Formular **151101_F02_01**	**Interpretation of the Union Format for Manufacturer/Importer Authorisation der Compilation of Community Procedures mit weiteren Erläuterungen zum Erstellen der Erlaubnis**	
Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten		

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VORWORT

Das nachfolgend wiedergegebene Dokument **Interpretation of the Union Format for Manufacturer/Importer Authorisation** wurde inhaltlich 1 zu 1 übernommen.

Daran angehängt finden Sie inhaltliche **Auszüge aus Vorläuferdokumenten**, die zum Verständnis der vorgenommenen Änderungen sinnvoll sein können sowie Beispiele („worked examples“) mit der bisherigen und der jetzigen Darstellung der Herstellungstätigkeiten in den Erlaubnisurkunden.

Bitte beachten Sie, dass die „current“-Variante inzwischen veraltet und die „proposed“-Variante inzwischen gültig ist.

EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION
DIRECTORATE- GENERAL

Public Health and Risk Assessment
Pharmaceuticals

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Interpretation Documents

Interpretation of the Union Format for Manufacturer/Importer Authorisation

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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 EudraGMDP 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	☐	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>

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	☐	Solids and implants
1.1.2.5	☐	Other terminally sterilised prepared products <free text>

1.1.3 Batch certification

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

1.2 Non-sterile products

1.2.1 Non-sterile products (processing operations for the following dosage forms)

1.2.1.1	☐	Capsules, hard shell
1.2.1.2	☐	Capsules, soft shell
1.2.1.3	☐	Chewing gums
1.2.1.4	☐	Impregnated matrices
1.2.1.5	☐	Liquids for external use
1.2.1.6	☐	Liquids for internal use
1.2.1.7	☐	Medicinal gases
1.2.1.8	☐	Other solid dosage forms
1.2.1.9	☐	Pressurised preparations
1.2.1.10	☐	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 relation 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 carried 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 ☐ Cell therapy products
1.3.1.4 ☐ Gene therapy products
1.3.1.5 ☐ Biotechnology products
1.3.1.6 ☐ Human or animal extracted products
1.3.1.7 ☐ 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.

1.3.1.1 ☐ Blood products
1.3.1.2. ☐ Immunological products
1.3.1.3 ☐ Cell therapy products
1.3.1.4 ☐ Gene therapy products
1.3.1.5 ☐ Biotechnology products
1.3.1.6 ☐ Human or animal extracted products
1.3.1.7 ☐ Tissue engineered products
1.3.1.8 ☐ 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.

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-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>

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.

ANNEX 3 (Optional)

Address(es) of Contract Manufacturing Sites

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ANNEX 4 (Optional)

Address(es) of Contract Laboratories

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ANNEX 5 (Optional)

Name(s) of Qualified Person(s)

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.....

ANNEX 6 (Optional)

Name(s) of person(s) responsible for quality control

.....

.....

.....

Name(s) of person(s) responsible for production

.....

.....

.....

ANNEX 7 (Optional)

Date of Inspection on which authorisation was granted dd / mm / yyyy

Scope of last Inspection

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.....

.....

ANNEX 8 (Optional)

Products authorised to be manufactured/imported (in accordance with Article 41 and 42 of Directive 2001/83/EC and/or Article 45 and 46 of Directive 2001/82/EC, as amended).

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Auszüge aus Vorläuferdokumenten:

MIA Interpretation Document

Introduction

There has been a lot of discussion between Member States on how manufacturing activities should be incorporated into the MIA (and associated GMP certificate) format. One of the main issues with the current MIA format is the use of some terminology which includes several activities under one heading whereas other headings on the MIA exclude activities. In particular, “manufacture” includes manufacture of the dosage form, packaging (primary and secondary), batch certification, unless informed to the contrary, whereas, the sections on batch certification and packaging and are restricted only to these activities on the MIA. This method of defining activities on the MIA does not always lend itself to presenting the scope of authorised activities in a manner which can be clearly and easily interpreted by inspectors and assessors at various Competent Authorities who may be using the document.

The purpose of this document is to propose some changes to the MIA without incurring significant impact on the format of the current document. It would be anticipated that certain restrictions built into the EudraGMDP logic would have to be removed or switched off, in particular, the logic relating to “Batch Certification Only” or “Packaging Only” which prevents selection of certain other additional activities.

