Interpretation of the Union Format for Manufacturer/Importer Authorisation

Introduction

The purpose of this document is to provide guidance to industry and regulators on the interpretation of activities defined on Manufacturer's / Importer's Authorisation (MIA) issued by Competent Authorities in the EEA. The text from the 'Union Format for a Manufacturer's Authorisation' is reproduced below and where necessary, clarifying guidance text is provided under certain MIA entries in shaded text boxes. The guidance in these text boxes applies to human and veterinary medicinal products (Annex 1) and also to Investigational Medicinal Products (Annex 2). The headings in Annex 2 are not included in this document but any specific guidance which applies to IMPs only is identified where necessary. Clarifying remarks are often important in helping to define the scope of an MIA. When necessary and wherever possible these should be cross referenced to the number items within the MIA.

Union Format for Manufacturer's[1,2] Authorisation

1. Authorisation number

2. Name of authorisation holder

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

4. Legally registered address of authorisation holder

> Appropriate documentation should be provided by the manufacturer to the relevant Competent Authority as evidence of the name of the Authorisation Holder legally registered address. This address may differ from the address where manufacturing activities take place.

5. Scope of authorisation and dosage forms[2] ANNEX 1 and/ or ANNEX 2
   (Separate Annexes for different sites should be used if not covered by separate licences)

6. Legal basis of authorisation

> This should include reference to the national legislation which implements the legal requirement for a Manufacturer's / Importer's Authorisation as defined in the relevant Directives (2001/82/EC and 2001/83/EC)

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

8. Signature

9. Date

10. Annexes attached Annex 1 and/or Annex 2

Annex 1 describes manufacturing / importation operations relating to Human or Veterinary medicines. Annex 2 describes manufacturing / importation operations relating to Investigational Medicinal Products (IMPs)

Optional Annexes as required:

Annex 3 (Addresses of Contract Manufacturing Site(s))

Annex 4 (Addresses of Contract Laboratories)

Annex 5 (Name of Qualified Person)

Annex 6 (Name of responsible persons)

Annex 7 (Date of inspection on which authorisation granted, scope of last inspection)

Annex 8 (Manufactured/ imported products authorised)[3]

There are optional Annexes which may be used to various different extents by EEA Competent Authorities. The Annexes which are relevant to the MIA issued by the CA should be listed in this section.

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

2 Guidance on the interpretation of this template can be found in the Help menu of EudraGMP database

3 The Competent Authority is responsible for appropriate linking of the authorisation with the manufacturer's application (Art. 42(3) of Directive 2001/83/EC and Art. 46(3) of Directive 2001/82/EC as amended).

SCOPE OF AUTHORISATION (delete the sections that do not apply) **ANNEX 1**

Name and address of the site:

If an MIA includes a number of addresses, then, a separate Annex 1 should be completed in relation to the specific manufacturing operations carried out at each site address.

☐ Human Medicinal Products

☐ Veterinary Medicinal Products

AUTHORISED OPERATIONS

☐ Manufacturing Operations (according to part 1)

☐ Importation of medicinal products (according to part 2)

Part 1 - MANUFACTURING OPERATIONS

The scope of manufacturing operations which are authorised at the site is defined using the following unit operations. Each of the following individual operations carried out by the Authorisation holder should be identified on the MIA, as appropriate.

*Processing Operations:	this includes any or all processing steps in the manufacture of a dosage form.
*Primary Packing:	this 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:	this 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:	this refers to the certification of a finished product batch of medicinal product by a Qualified Person 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:	refers to types of laboratory testing which the MIA holder is authorised to perform.

* Using 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 should be identified in relation to the particular dosage form using the relevant items from the drop down list on EudraGMDP.

Any restrictions (e.g. if product is to be manufactured in a dedicated facility) which may apply in relation to these products should be included in the clarifying remarks with reference to the relevant dosage form.

Drop Down Menu Items from EudraGMDP

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

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

- Highly potent products

- Highly toxic products

Storage: Any site which holds an MIA 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 section 1.4.3 <Other> should be used to identify storage activity

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

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 this should be identified as a clarifying remark in relation to the processing operations for the particular dosage form. The type of real time release testing which is authorised should also be identified in the clarifying remark. The use of Real Time Release testing should reflect any relevant requirements described in a Marketing Authorisation or Clinical Trial Application.

