

Guide to Applications for Variation to a Manufacturer's Authorisation



CONTENTS

INTRODUCTION	4
OVERVIEW OF VARIATIONS TO MANUFACTURER'S AUTHORISATION	4
Structure of the standard variation application form	5
Clock stops	6
APPLICANT DETAILS	6
Guidance on addresses	7
ANNEXES OF THE EU FORMAT FOR A MANUFACTURER'S AUTHORISATION	9
ANNEX 1 AND ANNEX 2 MANUFACTURING AND IMPORTATION OPERATIONS	10
Guidance on terminology used in the MIA	10
Part 1 Manufacturing Operations	13
Part 2 Importation of medicinal products	20
ANNEX 3 CONTRACT MANUFACTURER(S)	23
Listing contract storage sites	23
Listing contract manufacturing sites	23
When are contract sites not required to be listed in Annex 3?	24
Important notes	25
Contract manufacturing site details and supporting documentation	26
Sites based in MRA territories	27
Sites based in non-MRA third country territories	28
ANNEX 4 CONTRACT LABORATORY	31
Listing contract laboratories	31
Contract laboratory details and supporting documentation	31
Sites based in MRA territories	32
New contract laboratories based in Ireland	33
ANNEX 5 QUALIFIED PERSON(S)	36
Qualifications	36
Practical experience	36
Training	37
ANNEX 6 PERSONNEL FOR PRODUCTION OPERATIONS AND QUALITY CONTROL	38
ANNEX 7 NOT USED BY THE HPRA	39

ANNEX 8	IMPORTATION OF PRODUCTS WHICH ARE CONTRACT MANUFACTURED AT A SITE OUTSIDE THE EEA	39
	Listing entries in Annex 8	39
	Details to be placed in Annex 8 Entry	40
APPENDIX 1	SUPPLY OF UNLICENSED/EXEMPT MEDICINAL PRODUCTS	43
APPENDIX 2	REMOTE BATCH CERTIFICATION BY THE QUALIFIED PERSON	44
APPENDIX 3	DECLARATIONS BY THE QUALIFIED PERSON	46
APPENDIX 4	FURTHER DETAIL ON SUPPORTING DOCUMENTATION REQUIRED FOR SITES BASED IN MRA/ACAA PARTNER TERRITORIES	47

INTRODUCTION

There are three types of manufacturer's/importer's authorisation (MIA) depending on the type of medicinal products within scope - human medicinal products, subject to marketing authorisation (H), veterinary medicinal products, subject to marketing authorisation (V) and human investigational medicinal products (IMP). This document provides guidance on applying to the HPRA to vary an existing MIA. These MIAs are required where the company performs manufacturing or importation activities related to the category of medicinal products.

This guide should be read in conjunction with the following relevant application forms:

- Application for variation to a manufacturer's authorisation (AUT-F0211)
- IMP expedited assessment of variations to Annex 3 and/or 4 application form (AUT-F0791)
- IMP immediate notification of variations to Annex 3 and/or 4 application form (AUT-F0819)

The MIA is formatted into the agreed EU format included in the Compilation of Union Procedures on Inspections and Exchange of Information published by the European Medicines Agency on behalf of the European Commission. This guidance is located on the EMA website at [Interpretation of the Union format for Manufacturer Importer Authorisation](#).

OVERVIEW OF VARIATIONS TO MANUFACTURER'S AUTHORISATION

There are three processes that can be used to vary an MIA. In each case, applicants must submit a completed application form, the required supporting documentation as detailed in this guide, and the appropriate fee.

Details of the variation type, timeline and scope of each process are provided in Table 1.

The timelines commence following acknowledgement of receipt of the application by the HPRA. These timelines can be suspended during periods, known as clock-stop, where further information is required from the applicant, or where the applicant indicates that they are not currently in a position to facilitate an inspection.

Table 1: Types of processes to vary manufacturer's authorisations

Variation process	Scope and timeline	Application form reference
Standard variation process	Applies to all variation types. The assessment timeline can vary from 30 to 90 days. In general, when an inspection is required, the timeline is extended to 90 days. Refer to later sections of this document, which outline the timelines for variations to specific Annexes, and provide further guidance on the type of standard variations which require inspection.	AUT-F0211
Expedited assessment of variations to Annex 3 and/or 4	Applicable to IMP MIAs only, and only for the addition or removal third country-based contract manufacturing sites and contract laboratories (Annex 3 and 4). This is an optional process to allow faster processing of these types of applications. The standard variation process can be applied if an expedited assessment is not required. Assessment timeline is seven days; however, the timeline is contingent on the provision of supporting documentation.	AUT-F0791
Immediate notification of variations to Annex 3 and/or 4	Applicable to of IMP MIAs only, and only for the addition or removal of EU/EEA-based contract manufacturing sites and contract laboratories (Annex 3 and 4). This process is only applicable to contract sites, which are appropriately authorised by an EEA competent authority for the requested manufacturing operations. This is an optional process as the standard variation process, with the associated timeline, can also be applied. Variations which do not meet these criteria should not be submitted through this process. MIA holders can commence proposed activities immediately after submission of the variation application. Assessment timeline is 30 days.	AUT-F0819

Structure of the standard variation application form

The application for variation to a manufacturer's authorisation (AUT-F0211) is used for the standard variation process. This form is divided into the following four sections, depending on the variation type and applicable timeline. Each section consists of variations which are of the same type (administrative or technical) and have the same timeline (30, 60, or 90 days).

- Administrative variations, 30-day procedure
- Technical variations, 30-day procedure
- Technical variations, 60-day procedure
- Technical variations, 90-day procedure

These are described throughout this guide.

Clock stops

When the HPRA receives an MIA variation application, we consider whether or not the application requires further supporting information and/or an inspection. Where further information is required, the HPRA assessment time is stopped (the so-called 'clock-stop' days) from the date the notice is given, and the clock recommences only on receipt of the information requested.

Issues that can result in 'clock-stop' include the following:

- The application form is not filled out correctly.
- Adequate supporting documentation is not enclosed.
- Assessment requires an inspection and the company is not ready for inspection.

Where multiple variations are submitted in the same application form, the HPRA will progress the approval of those variations that have adequate supporting evidence, while the outstanding variations will remain in progress until such time when adequate supporting evidence is provided or the company chooses to withdraw variations that cannot be supported.

Linked variations must be processed together, e.g. the addition of a third country contract manufacturer in Annex 3, which requires inspection (90-day timeline) and the addition of an imported product from that manufacturer in Annex 8 (30-day timeline) must be processed together resulting in both variations having the longer 90-day timeline.

Note: Addition of a third country manufacturer, which requires inspection due to absence of EU GMP certification for the products/processes concerned, is required to be notified in advance of submission of the variation application to the HPRA through a pre-submission process.

APPLICANT DETAILS

Variations may be made to the legally registered name and/or address, or the name and/or address of the manufacturing site of the MIA holder.

Guidance on addresses

The Location ID (LOC-ID) of sites is required on all applications for variation to an MIA. For this, applicants must check that the manufacturing organisation is correctly registered in the EMA Organisation Management Service (OMS). Further information on this process is outlined on the European Medicines Agency (EMA) website. For more information refer to the following links.