The main proposals in this MIA Interpretation Document are outlined below:

1. Change the terminology “manufacture” in the introductory paragraph under Part 1to restrict the term to activities concerned with manufacture of the dosage form only (i.e. remove the all-inclusive definition of manufacture which includes packaging, batch certification etc). The term “Manufacture” is defined in legislation so the proposal would be to change the term to “Processing Operations”. Processing operations is terminology which is used in Chapter 5 of the GMP Guide in the context of the steps to manufacture an intermediate (e.g. granulate) or bulk products (e.g. bulk tablets). If used in this manner, then item 1.2.1.13 on the MIA would refer to manufacture of bulk tablets.
2. In relation to Packaging – remove “only” and the associated restrictions applied in EudraGMDP. If a site is involved in primary packaging of any dosage form then an entry should be made against the relevant dosage form under section 1.5. e.g. a site which manufactures tablets and also performs primary and secondary packaging would require entries for 1.2.1.13 (manufacture of bulk tablets), 1.5.1.13 (primary packaging of tablets) & 1.5.2 (secondary packaging). If packaging is the only activity carried out at the site then this will also be clear from the MIA.
3. In relation to Batch Certification – remove “only” and the associated restrictions applied in EudraGMDP. If the site manufacturing and packaging tablets mentioned above is also responsible for batch certification of the tablets then an entry should be made for item 1.2.2 Batch Certification on the MIA. If batch certification is the only activity carried out at the site it will be clear from the MIA in any case.
4. Inclusion of some guidance around completion of the MIA. It is not intended that this guidance would appear on the final MIA or GMP Certificate. This guidance is included in red font in this document.

There are some worked examples in Appendix 1 to this document which demonstrate the scope of activities which may need to be included on an MIA. The worked examples are presented both using the current MIA wording / business rules and also using the MIA wording / business rules as proposed in this MIA Interpretation Document. Clarifying remarks are often necessary and important for defining the scope of an MIA or GMP certificate. It is desirable, wherever possible, to define authorised activities using the numbered items within the MIA format without need for additional clarifying remarks. It is also desirable that where possible some business rules and terminology be put in place around when and how clarifying remarks should be entered so that there is consistency of approach across the EEA.

Appendix 2 includes text which was discussed in relation to the classification of manufacturing activities relating to biological active substances / medicinal products. A worked example using this terminology is also included in this appendix.

APPENDIX 1 ---- WORKED EXAMPLES

The following are worked examples of how the scope of activities carried out would appear on an MIA/GMP certificates for a manufacturer carrying out defined activities using: **(A)** current terminology & EudraGMDP business rules and **(B)** modified system as proposed in the MIA Interpretation Document above. The basic layout of the MIA / GMP certificate remains unchanged with the modified system.

WORKED EXAMPLE 1

This example relates to a site authorised to carry out the following activities:

(i) Manufacture of tablets which undergo packaging and final certification at another site.

1A Scope of activities defined on MIA using current terminology and EudraGMDP rules

1.2	Non Sterile Products
1.2.1	Non-sterile products (list of dosage forms)
1.2.1.13	Tablets

Clarifying Remarks: 1.2.1.13 – excludes packaging (primary & secondary) and batch certification

1B Scope of activities defined on MIA using proposed modified MIA interpretation

1.2	Non Sterile Products
1.2.1	Non-sterile products (processing operations for the following dosage forms)
1.2.1.13	Tablets

Clarifying Remarks: - (None Required)

WORKED EXAMPLE 2

This example relates to a site which is authorised to carry out the following activities:

(i) Manufacture of bulk tablets at the MIA holders site but which are packed and undergo final batch certification at another site.

(ii) Primary, secondary packaging and batch certification for a capsule product. (Bulk capsules manufactured at another site)

2A Scope of activities defined on MIA using current terminology and EudraGMDP rules

1.2 Non Sterile Products
1.2.1 Non-sterile products (list of dosage forms)
1.2.1.1 Capsules, hard shell
1.2.1.13 Tablets

Clarifying Remarks: Activities under item 1.2.1.1 - excludes manufacture of the dosage form

Activities under item 1.2.1.13- excludes packaging and batch certification

2B Scope of activities defined on MIA using proposed modified MIA interpretation

1.2 Non Sterile Products
1.2.1 Non-sterile products (processing operations for the following dosage forms)
1.2.1.13 Tablets

1.2.2 Batch Certification

1.5 Packaging
1.5.1 Primary packing
1.5.1.1 Capsules, hard shell
1.5.2 Secondary Packaging

Clarifying remarks: - (None required)

WORKED EXAMPLE 3

This example relates to a site authorised to carry out the following activities:

(i) Manufacture of granules which undergo further processing and final certification at another site
(ii) Batch certification of capsules which are manufactured and packaged at another site.

