporting documentation as per guidance in Annex 3 contract manufacturers.

Variation	Standard process: variation type, timeline	Expedited process (IMP only): variation type, timeline	Immediate notification (IMP only): variation type, timeline
Addition of production activities at approved contract manufacturing site	Technical, 30/90 days ⁷	Technical, 7 working days	Administrative, n/a

Supporting documentation:

- Specify the proposed new manufacturing operation(s) which will be undertaken in relation to the relevant dosage form as per the guidance provided in part 1.
- Supporting documentation as per guidance in Annex 3 contract manufacturers.

Variation	Standard process: variation type, timeline	Expedited process (IMP only): variation type, timeline	Immediate notification (IMP only): variation type, timeline
Deletion of operations carried out at a contract manufacturing site or deletion of a contract manufacturer	Administrative, 30 days	Administrative, 7 working days	Administrative, n/a

No supporting documentation required.

⁷ The timeline for technical variations can vary from 30 to 90 days depending on whether additional information is requested by the HPRA and if an inspection is required.

ANNEX 4 CONTRACT LABORATORY

Please complete a separate Annex 4 for **each** contract laboratory.

- When a contract manufacturer is also performing testing operations, then these testing activities appear for the site in Annex 3. Do not duplicate the information in Annex 4.
- Details must be submitted for contract laboratories used for the following types of testing:
 - (i) in-process tests or finished product tests which are described in a marketing authorisation for batch certification
 - (ii) identity testing of micro-organisms associated with the manufacture of sterile medicinal products
 - (iii) identity testing of starting materials
 - (iv) stability tests which are described in a marketing authorisation.
- Laboratories used by contract manufacturers listed in Annex 3, which perform testing other than the tests included in the finished product specification are **not** required to be named in Annex 4.

Applicants **must** submit the following details relating to contract laboratories:

- Name and address of facility (as it appears on a GMP certificate for the site, if one exists).
- Evidence of satisfactory inspection, e.g. copy of GMP certificate or reference to certificate on EudraGMDP.
 - o The GMP certificate should be issued by a relevant competent authority in the EEA (preferably within the last 3 years).
 - o The scope of the certificate should include the proposed testing operation proposed at the site.
 - For example, a GMP certificate related to investigational medicinal products would not support the addition of a contract site to an authorised **h**uman medicines manufacturer's authorisation.
- Alternatively, the equivalent document as specified in relevant MRA (e.g. Canada – Establishment Licence) issued by an MRA partner where the laboratory is located in an MRA territory and the product type concerned is within the scope of that MRA.
- For sites located in the United States, the date of the last FDA inspection and the FDA Establishment Identification (FEI) number must be provided.
- Where the laboratory will only be used for testing in relation to **IMPs** or stability testing of medicinal products, submit a declaration of GMP compliance from a QP named on the authorisation. The HPRA reserves the right to perform its own inspection if deemed necessary or request another relevant authority to inspect where appropriate.
- If a manufacturer is intending to use a new contract laboratory located in Ireland that does not currently hold a GMP certificate:
 - o The MIA holder should submit a variation application to the HPRA to add the contract laboratory to its MIA, specifying the type of testing which it intends to outsource.

- The HPRA will make arrangements for inspection directly with the contract laboratory and fees associated with the inspection will be charged to the contract laboratory.
- Pending a satisfactory inspection, the resultant GMP certificate will be used as the basis of approval of the variation to the contract-giver's MIA.

Testing operations are identified for each contract laboratory using the following categories:

- Microbiological: Sterility
- Microbiological: Non Sterility
- Chemical/physical
- Biological
- Stability

Stability testing is selected when the site only performs activities in relation to stability testing. In addition to selecting the stability category, applicants should also identify the specific category of testing by selecting Microbiological: Sterility, non-sterility, chemical/physical and/or biological as appropriate.

Variations to Annex 4 contract laboratories⁸

Variation	Standard process: variation type, timeline	Expedited process (IMP only): variation type, timeline	Immediate notification (IMP only): variation type, timeline
Addition of a new contract laboratory	Technical, 30/90 days ⁹	Technical, 7 working days	Administrative, n/a

Supporting documentation as per guidance in Annex 4 contract laboratories.

⁸ Refer to the table in the variation section of this guide for full detail regarding scope of standard, expedited and immediate notification variation processes.

⁹ The timeline for technical variations can vary from 30 to 90 days depending on whether additional information is requested by the HPRA and if an inspection is required.

Variation	Standard process: variation type, timeline	Expedited process (IMP only): variation type, timeline	Immediate notification (IMP only): variation type, timeline
Change in the name of a contract laboratory	Administrative, 30 days	Administrative, 7 working days	Administrative, n/a

Supporting documentation:

- Submit a formal document from a relevant official body (e.g. Companies Registration Office or Chamber of Commerce or equivalent) in which the new name is mentioned.
- Submit a statement from a QP named on the manufacturer's authorisation regarding any implications that this change may have on the quality management system or its operation at the contracted site.
- Alternatively, submit a revised GMP certificate including the new name of the contract laboratory.

Variation	Standard process: variation type, timeline	Expedited process (IMP only): variation type, timeline	Immediate notification (IMP only): variation type, timeline
Change in the address of a contract laboratory	Technical, 30/90 days ¹⁰	Technical, 7 working days	Administrative, n/a

Supporting documentation:

- Submit a formal document from a relevant official body (e.g. Companies Registration Office or Chamber of Commerce) in which the new address is mentioned.
- Supporting documentation as per guidance in Annex 4 contract laboratories.

Note: the HPRA reserves the right to perform an inspection or request another relevant authority to inspect where appropriate.