- [SPOR Data Management Service portal](#)
- [Organisation Management Service \(OMS\)](#)
- [Video tutorial: Overview of OMS](#)
- [Webinar for Industry: Introduction to OMS services and activities](#)

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 the responsibility of the same key personnel named on the application, then include the main contact address for the manufacturing site.

- Provide details of other 'units', which will operate under the scope of this MIA below the main contact address. The scope of operations at each address/unit should be made clear in the application.
- A single MIA 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.

- 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 MIA application.
- In the event that this application is successful then a single MIA, 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.

Further detail on timelines and supporting documentation is detailed in table 2.

Table 2: Variations to applicant details

Variation	Type, timeline and form	Supporting documentation
Minor corrections of typographical errors to authorisation	- Admin variation - 30 days - AUT-F0211, section 1	None required. Note: The HPRA may request further information related to this variation.
Change in the name of authorisation holder	- Admin variation - 30 days - AUT-F0211, section 1	Certificate of Incorporation. A statement from a Qualified Person (QP) named on the MIA outlining any implications that this change may have on the quality management system or its operation at the site. Note: When a change to the name of the MIA holder is a result of a proposed sale or transfer to another company, this is not a variation application and requires a transfer application. please refer to the HPRA website (MIA transfers) for further information.
Change in the legally registered address of the MIA holder	- Admin variation - 30 days - AUT-F0211, section 1	Certificate of Incorporation.
Change in the main address of the manufacturing site Or Addition of new manufacturing address Note: This refers to a new site where manufacturing/ importing activities are performed by the MIA holder, and not to the addition of a new contract manufacturing site or contract laboratory, which	- Technical variation - 90 days - AUT-F0211, section 4	An inspection may take place as part of the assessment of such a variation. If the company is not relocating to different premises and the address of the current site is being updated, the QP must submit a declaration confirming no change to the physical location of the premises or the activities carried out therein. An updated version of the site master file should be submitted to the HPRA when a variation to

Variation	Type, timeline and form	Supporting documentation
are covered in Annex 3 and 4 respectively.		change the manufacturing address has been approved.

ANNEXES OF THE EU FORMAT FOR A MANUFACTURER'S AUTHORISATION

Table 3 gives an overview of the Annexes that can be completed for an MIA, which will be reflected in the format of the authorisation. Further clarity on completion of each Annex is given in subsequent sections.

Table 3: Summary of Annexes

Annex	Annex title	Notes
1	Scope of authorisation relating to medicinal products, subject to marketing authorisation for human and/or veterinary use	This describes the manufacturing/ importation/ testing operations/ batch certification carried out directly under the MIA at the company's own address in relation to medicinal products, subject to marketing authorisation for human and/or veterinary use. Activities carried out at contract sites must not be indicated in Annex 1. This information is published on the EudraGMDP database.
2	Scope of authorisation relating to investigational medicinal products	This describes manufacturing, importation, testing operations or batch certification carried out directly under the MIA at the company's own address in relation to IMPs. Activities carried out at contract sites must not be indicated in Annex 2. This information is published on the EudraGMDP database.
3	Names and addresses of contract manufacturing site(s)	This includes manufacturing, storage, importation or testing operations which are carried out at contract manufacturing site(s). This information is not published on the EudraGMDP database.
4	Names and addresses of contract laboratories	This includes testing operations carried out at contract laboratories. This information is not published on the EudraGMDP database.
5	Name(s) of Qualified Person(s)	This information is not published on the EudraGMDP database.

Annex	Annex title	Notes
6	Names of personnel responsible for production and quality control	This information is not published on the EudraGMDP database.
7	Date of inspection on which authorisation granted	This optional annex within the EU format for an MIA is not currently used by the HPRA. The annex number/title is referenced merely for completeness.
8	Importation of products which are contract manufactured at a site outside the EEA	This information is not published on the EudraGMDP database.

ANNEX 1 AND ANNEX 2 MANUFACTURING AND IMPORTATION OPERATIONS

The principal operations performed at the site of a manufacturer are outlined in Annex 1 and Annex 2. Annex 1 is selected when medicinal products, subject to marketing authorisation, are manufactured for human and/or veterinary use. Annex 2 is selected when medicinal products are manufactured for IMPs.

When completing Annex 1 and Annex 2, all activities proposed at the address must be indicated separately, e.g. if the applicant proposes to manufacture bulk tablets, perform primary and secondary packaging, quality control testing and batch certification, all these activities must be ticked in the application form. Table 4 indicates the timelines along with supporting evidence for variation to Annex 1 and Annex 2.

Guidance on terminology used in the MIA

Each operation carried out by the MIA holder is identified in the authorisation, as appropriate. The scope of manufacturing operations which are authorised at the site is defined using the unit operations listed as follows.

Processing operations

This includes any or all processing steps in the manufacture of a dosage form.

Production of intermediates

If the site manufactures intermediates as part of the manufacturing process for bulk products, this does not need to be indicated separately in the application. However, if a company exclusively manufactures intermediates that contain one or more active substances, the company must apply for authorisation of the '1.4.1.3 Other' activity and indicate the formulations (e.g. granules, powder, fluid, etc.) that are manufactured.

Primary packing

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

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.

Repackaging

A manufacturer that repackages and certifies the repackaging of the product for release of the product (e.g. repackaging of parallel imported product) need only list 1.5.2 'Secondary Packaging' in Annex 1 or Annex 2, as applicable.

Batch certification

Refers to the certification of a finished product batch of medicinal product by a QP before its release into the marketplace 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.

For sites that only perform batch certification, include a statement clarifying the security arrangements at the site address, storage arrangements for retention and reference samples for product certified and general arrangements for access to the HPRA authorised officers to the site on a constant basis (e.g. for sites which are leased/shared office spaces).

QP confirmation

The QP confirmation of a specific operation is inherent in the listed operation, e.g. activity 1.5.2 'secondary packaging' covers the confirmation of that packaging process. Where a manufacturer also performed QP certification to allow release to the market, batch certification operations in Annex 1 or Annex 2, as applicable, must also be selected.

Quality control

Refers to types of laboratory testing which the MIA holder is authorised to perform.

Storage

Any site which holds an MIA and carries out processing operations or packaging of medicinal products is also authorised for storage.

If the site carries out storage of intermediates or bulk products as a stand-alone activity, the company must apply for authorisation for storage under '1.4.3 Other' and indicate the formulations (e.g. granules, powder, fluid, etc.) that are stored. This also applies to the storage of unreleased medicinal products that are manufactured and packaged.

Note: All components released for the manufacture of a medicinal product are considered as intermediates. Consequently, an MIA is required to store released raw materials and packaging components, if such components are not released again prior to the manufacture of the medicinal product.

Distribution

Any site, which holds an MIA, 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 by another MIA holder require a wholesale distribution authorisation (WDA).

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 WDA for distribution activities in relation to those batches or products.

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.

Note: For activities included under 'processing operations', primary and secondary packaging, batch certification and quality control, 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, using the guidance described in Chapters 3 and 5 of the EU Guide to GMP.

