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Interpretation of the Union format for GMP certificate

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Interpretation of the Union format for GMP certificate

1. Introduction

The purpose of this document is to provide guidance to industry and regulators on the interpretation of activities defined on GMP certificates issued by Competent Authorities in the EEA. Where necessary, clarifying guidance text is provided under certain GMP certificate entries in shaded text boxes. The guidance in these text boxes applies to human medicinal products, veterinary medicinal products and Investigational Medicinal Products (IMPs). Any specific guidance which applies to IMPs only is identified where necessary. Whilst there is no European legal requirement for the authorisation of active substance manufacturers, GMP certificates may be issued following inspection of these sites either within the EEA or in third countries. Details for GMP certification of active substance manufacturers are included in sections 3 & 4 of this document.

Guidance is provided in certain other EudraGMDP Q&As in relation to information to be provided in Part 1 of the EU format for a GMP certificate and no further guidance is provided in relation to Part 1 in this document. The following guidance relates to Part 2 only.

1. MANUFACTURING OPERATIONS – MEDICINAL PRODUCTS

1.

The scope of manufacturing operations which are certified at the site is defined using the following unit operations. Each of the following individual operations carried out at the certified site should be identified as appropriate.

*Processing Operations:	this includes any or all processing steps in the manufacture of a dosage form.
*Primary Packaging:	this refers to placing and sealing of the medicinal product within the finished product packaging material which is in direct contact with the product, i.e. immediate packaging.
Secondary Packaging:	this refers to placing the medicinal product, which is already sealed within its primary packaging material within an outer packaging material, i.e. outer packaging. 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 at an authorised manufacturing site in the EEA 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 at an authorised manufacturing site before its release to the clinical trial sponsor or before export.
Quality Control:	refers to types of laboratory testing for which the site is certified.

*Using the guidance described in Chapters 3 and 5 of the EU GMP Guidelines, Volume 4 of the EudraLex, Part I, 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 considered GMP certified with regard to 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 the 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 carries out processing operations or packaging of medicinal products is also understood to be GMP certified 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 a Manufacturers / Importers Authorisation (MIA) in the EEA and 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. Such sites are also considered GDP certified in relation to these activities unless there is a comment to the contrary within the clarifying remarks.

Real Time Release Testing

If a manufacturer is considered GMP certified in relation to the performance of 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 certified 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 <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 which is issuing the GMP certificate.

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 certified site 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 <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 <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)*

'Over-encapsulation' *(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. If the certifying authority does not consider the processing steps to be partial manufacture of a biological medicinal product then the activities should be recorded, as appropriate, in sections 3 & 4 of the GMP certificate which relate to manufacturing operations for active substances.

Where the certified operations also include manufacture of the finished dosage form for the biological product then the relevant dosage form should also be selected on the GMP certificate (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 a GMP certificate 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, allergens).

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 a GMP certificate 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 a GMP certificate 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 human blood, cells or tissues in which case the products may be more be more appropriately categorised as "Blood products", "Cell therapy products" or "Tissue engineered products".

Tissue engineered products

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

Other 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 named categories.

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 <free text>

1.3.2 Batch certification (list of product types)

This section should be completed with regard to 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 <free text>

1.4 Other products or manufacturing activity

Note: where a manufacturer carries out processing steps in relation to manufacture of herbal or homoeopathic dosage form (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 certified for manufacture of herbal or homoeopathic products then a clarifying remark (herbal products only or homoeopathic products only) should be included in relation to the dosage forms.

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 certificate 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. Storage of stability samples could also be listed here where this is the specific activity which is being carried out at the certified site.

'Manufacture of Excipient Material'

The name of the excipient material covered within the scope of the GMP certificate should be also be specified. Include summary detail on the nature of the excipient and the type of manufacturing operations being certified within the clarifying remarks section.

1.5 Packaging

1.5.1 Primary packaging

Primary packing of a sterile product is taken as being included as part of the processing operations covered under section 1.1 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 <free text>

Examples of activities to be captured under 1.5.1.17 'Other'

If the certified site 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' 1.5.1.17.

'Primary packing of *(name of dosage form)* which undergoes terminal sterilisation'

1.5.2 ☐ *Secondary packaging*

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

1.6 Quality control testing

The Quality Control testing covered within the scope of the GMP Certificate should be identified using categories described 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 GMP certificate 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.

Clarifying remarks which extend or restrict the validity period for a GMP certificate should be entered in the section used for public remarks.

2. IMPORTATION OF MEDICINAL PRODUCTS

2.1 Quality control testing of imported medicinal products

Where Quality Control testing is carried out at the site located in the EEA in relation to imported medicinal products, the certified 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 certified operations at a site located in the EEA includes batch certification of either an imported finished product or a bulk dosage form which undergoes packing after importation. If the certified site is also the site of physical importation then an entry should also be made under 2.3.1.

For **IMP** manufacturers (Annex 2), batch 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 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 <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 certified for receipt and storage of imported product which is awaiting QP certification. QP 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. This point covers not only finished product intermediate but also bulk products.

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 the clarifying remark is intended as a general comment relating to activities at the site, a numerical reference, as per the item listing in the GMP certificate format, should be included wherever a clarifying remark or restriction is applied.
>
> Clarifying 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. Clarifying remarks which extend or restrict the validity period for a GMP certificate should be entered in the section used for public remarks.