¹⁰ The timeline for technical variations can vary from 30 to 90 days depending on whether additional information is requested by the HPRA and if an inspection is required.

Variation	Standard process: variation type, timeline	Expedited process (IMP only): variation type, timeline	Immediate notification (IMP only): variation type, timeline
Addition of activities at an approved contract laboratory	Technical, 30/90 days	Technical, 7 working days	Administrative, n/a

Supporting documentation:

- Submit either a GMP Certificate or a QP declaration to cover the additional testing activities (for **IMP** or stability testing applications only). The HPRA reserves the right to perform an inspection or request another relevant authority to inspect where appropriate.

Variation	Standard process: variation type, timeline	Expedited process (IMP only): variation type, timeline	Immediate notification (IMP only): variation type, timeline
Deletion of testing activities carried out at a contract laboratory or deletion of a contract laboratory	Administrative, 30 days	Administrative, 7 working days	Administrative, n/a

No supporting documentation required.

ANNEX 5 QUALIFIED PERSON(S)

Applicants **must** submit the following details:

- A copy of relevant qualifications as issued by relevant third level institution to support educational requirements for a QP.
- A copy of the proposed QP's CV.
- The current e-mail address for each proposed QP.
- A summary of training in the pharmaceutical quality system of the site in the form of a curriculum/training plan relevant to the role of the QP, which should be signed by the proposed QP and his/her relevant superior.
 - o Details of product specific training should also be included in cases when the product types are new to a site.

Variations to Annex 5 Qualified person(s)

Variation	Variation type and timeline	Supporting documentation
Addition of Qualified Person (primary or deputy)	Technical timeline: 30 days	As per guidance above for Annex 5 Qualified Person(s).
Removal of Qualified Person	Admin timeline: 30 days	None required.
Update to qualifications for Qualified Person	Technical: 30 days	Submit a copy of the relevant qualifications for the individual.

ANNEX 6 PERSONNEL FOR PRODUCTION OPERATIONS AND QUALITY CONTROL

Personnel responsible for production and quality control are required to be named when the manufacturer's authorisation includes authorisation for the corresponding activity.

For example, when a manufacturer's authorisation is granted in relation to batch certification only, no personnel for production or quality control should be named.

Variations to Annex 6 Responsible person(s)

Variation	Variation type and timeline	Supporting documentation
Addition of a person responsible: - Production - Quality control	Technical Timeline: 30 days	Submit a copy of the person's CV.
Removal of a person responsible for: - Production - Quality control	Admin Timeline: 30 days	None required.
Update to qualifications for personnel	Technical Timeline: 30 days	Specify the qualifications that require updating for the individual. Submit a copy of the person's CV.

ANNEX 7 (OPTIONAL) – NOT USED BY THE HPRA

This is an optional ~~Annex annex~~ which includes certain details relating to the last inspection and is not used by the HPRA.

ANNEX 8 IMPORTATION OF PRODUCTS WHICH ARE CONTRACT MANUFACTURED AT A SITE OUTSIDE THE EEA

Please complete a separate Annex 8 for **each** site from which products are imported (i.e. last third country site in the manufacturing chain).

- Annex 8 is required in the following scenarios:
 - o When the MIA holder performs batch certification of imported products.
- Annex 8 is not required:
 - o Where physical importation is the only activity performed under the manufacturer's authorisation.
 - o For **IMP** manufacturer's authorisations.
- Only enter details of imported dosage forms, either as bulk (e.g. bulk tablets or bulk nude vials) or as finished product in this section.
- Specify the proposed dosage form(s) to be imported from each third country manufacturer including the general product class, description of the dosage form, active ingredient and strength. The third country manufacturing site should be listed in Annex 3.
- The product description entered in the first column should complement the basic information on the dosage form as necessary.
 - o For example, in the case of a tablet product it may be sufficient to enter 'tablets' in this field.
 - o However, in the case of an aseptically prepared small volume liquid which is presented as a prefilled syringe then 'Prefilled syringe' should be entered under product description.
 - o Another example of a relevant description could be 'Powder for solution for infusion' in the case of a lyophilised powder intended for infusion.
- The columns under 'activities by manufacturer's authorisation holder' refer to the activities which are intended to be carried out by the applicant for this authorisation in relation to the specific product.
 - o Specify the site of physical importation for the products.
 - o If batch certification and/or physical importation take place at the manufacturer's authorisation holder's site, then specify both activities in relation to the particular product.
- Approval of a product entry to Annex 8 does not infer that the product is approved for any particular market. - The QP should ensure that the product has received relevant market approvals prior to certification of batches.

Variations to Annex 8

Variation type	Variation type and timeline
Addition of imported products resulting from a new contract manufacturer located outside the EEA.	Technical 30 days
Supporting Documents: As per guidance in Annex 8 importation of products which are contract manufactured at a site outside the EEA.	
Variation type	Variation type and timeline
Addition of a new product type and/or dosage form to the list of imported products for a contract manufacturer which is already approved on the authorisation, e.g. tablets already listed but sterile small volume liquids to be added.	Technical 30 days
Supporting Documents: As per guidance in Annex 8 importation of products which are contract manufactured at a site outside the EEA.	
Variation type	Variation type and timeline
Addition to the list of imported products where manufacturer is already approved on authorisation for manufacture of the same dosage form, e.g. addition of another tablet product sourced from a contract manufacturer which has already been authorised for supply of tablets.	Administrative 30 days
Supporting Documents: As per guidance in Annex 8 importation of products which are contract manufactured at a site outside the EEA.	
Variation type	Variation type and timeline
Deletion of an imported product	Administrative 30 days
No supporting documentation required.	

CONTACT DETAILS

For further information or guidance, please contact:

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