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.

List of specific hazards for a dosage form (as per dropdown menu items from EudraGMDP):

- β -Lactam antibiotics
- Other highly sensitising materials
- Live cells
- Pathogenic Organisms (Biosafety 3 or 4)
- Radiopharmaceuticals
- Ectoparasitocides
- Others (free text entry)

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.

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

- Highly potent products
- Highly toxic products

Note: see guidance in Appendix 1 on unlicensed/exempt medicinal products.

Part 1 Manufacturing Operations

The following section reflects the manufacturing operations available to the applicant in the variation types related to Part 1 of Annex 1 or Annex 2 in the application form. Guidance is provided to help select the correct options.

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 MIA 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.

Remote batch certification: See Appendix 2 regarding requirements for remote batch certification by the Qualified Person.

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

'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)
- 'Over-encapsulation' (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.

Remote batch certification: See Appendix 2 regarding requirements for remote batch certification by the Qualified Person.

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 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 MIA.

1.3.1 Biological medicinal 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.

For variations to add biological drug product manufacture, where the site produces the final dosage form, both the category of biological medicinal product (1.3) and the dosage form (1.1 or 1.2) must be selected. e.g. a manufacturer producing 10ml filled vials of an aseptically prepared monoclonal antibody should select 1.1.1.4 and 1.3.1.5 Biotechnology products, with the clarifying remark 'manufacture of the finished dosage form', as outlined below:

- 1.1.1.4 Small volume liquids
- 1.3.1.5 Biotechnology products

Clarifying remark: 1.3.1.5 relates manufacture of the finished dosage form.

1.3.1.1 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 an MIA, are those processing steps which are not covered under Directive 2002/98/EC.

1.3.1.2 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

Somatic cell therapy medicinal product is defined in Part IV of Annex I to Directive 2001/83/EC. 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 an MIA, are those steps which are not covered under Directive 2004/23/EC.

1.3.1.4 Gene therapy products

A gene therapy medicinal product is defined in Part IV of Annex I to Directive 2001/83/EC. 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 an MIA, are those steps which are not covered under Directive 2004/23/EC.

1.3.1.5 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 (multiple options may apply):

- Cell culture mammalian
- Cell culture bacterial
- Isolation/purification
- Modification (e.g. pegylation, glycosylation, etc.)
- Low bioburden bulk intermediate
- Final dosage form

Production of monoclonal antibodies (mAbs) is included as an activity under biotechnology products.

1.3.1.6 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 products, which come under an MIA, are those steps which are not covered under Directive 2004/23/EC.

1.3.1.7 Tissue engineered products

A tissue engineered product is defined in Article 2(1)(b) of Regulation (EC) No 1394/2007. 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 an MIA are those steps which are not covered under Directive 2004/23/EC.

1.3.1.8 Other biological medicinal products <free text>

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. An entry should also be made under 1.1.3 or 1.2.2, as appropriate to identify if the dosage being certified is a sterile or non-sterile product respectively. See Appendix 2 regarding requirements for remote batch certification by the Qualified Person.

- 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 MIA.

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 MIA holder is a contract sterilisation facility performing gamma irradiation of products on behalf of other manufacturers. If the site carries out sterilisation as part of the manufacturing process for a given dosage form in section 1.1 of the MIA, this does not need to be separately indicated.

- 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 the MIA-holder only carries out batch certification and storage of medicinal products.

Note that an MIA-holder, which carries out processing operations or packaging of medicinal products is also authorised for storage, without having to specifically mention 'storage' under 1.4.3.

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 and therefore this section is not required to be completed for 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 MIA 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*

Endotoxin testing should be indicated under biological testing. Where endotoxin testing is the only biological test performed, include a clarifying remark '1.6.4 refers to endotoxin testing only'.

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

The addition of clarifying remarks by the applicant is outlined in the guidance above.

The HPRA may also add 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 MIA 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.

Part 2 Importation of medicinal products

The following section reflects operations concerning imported medicinal products in Part 2 of Annex 1 or Annex 2 in the application form.

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. Endotoxin testing should be indicated under biological testing. Where endotoxin testing is the only biological test performed, include a clarifying remark '2.1.4 refers to endotoxin testing only'.

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

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 MIA 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. See Appendix 2 regarding requirements for remote batch certification by the Qualified Person.

2.2.1 *Sterile Products*

2.2.1.1 Aseptically prepared

2.2.1.2 Terminally sterilised

2.2.2 *Non-sterile 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 *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 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*

When selecting this operation, also specify the type of intermediate imported, e.g. granulate, sterile active substance, partially manufactured biological product.

2.3.3 *Biological active substance*

Select this operation when importing biological drug substance, either for further processing or for storage and further distribution.

2.3.4 *Other* <free text>

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

The HPRA may add restrictions or clarifying remarks related to the scope of 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 MIA 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.

Table 4: Variations to Part 1 and/or Part 2, Annex 1 or Annex 2

Variation	Type, timeline and form	Supporting documentation
Addition to the currently approved operations or Addition of new dosage form or product type	- Technical variation - 90 days - AUT-F0211, section 4 These variation types often require an inspection, subject to clock stops.	An updated version of the site master file should be submitted to the HPRA when a variation to change the manufacturing operations has been approved. Submit evidence of the site QPs' training or experience in the new product/dosage form to be batch certified. This should include: - A CV of the relevant QP(s), - A comprehensive summary of the training conducted demonstrating that the QP has detailed knowledge of the product type and production processes.
Deletion of currently approved operations	- Admin variation - 30 days - AUT-F0211, section 1	None required.

ANNEX 3 CONTRACT MANUFACTURER(S)

Annex 3 should be completed in relation to contract storage or contract manufacturing sites and the requirements relating to each of these outsourced activities are described under separate headings below.

Listing contract storage sites

Any site performing contract storage on behalf of the MIA holder should be listed in Annex 3 where the storage activity specifically relates to the following:

- Storage of intermediates/partially manufactured medicinal products.
- Storage of medicinal products which are awaiting QP certification.
- Storage of reference/retention samples.

Section 1.4.3 <Other> on the application form should be used to identify the storage activity performed at the contracted sites. It is not necessary to specify the particular product types to which these storage activities apply.

Listing contract manufacturing sites

The requirement to list contract manufacturing sites in Annex 3 is **only** applicable where the MIA-holder acts as the site of batch certification for a product, which is intended for supply to EU/EEA markets or a clinical trial in the EU/EEA.

- Contract manufacturers include sites involved in any part of the manufacture (including packaging) of the medicinal product. Please see the section below for scenarios when a contract site is not required to be listed in Annex 3.
- The operations described in Annex 3 for the contracted site should reflect the specific activities carried out at the site in relation to the product intended for batch certification as opposed to all the activities at the contract site listed on the relevant GMP certificate, e.g. if a contract manufacturing site is authorised to perform multiple manufacturing operations but will only conduct secondary packaging on behalf of the MIA holder, only secondary packaging operations would be specified for the site in Annex 3.
- In the case of biological medicinal products, manufacturers of the biological active substance are also required to be named in Annex 3.
- If the contract site performs testing in addition to manufacturing activities, then this testing activity should be included in Annex 3; if the site performs only testing activities in relation to the product, then the site must be listed in Annex 4 and not Annex 3.
- The contract site must hold a valid regulatory approval (GMP certificate or equivalent); please see the section on supporting documentation.
- Batch certification cannot be listed as an outsourced activity in Annex 3.