Note: where a category is selected which includes a provision for <free text> then relevant descriptive text must be entered in the <free text> box.

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	☐ Seml-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>

Examples of activities to be captured under 1.1.1.6 'Other'

'Manufacture of sterile active substance' - *(where this activity is normally authorised as a finished product manufacturing activity by the Competent Authority issuing the MIA).*

1.1.2 Aseptically prepared (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, a comment such as 'terminal sterilisation by gamma irradiation is outsourced to another site' should be entered 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	☐ Sollds 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
1.2.1.10	☐ 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>

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 would be categorised as 'Liquids for external use' or Liquids for internal use', as appropriate.

Examples of activities to be captured under 1.2.1.17 'Other'

'Manufacture of intermediates' *(these should be specified 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)*

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

Definition of a Biological Medicinal Product / Biological substance

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

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.

1.3.1 Biological Medicinal Products (List of product types)

Categorisation of Biological Products

The following product categories should be 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 should also be 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 should also be selected on the MIA (e.g. 1.1.1.2 Lyophilisates).

Blood products

This category should be selected 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 would not be 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.

Immunological products

This category should be selected where there are processing operations carried out in relatlon to manufacture of biological products which have an immunological mode of action (e.g. vaccines).

Cell therapy products

This category should be selected 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.

Gene therapy products

This category should be selected 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.

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 a biological products. This category should be selected where there are processing operations carried out in relation to the manufacture of biological products using biotechnology.

Human or animal extracted products

This category should be selected 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.

Tissue engineered products

This category should be selected where processing steps are carrled out in relation to the manufacture of tissue engineered products.

Other biological medicinal products (specify)

This category should be selected where processing steps are carried out in relation to manufacture of a biological product which includes a biological active substance which does not fit into the previously

1.3.1.1	☐ Blood products
1.3.1.2.	☐ Immunological products
1.3.1.3	☐ Celi therapy products
1.3.1.4	☐ Gene therapy products
1.3.1.5	☐ Biotechnology products
1.3.1.6	☐ Human or animal extracted products
1.3.1.7	☐ Tissue engineered products
1.3.1.8	☐ Other biological medicinal products <free text>

1.3.2 Batch certification (list of product types)

This section should be completed with regard to final QP certification of the finished dosage form of a biological product. Entries should 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 should be an entry for the relevant dosage form (sections 1.1 to 1.2) in addition to the entry in the section below. Where the facility is only authorised for manufacturing operations in relation to herbal or homoeopathic products then a clarifying remark ('herbal products only' or 'homoeopathic products only') should be included in relation to the dosage forms / manufacturing operation authorised on the MIA.

1.4.1 Manufacture of:

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

This section is intended to be completed 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.

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>

Examples of activities to be listed under 1.4.3
'Storage' – (for example 'storage' would be included here 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 section1.1 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-sollds
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>

Examples 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 sterilization, a statement as below should be entered under 'Other non-sterile medicinal products' 1.5.1.17.

'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 then 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 MIA format, should be included wherever a clarifying remark or restriction is applied.

Remarks may be entered as confidential or public remarks. Confidential remarks may only be viewed by Competent Authorities (Registered Users) whereas public remarks are viewable by anyone.

Part 2 - IMPORTATION OF MEDICINAL PRODUCTS

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, the authorised categories of testing should be identified below. This section should be completed, where applicable, even if entries have been made under section 1.6.

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

This section should be completed 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 should also be made under 2.3.1.

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

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.

The relevant dosage form under 2.2.1 or 2.2.2 should also be identified above in addition to the category of biological product below.

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 must be 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 should be specified e.g. granulate, sterile active substance, partially manufactured biological product.

2.3.3 ☐ *Biological Active Substance*

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, a numerical reference a, as per the item listing on the MIA format, should be included wherever a clarifying remark or restriction is applied.

Remarks may be entered as confidential or public remarks. Confidential remarks may only be viewed by Competent Authorities (Registered Users) whereas public remarks are viewable by anyone.