3A Scope of activities defined on MIA using current terminology and EudraGMDP rules

1.2 Non Sterile Products
1.2.1 Non-sterile products (list of dosage forms)
1.2.1.17 Other <free text>

Clarifying Remarks: 1.2.1.17 – refers to manufacture of intermediate bulk granules which undergo further processing / final certification at another site.

Batch certification of capsules is also authorised.

3B Scope of activities defined on MIA using proposed modified MIA interpretation

1.2 Non Sterile Products
1.2.1 Non-sterile products (processing operations for the following dosage forms)
1.2.1.17 Other <free text>

1.2.2 Batch Certification

Clarifying Remarks: 1.2.1.17 – refers to manufacture of intermediate bulk granules which undergo further processing / final certification at another site.

WORKED EXAMPLE 4

This example relates to a site authorised to carry out the following activities:

→ Manufacture biological active substance using a biotechnology process employing the following processes:

- Mammalian cell culture
- Isolation of biological active substance
- Purification of biological active substance
- Viral inactivation

The low bioburden bulk biological active substance is shipped off to another site where aseptic filling, packaging and batch certification take place.

→ The following steps are carried out in relation to vaccine manufacture at the site:

- Importation of partially manufactured biological active substance (polysaccharide - antigen)
- Modification of a biological active substance (chemical conjugation of antigen)
- Aseptic filling of vaccine

(no secondary packaging activity takes place at the site)

The bulk syringes are shipped off to another site where secondary packaging activities and final certification takes place.

→ Aseptic manufacture of a lyophilisate dosage form. Secondary packaging and final certification takes place at another site.

→ The site also carries out batch certification of an imported biological biotechnology product presented as a sterile lyophilisate. The product is not physically imported to this site.

→ Quality control testing in relation to products manufactured on site and imported products.

4A Scope of activities defined on MIA using current terminology and EudraGMDP rules

PART 1 – Manufacturing Operations

1.1	Sterile Products
1.1.1	Aseptically prepared (list of dosage forms)
1.1.1.2	Lyophilisates
1.1.1.4	Small volume liquids
1.3	Biological Medicinal Products
1.3.1.2	Immunological products
1.3.1.5	Biotechnology products
1.3.1.8	Other biological medicinal products <free text>
1.4.2	Sterilisation of active substances/excipients/finished product
1.4.2.1	Filtration
1.6	Quality Control Testing
1.6.1	Microbiology – sterility
1.6.3	Chemical / Physical
1.6.4	Biological

PART 2 - Importation activities

2.1	Quality Control Testing of Imported Medicinal Products
2.1.1	Microbiological: sterility
2.1.3	Chemical / Physical
2.1.4	Biological
2.2.1	Sterile Products
2.2.1.1	Aseptically prepared
2.2.3	Biological Medicinal Products
2.2.3.5	Biotechnology products
2.3	Other Importation Activities
2.3.4	Other <free text>

Clarifying Remarks: No secondary packaging performed on site.

1.1.1.4 & 1.3.1.2 - excludes batch certification.

1.3.1.2 & 1.3.1.5 - includes manufacture of low bioburden biological active substances and dosage forms containing biological active substance.

2.2.1.1 & 2.2.3.5 - product not physically imported to this site.

2.3.4 - other authorised importation activities are importation of intermediate biological (immunological) active substance which undergoes further processing on site.

4B Scope of activities defined on MIA using proposed modified MIA interpretation

PART 1 – Manufacturing Operations

1.1	Sterile Products
1.1.1	Aseptically prepared (processing operations for the following dosage forms)
1.1.1.2	Lyophilisates
1.1.1.4	Small volume liquids
1.1.3	Batch certification
1.3	Biological Medicinal Products (Processing Operations)
1.3.1.2	Immunological products
1.3.1.5	Biotechnology products
1.3.1.8	Other biological medicinal products <free text>
1.3.2	Batch certification
1.3.2.5	Biotechnology products
1.4.2	Sterilisation of active substances/excipients/finished product
1.4.2.1	Filtration
1.6	Quality Control Testing
1.6.1	Microbiology – sterility
1.6.3	Chemical / Physical
1.6.4	Biological

PART 2 - Importation activities

2.1	Quality Control Testing of Imported Medicinal Products
2.1.1	Microbiology : sterility
2.1.3	Chemical / Physical
2.1.4	Biological
2.2.1	Sterile Products
2.2.1.1	Aseptically prepared
2.2.3	Biological Medicinal Products
2.2.3.5	Biotechnology products
2.3	Other Importation Activities
2.3.4	Other <free text>

Clarifying Remarks: 1.3.1.2 & 1.3.1.5 - include manufacture of low bioburden biological active substances and dosage forms containing biological active substance.