When are contract sites not required to be listed in Annex 3?

- If the MIA holder itself is contracted to perform any part of the manufacture (including packaging) of medicinal product on behalf of another site but is not responsible for performing batch certification, then the sites in its supply chain do not need to be added in Annex 3.

For example:

- o If the MIA holder performs secondary packaging on vials but is not responsible for batch certification of the final product, then the sites from which it receives such vials do not need to be listed in Annex 3.
 - o If the MIA holder only acts as the site of physical importation, then third country sites in the supply chain do not need to be listed in Annex 3.
- There is no requirement to list contract storage sites which store:
 - o QP certified finished product
 - o Stability samples
 - o Starting materials
- Contract manufacturers involved in the generation and/or storage of Master or Working Cell Banks are not required to be added to Annex 3.
- Storage sites located in a third country are also not required to be listed in Annex 3.
- Contract sites are not required to be named when the product supplied is to be used as a comparator product in an ongoing clinical trial. If, however, the comparator product is modified (e.g. primary/secondary packaging), then the site that performs such modification is to be added in Annex 3.
- In the case of an IMP MIA: If the IMP is produced by modification to an authorised product, then manufacturers which carry out steps up to the point of modification need not be named in Annex 3 provided a QP has confirmed that the steps have been carried out in accordance with the marketing authorisation.

For example: A drug substance is manufactured in line with the steps authorised in an MA at site A, and subsequent formulation of the DS, not in line with the MA, is performed at site B. In this scenario, site B needs to be included in Annex 3 of the IMP MIA, while site A does not need to be included given the QP has confirmed that the steps performed at site A are in line with the MA. Contract manufacturers involved in the generation and/or storage of master or working cell banks are not required to be added to Annex 3.

- Contract sites that only sterilise empty containers (primary or secondary packaging) do not need to be added.
- Sites that manufacture active substance via chemical synthesis do not need to be added in Annex 3. Please see the note below about sterilisation of active substances.

For example:

- o A site that manufactures RNA via chemical synthesis such as a solid phase phosphoramidite method does not need to be listed as a contract site in Annex 3, while

a site that manufactures RNA using biological methods such as the use of a polymerase needs to be added to Annex 3.

Important notes

- Activities relating to the sterilisation of active substances/excipients/finished product (e.g. filtration) need only be specified when these activities are not performed as part of the manufacturing process for the finished dosage form.
For example; in circumstances where a contract sterilisation facility performs gamma irradiation of products on behalf of a manufacturer, sterilisation activities should be selected.
In the case of a product that contains both chemical and biological components (e.g. antibody drug conjugates), the manufacturers of the chemical component/active do not need to be listed in Annex 3, but the manufacturers of the biological component/active must be listed. Also, in the example of an antibody-drug conjugate, the site that performs the conjugation needs to be added to Annex 3.
- For contract sites that manufacture biological medicinal products manufactured using biotechnology, applicants must specify appropriate clarification for the scope of operations under 1.3.1.5 'Biotechnology products'. Activities may include the following:
 - o Cell culture mammalian
 - o Cell culture bacterial
 - o Fermentation
 - o Isolation/purification
 - o Low bioburden bulk intermediate
 - o Final dosage form
- Where proposed manufacturing operations include the manufacture of the finished dosage form for a biological product (section 1.3), the relevant dosage form must also be selected in section 1.1 (sterile products) or section 1.2 (non-sterile products) in Annex 3.
For example, if a site manufactures a monoclonal antibody via mammalian cell culture, purifies it and performs aseptic fill-finish to manufacture 10 ml vials, then the application should indicate the following to document these activities:
 - o 1.1.1.4 Manufacture of aseptically prepared small volume liquid
 - o 1.3.1.5 Biotechnology products, with a selection on cell culture mammalian, isolation/purification, low bioburden bulk intermediate and final dosage
- Primary packaging of sterile products is inherent in the processing operations covered under section 1.1 unless a comment to the contrary is entered in the clarifying remarks, in relation to the dosage form. Therefore, in general, primary packaging of sterile products is not required to be included separately in the application for manufacturers of sterile products. In the previous example where the site aseptically manufactures 10 ml vials, there is no need to indicate primary packaging separately.

- Endotoxin testing should be captured under biological testing. The applicant must specify if endotoxin testing is the only form of biological testing performed. In such cases, a clarifying remark to this effect will be included in the MIA such as 'Biological testing refers to endotoxin testing only.' It is acknowledged that endotoxin testing may be listed as non-sterile microbiological testing on some supporting documentation. Where the supporting GMP certificate lists non-sterile microbiological testing, a supporting statement from the applicant is required, clarifying that endotoxin testing is within the scope of authorised activities.
- Under QC testing, applicants should specify whether the site performs release testing, stability testing or both. If the site performs only stability testing, applicants should also identify the specific category of the stability tests by selecting microbiological: sterility, microbiological: non-sterility, chemical/physical and/or biological, as appropriate.
- Where physical importation is outsourced to a contract site, this activity will be recorded under operation 1.4.3. Where physical importation is conducted at a site located in another Member State, the applicant should be satisfied that each site used for physical importation is appropriately authorised by the relevant competent authority of that Member State.

Contract manufacturing site details and supporting documentation

Applicants must submit the following details relating to add contract manufacturing sites:

- Name and address of facility (as it appears on a GMP certificate issued to the site by an EEA competent authority, if one exists, unless otherwise justified).
- Manufacturing operations performed and quality control testing, where the testing is performed at the same site (as per guidance for Annex 1 or 2).

Required documentation for the addition of a contract manufacturing site varies depending on the country where the site is located, as well as the type of medicinal product, i.e. human medicinal products, veterinary medicinal products or IMPs.

Contract manufacturing site address

Before applying to add a manufacturing site, applicants should check that the manufacturing site is registered in OMS. If the site is registered in OMS, then the site name and address (including the LOC-ID) presented on the variation application should be aligned to the details on OMS. Further information on the process for registration with OMS is outlined on the European Medicines Agency (EMA) website.

Supporting evidence to add contract sites to a human or veterinary MIA

Evidence of satisfactory GMP inspection should be provided.

- The GMP certificate should be issued to the site by a relevant EEA competent authority.

- The inspection referenced on the GMP certificate should have been conducted within the last three years.
- The dosage form, operation details, name and address must align with the GMP certificate (or equivalent). The scope of the certificate should include the proposed manufacturing operations for the relevant dosage form which will be manufactured at the site.
- For example, a GMP certificate related to IMPs would not support the addition of a contract site to an authorised human medicines MIA.
- All operations applied for must be listed on the certificate unless inherent in the activities stated, e.g. primary packaging of sterile products is inherent in the processing operations.
- Justification should be provided if the supporting documentation does not clearly reflect the activities included in the application.