3. MANUFACTURING OPERATIONS - ACTIVE SUBSTANCES

Active Substance:

The names of the active substance manufactured at the site should be entered above and the applicable manufacturing operations which are being certified in relation to that active substance should be identified in Sections 3.1 – 3.5 below. This should be repeated for each active substance manufactured at the site. If the site manufactures an active substance intermediate then the text "active substance intermediate(s)" should be entered above and the relevant manufacturing operations identified as described previously. The name of the active substance intermediate(s) should be entered as a clarifying remark.

Real-Time Release Testing

Where an active substance manufacturer is considered GMP certified in relation to performance of real time release testing instead of one or more quality control tests then this should be identified as a clarifying remark in relation to the relevant active substance. The type of real time release testing which is authorised should also be identified in the clarifying remarks.

3.1.1 includes any steps from manufacture of the defined starting materials until the step prior to manufacture of the crude active substance

3.1.1 ☐ Manufacture of active substance intermediates

3.1.2 ☐ Manufacture of crude active substance

3.1.3 ☐ Salt formation / Purification steps : <free text> (e.g. crystallisation)

3.1.4 ☐ Other <free text>

Items 3.2.1, 3.2.2 and 3.2.3 are completed below where the activities are not considered by the certifying authority to be partial manufacture of a medicinal product and therefore not covered under section 1.3 of the GMP certificate. Item 3.2.5 relates to either physical or chemical modification of the extracted active substance. Activities such as drying or milling are captured under the section on general finishing steps (3.5).

The term "extraction" used in the title of this section is a general term to cover a number of methods by which an active substance can be isolated from a natural source. The following are some examples:

- extraction of a herbal substance from plants should be entered under 3.2.1.
- purification of a herbal extract by distillation or fractionation should be entered under 3.2.6 and a reference to the plant source from which the extract has been obtained should be included (3.2.1.).
- manufacture of an active substance gas by an air separation process should be entered under 3.2.7.

3.2.1 ☐ Extraction of substance from plant source

3.2.2 ☐ Extraction of substance from animal source

3.2.3 ☐ Extraction of substance from human source

3.2.4 ☐ Extraction of substance from mineral source

3.2.5 ☐ Modification of extracted substance <specify source 1,2,3,4>

3.2.6 ☐ Purification of extracted substance <specify source 1,2,3,4 >

3.2.7 ☐ Other <free text>

3.3 Manufacture of Active Substance using Biological Processes

This section is completed where the manufacturing activities in relation to a biological active substance are not considered to be covered under section 1.3 of the GMP certificate.

3.3.1 ☐ Fermentation

3.3.2 ☐ Cell Culture <specify cell type> (e.g. mammalian / bacterial)

3.3.3 ☐ Isolation / Purification

3.3.4 ☐ Modification

3.3.5 ☐ Other <free text>

3.4 Manufacture of sterile active substance (sections 3.1, 3.2, 3.3 to be completed as applicable)

This section is completed in relation to certification of those steps in the manufacturing process which render an active substance sterile. If a Competent Authority considers the steps which render an active substance sterile as partial manufacture of the medicinal product then relevant entries should also be made under Section 1.1. of the GMP certificate.

3.4.1 ☐ Aseptically prepared

3.4.2 ☐ Terminally sterilised

3.5 General Finishing Steps

3.5.1 ☐ Physical processing steps < specify > (e.g. drying, milling / micronisation, sieving)

3.5.2 ☐ Primary Packaging (enclosing / sealing the active substance within a packaging material which is in direct contact with the substance)

3.5.3 ☐ Secondary Packaging (placing the sealed primary package within an outer packaging material or container. This also includes any labelling of the material which could be used for identification or traceability (lot numbering) of the active substance)

3.5.4 ☐ Other <free text> (for operations not described above)

3.6 Quality Control Testing

This section should be completed in relation to quality control testing of active substances or intermediates which are manufactured at the site. This section should be completed even if entries have been made under sections 1.6 and 2.1 relating to medicinal products manufactured at the same site.

A site which is GMP certified under 3.6.3 is also considered GMP certified in relation to microbiological testing activities other than sterility testing (i.e. activities under 3.6.2) unless a comment to the contrary is included in the restrictions /clarifying remarks section.

3.6.1 ☐ Physical / Chemical testing

3.6.2 ☐ Microbiological: testing (excluding sterility testing)

3.6.3 ☐ Microbiological: testing (including sterility testing)

3.6.4 ☐ Biological Testing

4. OTHER ACTIVITIES- ACTIVE SUBSTANCES

This section should be completed in relation to activities which are not described above. A description of the activity should be entered below.

<free text>

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

Unless the clarifying remark is intended as a general comment relating to activities at the site, a numerical reference, as per the item listing in the GMP certificate format, should be included wherever a clarifying remark or restriction is applied. Where remarks apply to a particular active substance then the name of the active substance should be listed in the remark in addition to the numerical reference for the relevant activities.

Clarifying 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. Clarifying remarks which extend or restrict the validity period for a GMP certificate should be entered in the section used for public remarks.