2.3.4 - other authorised importation activities are importation of immunological intermediate biological active substance which undergoes further processing on site.

WORKED EXAMPLE 5

This example relates to a site authorised to carry out the following activities:

→ Manufacture of sterile lyophilisate. This is a biological product but the biological active substance which is derived from a biotechnology process is not manufactured on site.

→ Importation of biological active substance which undergoes aseptic filling / lyophilisation on site.

→ Batch certification of imported aseptically prepared small volume liquid product and a lyophilisate product both of which contain biological active substance derived from a biotechnology process.

→ Quality control testing in relation to products manufactured on site and imported products.

5A Scope of activities defined on MIA using current terminology and EudraGMDP rules

PART 1 – Manufacturing Operations

1.1	Sterile Products
1.1.1	Aseptically prepared (list of dosage forms)
1.1.1.2	Lyophilisates
1.3	Biological Medicinal Products
1.3.1.5	Biotechnology products
1.4.2	Sterilisation of active substances/excipients/finished product
1.4.2.1	Filtration
1.6	Quality Control Testing
1.6.1	Microbiology – sterility
1.6.3	Chemical / Physical
1.6.4	Biological

PART 2 - Importation activities

2.1	Quality Control Testing of Imported Medicinal Products
2.1.1	Microbiology sterility
2.1.3	Chemical / Physical
2.1.4	Biological
2.2.1	Sterile Products
2.2.1.1	Aseptically prepared
2.2.3	Biological Medicinal Products
2.2.3.5	Biotechnology products
2.3	Other Importation Activities
2.3.3	Biological Active Substances

Clarifying Remarks: 1.3.1.5 - refers to manufacture of dosage forms containing biological active substance.

5B Scope of activities defined on MIA using proposed modified MIA interpretation

PART 1 – Manufacturing Operations

1.1	Sterile Products
1.1.1	*Aseptically prepared (processing operations for the following dosage form)*
1.1.1.2	Lyophilisates
1.1.3	Batch certification
1.3	Biological Medicinal Products (processing operations)
1.3.1.5	Biotechnology products
1.3.2	Batch certification
1.3.2.5	Biotechnology products
1.4.2	Sterilisation of active substances/excipients/finished product
1.4.2.1	Filtration
1.6	Quality Control Testing
1.6.1	Microbiology – sterility
1.6.3	Chemical / Physical
1.6.4	Biological

PART 2 - Importation activities

2.1	Quality Control Testing of Imported Medicinal Products
2.1.1	Microbiology : sterility
2.1.3	Chemical / Physical
2.1.4	Biological
2.2.1	Sterile Products
2.2.1.1	Aseptically prepared
2.2.3	Biological Medicinal Products
2.2.3.5	Biotechnology products
2.3	Other Importation Activities
2.3.3	Biological active substance

Clarifying Remarks: 1.3.1.5 - refers to manufacture of dosage forms containing biological active substance.

APPENDIX 2 - Processing Operations for biological active substance

The section below lists specific processing operations carried out in relation to the manufacture or modification of a biological active substance / antigen. (NOTE: this terminology was last discussed during GMDP Meeting no.49 in December 2007. The information in this Appendix is not part of the current EU MIA format but is included here for completeness. It had originally been intended that a description of these activities be included under clarifying remarks but IT at EMA anticipated some problems with this at the time)

A. General processing operations relating to establishing and growth of cells/viruses

A.1 Establishing Master Cell Bank
A.2 Establishing Working Cell Bank
A.3 Establishing Cell Pool
A.4 Establishing Master Transgenic Bank
A.5 Establishing Working Transgenic Bank
A.6 Establishing Master Seed Lot
A.7 Establishing Working Seed Lot
A.8 Viral production using eggs
A.9 Viral production on cultured cells
A.10 Fermentation / Inactivation
A.11 Mammalian Cell Culture
A.12 Other < Specify >