Supporting evidence to add contract sites to an IMP MIA

A GMP certificate with specifications outlined above can be provided. In the absence of a GMP certificate, a QP declaration can be provided as evidence. Please refer to Appendix 3 for details on QP declarations.

Addition of contract storage sites

- In the absence of GMP certification, a declaration by a QP named on the MIA stating that they are 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 WDA can be used to support the addition of a storage site for products awaiting batch certification. The WDA must include authorisation for holding of medicinal products.
- Appropriate active substance registrations may also be considered to support the addition of a storage site.

Sites based in MRA territories

The European Union has signed mutual recognition agreements (MRAs) with several third-country competent authorities concerning the conformity assessment of regulated products. These countries include the United States, Australia, Canada, Japan, New Zealand, Israel and Switzerland. The MRA with Israel is an agreement on conformity assessment and acceptance of industrial products (ACAA). This is a specific type of MRA based on the alignment of the legislative system and infrastructure of the country concerned with those of the EU. The scope of these MRAs differ depending on the country. Where a product type is within the scope of an MRA, an applicant can submit documentation confirming compliance of the contractor by the regulator in the MRA territory or an EEA GMP certificate. Please refer to Appendix 4 for information on MRA/ACAA countries and type of evidence provided.

Sites based in non-MRA third country territories

For contract manufacturers based in other non-MRA third countries, a copy of the GMP certificate issued on the EudraGMDP database by a relevant EEA competent authority should be submitted. A copy of a GMP certificate issued by Medicines and Healthcare products Regulatory Agency (MHRA), UK can also be submitted, as applicable. Where no certificate is available and an inspection is required for the site, prior to including this site on an application, the applicant should contact the HPRA.

A summary of the timelines and supporting documentation required for variations to contract manufacturers in Annex 3 is given in Table 5.

Table 5: Variations to contract manufacturing sites, Annex 3

Variation	Type, timeline and form	Supporting documentation
Addition of contract manufacturing site If this variation requires an inspection, the timeline can be extended to 90 days.	Standard process: - Technical variation - 30 days - AUT-F0211, Section 2 Expedited process (IMP only): - Technical variation - 7 days - AUT-F0791 Immediate notification (IMP only): - Admin variation - 30 days - AUT-F0819	Refer to 'Contract manufacturing site details and supporting documentation' section above.
Change in the name of a contract manufacturing site	Standard process: - Technical variation - 30 days - AUT-F0211, Section 2 Expedited process (IMP only): - Technical variation - 7 days - AUT-F0791	- 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. - A statement from a QP named on the MIA regarding any implications that this change may have on the quality management system or its operation at the contracted site.

Variation	Type, timeline and form	Supporting documentation
	Immediate notification (IMP only): - Admin variation - 30 days - AUT-F0819	OR A revised GMP certificate including the new name may be provided.
Change in the address of a contract manufacturing site	Standard process: - Technical variation - 30 days - AUT-F0211, Section 2 Expedited process (IMP only): - Technical variation - 7 days - AUT-F0791 Immediate notification (IMP only): - Admin variation - 30 days - AUT-F0819	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 If the site is moving to a different location, then refer to 'Contract manufacturing site details and supporting documentation' section above.
Addition of production activities at approved contract manufacturing site	Standard process: - Technical variation - 30 days - AUT-F0211, Section 2 Expedited process (IMP only): - Technical variation - 7 days - AUT-F0791 Immediate notification (IMP only): - Admin variation - 30 days - AUT-F0819	Refer to 'Contract manufacturing site details and supporting documentation' section above.

Variation	Type, timeline and form	Supporting documentation
Deletion of operations or removal of a contract manufacturer	Standard process: - Admin variation - 30 days - AUT-F0211, section 1 Expedited process (IMP only): - Admin variation - 7 days - AUT-F0791 Immediate notification (IMP only): - Admin variation - 30 days - AUT-F0819	None required.

ANNEX 4 CONTRACT LABORATORY

Listing contract laboratories

All sites involved in the conduct of in-process tests, finished product tests and stability tests described in a marketing authorisation or the clinical trial application should be included in Annex 4. This includes additional laboratories subcontracted to perform this testing.

If a contract site performs both testing activities and manufacturing activities, it should appear in Annex 3 and not be duplicated in Annex 4.

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

Table 6: Testing categories

Test categories	Category obligatory for these tests
Microbiology Sterility	Sterility
Microbiology non-sterility	Testing involves culturing, enumeration and identification of micro-organisms, preservative efficacy testing
Chemical/physical testing	Testing of quality attributes by physical or chemical means, e.g. physical measurements, wet chemistry, chromatographic techniques
Biological testing	Tests involving use of live cultured animal cells or animals and tests utilising materials of biological origin (e.g. antibodies, antigens). For example, rabbit pyrogen, ELISA, Monocyte Activation Test & qPCR, Endotoxin testing (e.g. gel clot, turbidimetric or chromogenic methods)

In the application form, testing activities are differentiated into the following types.

- Stability testing
- Release testing

Contract laboratory details and supporting documentation

Applicants must submit the following details relating to contract laboratories:

- Name and address of facility (as it appears on a GMP certificate issued to the site by an EEA competent authority, if one exists, unless otherwise justified).
- Testing operations performed and quality control testing, where the testing is performed at the same site (as per guidance for Annex 1 or 2).

Required documentation for the addition of a contract manufacturing site varies depending on the country where the site is located, as well as the type of testing performed at the site.

Contract laboratory address

Before applying to add a testing site, applicants should check that the laboratory is registered in OMS. If the site is registered in OMS, then the site name and address (including the LOC-ID) should be aligned to those on OMS. Further information on this process is outlined on the European Medicines Agency (EMA) website.

Supporting evidence to add contract sites to a human or veterinary MIA

Evidence of satisfactory GMP inspection should be provided.

- The GMP certificate should be issued to the site by a relevant EEA competent authority.
- The inspection referenced on the GMP certificate should have been conducted within the last three years.
- The testing activities, name and address must align with the GMP certificate (or equivalent). The scope of the certificate should include the proposed testing operations. For example, a GMP certificate related to IMPs would not support the addition of a contract site to an authorised human medicines MIA.

Addition of contract sites to IMP MIA

A GMP certificate with specifications outlined above can be provided. In the absence of a GMP certificate, a QP declaration can be provided as evidence. Please refer to Appendix 3 for details on QP declarations.

Addition of contract sites performing stability testing

Contract laboratories which perform only stability testing of authorised medicines can be added to the MIA on the basis of a declaration by a QP named on the MIA, regarding GMP compliance of the contracted site in relation to the stability testing. The HPRA reserves the right to perform its own inspection if deemed necessary or request another relevant authority to inspect where appropriate.

Sites based in MRA territories

The information provided regarding MRA or ACAA sites in Annex 3 is also applicable for the addition of contract laboratories based in those territories. Applicants should refer to Appendix 4 of this document.

New contract laboratories based in Ireland

If a manufacturer is intending to use a contract laboratory located in Ireland that does not currently hold a GMP certificate, the HPRA should be notified in advance of submitting a variation through a pre-submission process.

- 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 supporting documentation and a variation application to the contract-giver's MIA can be submitted.

Note: Under regulation 2019/6, testing of veterinary medicines requires the testing facility to hold a veterinary MIA.

The supporting documentation required for variations to contract laboratories in Annex 4 is detailed in Table 6.

Table 6: Variations to contract laboratories, Annex 4

Variation	Type, timeline and form	Supporting documentation
Addition of a new contract laboratory	Standard process: - Technical variation - 30 days - AUT-F0211, section 2 Expedited process (IMP only): - Technical variation - 7 days - AUT-F0791 Immediate notification (IMP only): - Admin variation - 30 days - AUT-F0819 If this variation requires an inspection, the timeline can be extended to 90 days.	Refer to 'Contract laboratory details and supporting documentation' section above.

Variation	Type, timeline and form	Supporting documentation
Change in the name of a contract laboratory	Standard process: - Technical variation - 30 days - AUT-F0211, section 2 Expedited process (IMP only): - Technical variation - 7 days - AUT-F0791 Immediate notification (IMP only): - Admin variation - 30 days - AUT-F0819	- 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. - A statement from a QP named on the MIA regarding any implications that this change may have on the quality management system or its operation at the contracted site. OR A revised GMP certificate including the new name may be provided.
Change in the address of a contract laboratory	Standard process: - Technical variation - 30 days - AUT-F0211, section 2 Expedited process (IMP only): - Technical variation - 7 days - AUT-F0791 Immediate notification (IMP only): - Admin variation - 30 days - AUT-F0819	- A formal document from a relevant official body (e.g. Companies Registration Office or Chamber of Commerce) in which the new address is mentioned. - Submit a statement from a QP named on the MIA regarding any implications that this change may have on the quality management system or its operation at the contracted site. OR A revised GMP certificate including the new name of the contract laboratory. Note: The HPRA reserves the right to perform an inspection or request another relevant authority to inspect where appropriate.
Addition of activities at an approved contract laboratory	Standard process: - Technical variation - 30 days	Refer to 'Contract manufacturing site details and supporting documentation' section above.

Variation	Type, timeline and form	Supporting documentation
	- AUT-F0211, section 2 Expedited process (IMP only): - Technical variation - 7 days - AUT-F0791 Immediate notification (IMP only): - Admin variation - 30 days - AUT-F0819	Note: The HPRA reserves the right to perform an inspection or request another relevant authority to inspect where appropriate.
Deletion of testing activities carried out at a contract laboratory or deletion of a contract laboratory	Standard process: - Admin variation - 30 days - AUT-F0211, section 1 Expedited process (IMP only): - Admin variation - 7 days - AUT-F0791 Immediate notification (IMP only): - Admin variation - 30 days - AUT-F0819	No supporting documentation required.

ANNEX 5 QUALIFIED PERSON(S)

This section must be read alongside the HPRA 'Guide to Attainment of Qualified Person Status in Ireland: Educational Requirements, Training and Licensing' (AUT-G0080). In order to progress the addition of a Qualified Person (QP) to the MIA, three key pieces of supporting documentation must be provided: qualification, evidence of practical experience and training.

Qualifications

To fulfil the qualification requirements, the following documents must be submitted:

- Certificates of the primary degree and the QP-qualifying course of the proposed QP
- A university-issued letter confirming successful course completion if the formal qualification is pending

For candidates who completed a pharmacy or QP course outside of Ireland, please provide either:

- Proof of registration with the Pharmaceutical Society of Ireland (PSI) for Pharmacy graduates,
- A letter from the EEA competent authority in the country where the pharmacy or QP-qualifying degree was obtained. confirming that the candidate's qualifications satisfy the educational requirements outlined in Article 49 of EU Directive 2001/83/EC and Article 97 of EU Regulation 2019/6. The candidate must also have fulfilled any other requirement set out under the framework in the relevant Member State, or
- A copy of the MIA issued by the relevant EEA authority listing the candidate as the QP.

All documents must be provided in English or accompanied by certified English translations.

Practical experience

A copy of the proposed QP's CV, clearly indicate the name and address of the site(s) at which the proposed QP has had relevant experience should be provided.

Please refer to the HPRA 'Guide to Attainment of Qualified Person Status in Ireland: Educational Requirements, Training and Licensing' for further information on relevant work experience.

If the proposed QP has relevant experience in an EEA country outside of Ireland, applicants are required to submit proof of this experience. Acceptable forms of evidence may include:

- A letter issued by the relevant competent authority confirming the site's MIA status during the applicant's employment,
- A signed statement from the previous employer confirming that the proposed QP candidate was employed at the site during the period when the site held an MIA, in a relevant role,
- If the proposed QP has previously worked as QP, the MIA issued to the site with the proposed QP named on it.

Candidates acting as QPs for manufacturing sites based in Northern Ireland may be accepted where the training, experience and qualification requirements outlined in this section are met. For other UK candidates, those candidates must have been deemed eligible as qualified persons prior to Brexit (i.e. prior to 31 January 2020).

Training

A training summary for the proposed QP must be submitted. This is a summary of training, relevant to the role of QP, conducted at the specific manufacturing site. The training summary can include prior experience and training to demonstrate that the QP candidate has gained the requisite knowledge and experience for the types of products they will be certifying. The training plan and the summary must be signed and dated by the proposed QP, and the relevant trainer/manager/supervisor.

The proposed QP should have completed training in all key elements of the company's pharmaceutical quality system to enable them to effectively carry out the routine duties of a QP (e.g. key company QMS systems, quality technical agreements, supplier audits, batch certification activities, regulatory compliance systems, product/dosage forms, authorisation(s) held by the company, manufacturing processes, product types and dosage forms, among others).

It is not expected that all training is completed prior to the application. The training plan may include the training status up to the time of the application submission (for instance, by dating each completed training).

In the event that training is ongoing at time of application, a statement affirming that all necessary training will be concluded prior to commencement of batch certification activity by the proposed QP can be accepted. This statement should be signed by the proposed QP, and trainer/manager/supervisor, as appropriate.

If the proposed QP is designated to certify batches of a specific product type exclusively, this limitation must be clearly stated in either the training summary or the application. The

company's Pharmaceutical Quality System, including the site master file, should clearly reflect the types of dosage forms each QP is authorised to certify, when applicable.

The supporting documentation required for variations to Qualified Person(s) in Annex 5 is detailed in Table 7.

Table 7: Variations to Qualified Person(s), Annex 5

Variation	Type, timeline and form	Supporting documentation
Addition of Qualified Person	- Technical variation - 60 days - AUT-F0211, section 3	Refer to the guidance provided in the Qualifications, Experience and Training sections.
Removal of Qualified Person	- Admin variation - 30 days - AUT-F0211, section 1	None required.

ANNEX 6 PERSONNEL FOR PRODUCTION OPERATIONS AND QUALITY CONTROL

Personnel responsible for production and quality control are required to be named when the MIA includes operations at the site for the corresponding activity.

For example, when an MIA is granted in relation to batch certification only, no personnel for production or quality control should be named. In line with the requirements of Chapter 2 of the EU GMP guidelines, the person responsible for production may not be the same as the person responsible for quality control.