B. Operations relating to isolation, purification or modification of an active/antigen

B.1 Initial processing of organ, cell suspension, fluid, tissue
(processing here includes cutting / mixing of tissues)
B.2 Isolation of substance
(includes isolation from cells, organs, fluid, tissue or plant materials)
B.3 Purification of substance
B.4 Modification of substance
(includes chemical modification of the substance (eg Pegylation)
B.5 Inactivation of adventitious bacteria / viruses
B.6 Inactivation of cells / substances
(inactivation of some or all of the cell activities eg tumour cells in tumour cell vaccines)
B.7 Other < Specify >

C. Specific Cell Therapy Product operations

C.1 Isolation of cells
(isolation from (blood) cell suspensions, organs and tissues) where this is not covered by the Blood & Tissues directive
C.2 Purification / depletion / enrichment
(e.g. Cell-sorting, fractionation, density gradient centrifugation)
C.3 Differentiation or modification or manipulation
(e.g. using specific growth factors, specific matrices, or substances for loading of cells)
C.4 Tissue engineering / three dimensional culturing
(e.g. scaffold, skin, cartilage, vessels….)
C.5 Other < Specify >

D. Specific Gene Therapy Product operations

D.1 Preparation of (e.g. viral) vectors
(e.g. inserting plasmids into cells by electroporation or liposome inclusions or inserting vectors into cells by incubation)

D.2 Genetic modification of cells: transfection or infection

D.3 Other < Specify >

Special Precautions which may be identified in relation to the processing operations for biologicals

Manufacture of Sterile Substance
Manufacture of BCG vaccine
Handling of Bacillus anthracis
Handling of Clostridium botulinum
Handling of Clostridium tetani
Use of Animals for manufacture
Other (specify) <free text>

These “special precautions” may need further review following completion of the ongoing dedicated facilities discussions.

<u>WORKED EXAMPLE - using terminology described in Appendix 2</u>

This example relates to a site authorised to carry out the following activities:

→ Manufacture biological active substance using a biotechnology process employing the following processes:

- Mammalian cell culture
- Isolation of biological active substance
- Purification of biological active substance
- Viral inactivation

The low bioburden bulk biological active substance is shipped off to another site where aseptic filling, packaging and batch certification take place.

→ The following steps are carried out in relation to vaccine manufacture at the site:

- Importation of partially manufactured biological active substance (polysaccharide - antigen)
- Modification of a biological active substance (chemical conjugation of antigen)
- Aseptic filling of vaccine

(no secondary packaging activity takes place at the site)

The bulk syringes are shipped off to another site where secondary packaging activities and final certification takes place.

→ Aseptic manufacture of a lyophilisate dosage form. Secondary packaging and final certification takes place at another site.

→ The site also carries out batch certification of an imported biological biotechnology product presented as a sterile lyophilisate. The product is not physically imported to this site.

→ Quality control testing in relation to products manufactured on site and imported products.

<u>Scope of activities defined on MIA using proposed modified MIA interpretation + Appendix 2</u>

PART 1 – Manufacturing Operations

1.1	Sterile Products
1.1.1	Aseptically prepared (processing operations for the following dosage forms)
1.1.1.2	Lyophilisates

1.1.1.4 Small volume liquids

1.1.3 Batch certification

1.3 Biological Medicinal Products (Processing Operations)
1.3.1.2 Immunological products
1.3.1.5 Biotechnology products
1.3.1.8 Other biological medicinal products <free text>

1.3.2 Batch certification
1.3.2.5 Biotechnology products

1.4.2 Sterilisation of active substances/excipients/finished product
1.4.2.1 Filtration

1.6 Quality Control Testing
1.6.1 Microbiology – sterility
1.6.3 Chemical / Physical
1.6.4 Biological

PART 2 - Importation activities

2.1 Quality Control Testing of Imported Medicinal Products
2.1.1 Microbiology: sterility
2.1.3 Chemical / Physical
2.1.4 Biological

2.2.1 Sterile Products
2.2.1.1 Aseptically prepared

2.2.3 Biological Medicinal Products
2.2.3.5 Biotechnology products

2.3 Other Importation Activities
2.3.4 Other <free text>

Clarifying Remarks: 1.3.1.2 & 1.3.1.5 - include manufacture of low bioburden biological active substances and dosage forms containing biological active substance.

1.3.1.8 - Authorised activities (with reference to activities described in Appendix 2) A11, B2, B3, B4, & B5.

2.3.4 - other authorised importation activities are importation of immunological intermediate biological active substance which undergoes further processing on site.