The supporting documentation required for variations to persons responsible for quality control/production in Annex 6 is detailed in Table 8.

Table 8: Variations to Responsible Person(s), Annex 6

Variation	Type, timeline and form	Supporting documentation
Addition of a person responsible for production/quality control	- Technical variation - 60 days - AUT-F0211, section 3	A copy of the candidate's CV outlining the job responsibilities of the role. Note: The candidate must have appropriate qualifications and practical experience relevant to the site activities, as well as adequate authority to carry out their responsibilities.

Variation	Type, timeline and form	Supporting documentation
		The responsibilities of the persons responsible for production and quality control are outlined in Chapter 2 of the EU Guide to GMP.
Removal of a person responsible for production/quality control	- Admin variation - 30 days - AUT-F0211, section 1	None required.

ANNEX 7 NOT USED BY THE HPRA

This is an optional annex which includes details relating to the last inspection. It is not used by the HPRA.

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

Listing entries in Annex 8

Annex 8 is required when the MIA holder performs batch certification of imported products which are imported either as a bulk dosage form (e.g. bulk tablets or bulk nude vials) or finished packed product.

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

Note: Third country sites involved in storage **only** prior to importation should not be listed in Annex 8.

Annex 8 is **not** required in the following cases:

- Annex 8 entries are not required for IMP MIAs.
- Where site of physical importation is the only activity performed under Annex 1 of the MIA
- For importation of product intermediates (where this activity is performed it should be listed under section 2.3.2 of Annex 1 of the MIA.)
- Third country sites involved in storage **only** prior to importation

The third country site listed in Annex 8 should also be included in Annex 3, with appropriate operations for the manufacture and packaging of the product specified. The name and address of this site must accurately reflect the Annex 3 details and the supporting documentation for the manufacturer. These table entries in Annex 8 are specific to a single contract manufacturer, product type and dosage form. A separate Annex 8 table is required for each contract manufacturer.

Details to be placed in Annex 8 Entry

Product type

The 'product type' field of the table refers to whether the products are non-sterile products, aseptically prepared products or terminally sterilised products. Applicants should choose the appropriate product type from the drop-down in the field for this value.

Dosage form

The 'dosage form' field must correspond to the description of the manufacturing operation for the dosage form at the relevant contract manufacturing site as specified in Annex 3, e.g. 'Small volume liquids', 'Hard shell capsules', 'Tablets', etc. Applicants should choose the appropriate dosage form from the drop-down in the field for this value.

In instances where both the 'product type' field and 'dosage form' field are the same for a group of products imported from the same contract manufacturer, they will be included in the same table (see the example provided below). Where this information is not the same for the products, separate tables are required, e.g. where tablets and capsules are imported from the same contract manufacturer separate tables are required, as the 'dosage form' fields will be different.

Product description

This description should complement the basic information on the dosage form as necessary. Where the products are imported as bulk dosage forms this information should be included in this section.

The trade name of the product should **not** be included in this description. Examples of what may be considered appropriate entries under 'Product Description' for a number of dosage forms are suggested in the table below:

Dosage form	Product description
Aseptically prepared small volume liquid	Vials Pre-filled syringe Autoinjector Vial containing concentrate for solution for infusion

Dosage form	Product description
Aseptically prepared lyophilisate	Vial containing powder for solution for infusion
Non-sterile tablets	Enteric coated tablets Sustained release tablets Tablets
Non-sterile semisolid	Ointment Cream Gel Paste
Non-sterile liquid for internal use	Oral suspension Oral liquid

Activities by MIA holder

This refers to the activities which are intended to be carried out by the applicant under the MIA in relation to the specific product.

Example of a completed table

The below table outlines an example of the type of information to be included in each field. As outlined above, where the 'product type' fields and 'dosage form' fields are the same for the products they may be included in the one table. In the event that these fields are different, separate tables would be required.

Product type		Dosage form	
Terminally sterilised products		Small volume liquids If other: N/A	
Product description	Strength	Active ingredient	Activities by MIA holder
Prefilled syringe	150 mcg	Adrenaline	☒ Batch certification ☐ Site of physical importation
Single-dose eye drops	2%	Pilocarpine	☒ Batch certification ☐ Site of physical importation
Bulk Ampoules	50 mg/ml	Haloperidol	☒ Batch certification ☐ Site of physical importation

Note: Acceptance of a product entry in 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.

The supporting documentation required for variations to Annex 8 is detailed in Table 10.

Table 10: Variations to imported products, Annex 8

Variation	Type, timeline and form	Supporting documentation
Addition of imported products resulting from a new contract manufacturer located outside the EEA OR 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 variation - 30 days - AUT-F0211, section 2	See guidance for variation to manufacturing operations in Annex 3. No additional supporting documents required for entries in Annex 8 as the manufacturing details should reflect those for the relevant manufacturing site which is listed in Annex 3.
Addition to the list of imported products where the 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	- Technical variation - 30 days - AUT-F0211, section 2	None required.
Deletion of an imported product	- Admin variation - 30 days - AUT-F0211, section 1	None required.

APPENDIX 1 SUPPLY OF UNLICENSED/EXEMPT MEDICINAL PRODUCTS

Article 5 of Directive 2001/83/EC outlines circumstances when a medicinal product without a marketing authorisation may be supplied. In Ireland these medicines are referred to as exempt medicines and the relevant exemptions are described in the Medicinal Products (Control of Placing on the Market) Regulations 2007.

The guidance provided relates solely to the authorisation requirements for the import and supply of such medicines within Ireland. Applicants intending to supply (export) medicines under Article 5 of Directive 2001/83/EC to other countries should ensure compliance with any local requirements applicable in that country.

For the Irish market, the import and supply of these medicines may take place under an MIA or a WDA. The import and supply of these medicines may be performed under an MIA provided that the holder conducts manufacturing or importation operations for the products as described in part 1 or part 2 of the MIA. When these activities take place under an MIA, the following clarifying remark will be inserted on the MIA to authorise the activities:

'This site is authorised to supply medicinal products in accordance with the provisions of Article 5 of Directive 2001/83/EC providing that it would normally conduct a manufacturing activity, as listed above, for the product concerned.'

MIA holders wishing to supply products meeting these criteria under Article 5 of Directive 2001/83/EC should apply for the addition of such clarifying remarks to the MIA.

In all other circumstances the import and supply of exempt medicines is to be conducted under a WDA. Further information and guidance in relation to applications and variations to WDAs can be found on the HPRA website.

Applicants should also refer to the HPRA 'Guide to The Notification System for Exempt Medicinal Products' and any other national requirements, which may be applicable for the supply of these products in Ireland.

APPENDIX 2 REMOTE BATCH CERTIFICATION BY THE QUALIFIED PERSON

Manufacturing operations which are detailed on the MIA should only be performed at the authorised site address. Batch certification is an operation which is specified on the MIA, and it is expected that the QP is present at the authorised site when performing batch certification unless otherwise approved on the MIA by the HPRA.

A pre-requisite for HPRA approval of remote batch certification on an MIA is a satisfactory inspection following on-site batch certification activities being undertaken. This would normally occur one to three years post the first inspection at the site. Where approved, a clarifying remark is added to the MIA stating 'Authorised operations include remote batch certification by a Qualified Person when operating within the EEA or Northern Ireland'.

MIA holders applying for a variation to include remote batch certification by QPs should submit the following supporting documents:

- Signed declaration on behalf of the MIA holder to confirm that certification, when performed remotely, will only be performed by QPs when operating within the EEA (or Northern Ireland).
- Summary of the means by which the QP will maintain familiarity and current knowledge in relation to the products, manufacturing process(es), the pharmaceutical quality system at the manufacturing site and its effectiveness in relation to the products concerned. This should include details of when QPs who are operating remotely will be required to attend the authorised manufacturing site. The time spent on the site should be commensurate with the nature and frequency of manufacturing operations conducted at the site.
- Details of how the MIA holder will facilitate the QPs to perform their duties remotely and in a secure manner including:
 - o Summary description of how it will be ensured that the QPs can access the same information concerning the manufacture and control of batches as would be provided if carrying out the duties at the authorised manufacturing site.
 - o Summary of the remote certification process and means by which the QP will complete the batch register (or equivalent), including reference to relevant procedures in the pharmaceutical quality system. The declaration should clearly state the means by which batch certification will be communicated to the authorised site and what documentation, if applicable, will be forwarded in this regard.
 - o In circumstances where GMP documentation is stored remotely from the site for periods of time, it is considered that risks associated with this practice are assessed and documented, e.g. controls to ensure the integrity of the records, protection from loss, damage, etc. Summary details of how it will be ensured that the HPRA will have access, in real time, at the authorised manufacturing site, to all relevant information relating to activities by QPs operating remotely and the concerned batches of medicinal product.

QP duties at a manufacturing site may also include providing QP confirmation, as defined in Annex 16 of the EU GMP guide. No variation to the MIA is required to perform the QP confirmation activity remotely; however, it is expected that the same principles, as outlined above, would be applied and this will be reviewed during GMP inspections.

APPENDIX 3 DECLARATIONS BY THE QUALIFIED PERSON

Where declarations by the QP are being provided to support activities (e.g. addition of contract manufactures in Annex 3 or contract laboratories in Annex 4), the following should be noted and considered:

- 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 at the contract site.
- When an applicant provides multiple product-specific QP declarations to facilitate the addition of a contract manufacturing site(s), written guidance should be provided outlining which QP declaration supports each of the manufacturing operations to be performed at the site.
- Sufficient detail must be provided on the scope of the audit referenced in the QP declaration, e.g. if the scope of the audit was 'aseptically prepared small volume liquids and microbiological sterility testing' then this must clearly be stated on QP declaration, as opposed to general remarks such as 'manufacturing' or 'testing'.

It is expected that the following is accounted for on the declaration provided by the QP:

- The scope of the declaration should clearly cover the operations to be included for the contract manufacturer in Annex 3.
- The basis of the declaration should be clearly outlined within the declaration. If the declaration is based on an audit the declaration should outline:
 - o When the audit was performed
 - o Sufficient detail on the scope of this audit
 - o Who performed this audit, and what their relationship is to the party being audited
- The name and address of any sites specified on the QP declaration should fully align to what is proposed to be added to the MIA.
- Justification should be provided if the QP declaration does not clearly reflect the activities included in the application.
- The declaration should be signed and dated by a QP named on the MIA.

APPENDIX 4 FURTHER DETAIL ON SUPPORTING DOCUMENTATION REQUIRED FOR SITES BASED IN MRA/ACAA PARTNER TERRITORIES

General guidance for the inclusion of contract sites based in MRA/ACAA partner territories is outlined in the Annex 3 guidance. Applicants should refer to this general guidance and provide the supporting documentation outlined below for sites covered within the scope of an MRA with the EU. Please note that in certain circumstances, it may be necessary for the HPRA to request further information from the relevant MRA partner. In these instances, it will not be possible to approve the addition of the contract facility until the information is provided by the MRA partner.

There are four different scenarios when a contract site located in an MRA/ACAA partner country is required to be included in an MIA:

- Addition of a contract site to a commercial MIA where the product concerned is covered by the scope of the MRA/ACAA: The MIA holder is required to provide evidence of appropriate GMP certification, as detailed below under each country. This should be provided in addition to any QP declaration for the site concerned.
- Addition of a contract site to a commercial MIA where the product concerned is not covered by the scope of the MRA: The MIA holder is required to provide a GMP certificate issued by an EU regulatory authority that covers the dosage form.

Addition of a contract site to an IMP MIA where the product concerned is covered by the scope of the MRA: The MIA holder is required to provide evidence of appropriate GMP certification or equivalent, as detailed below under each country.

- Addition of a contract site to an IMP MIA where the product concerned is not covered by the scope of the MRA: The MIA holder is required to provide a QP declaration to support the activities to be included in Annex 3 or Annex 4 of the MIA.

Australia

Applicants should provide a GMP certificate issued by the Therapeutic Goods Administration (TGA) of Australia, which includes within the scope of the certificate the operations to be conducted on behalf of the applicant. The inspection referenced on the certificate should preferably have been conducted within the last three years.

Canada

Applicants should, at minimum, provide evidence of compliant status of the Canadian site with regard to the relevant category of manufacturing activity (e.g. as available on the Health Canada website under Drug and Health Product Inspections). Applicants should also submit a copy of the inspection exit notice issued by Health Canada for the site in question, which assists in demonstrating that the site has been appropriately authorised for the product type and dosage form concerned.

Israel

Applicants should provide a GMP certificate issued on EudraGMDP by the Institute for Standardization and Control of Pharmaceuticals of Israel which includes within the scope of the certificate the operations to be conducted on behalf of the applicant. The inspection referenced on the certificate should preferably have been conducted within the last three years.

Japan

Applicants should provide a GMP certificate issued by the Ministry of Health, Labour and Welfare (MHLW) of Japan; an English language version of this document should be provided, or the document should be accompanied by an English translation. The certificate should preferably have been issued within the last three years. When issuing GMP certificates on the EudraGMDP database, the MHLW certifies pharmaceutical manufacturing operations with respect to specific products. The applicant should confirm if the imported product is the same as that referenced on the MHLW certificate.

New Zealand

Applicants should provide a copy of the GMP certificate issued by Medsafe. The inspection referenced on the certificate should preferably have been conducted within the last three years.

Switzerland

Applicants should provide a GMP certificate issued by Swissmedic which includes within the scope of the certificate the operations to be conducted on behalf of the applicant. The inspection referenced on the certificate should preferably have been conducted within the last three years.

United States

Applicants should provide the Food and Drug Administration (FDA) Establishment Identifier (FEI) number for the site in the section indicated on the application form. Applicants should also indicate in the relevant section the date of the most recent pharmaceutical inspection conducted by the FDA.

Please note the FDA may conduct other inspections such as food or cosmetic inspections so applicants should ensure the date of the most recent pharmaceutical inspection is provided. Information provided by the FDA will then be reviewed to determine if the addition of the requested site is acceptable.