Biologicals
for human use

Dr. Elisabeth Kiene
AGES MEA, LCM, REGA
A biological medicinal product is a product, the active substance of which is a biological substance.

A biological substance is a substance that is

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

Definition acc to Directive 2001/83/EC Annex I

- For biological medicinal products, starting materials shall mean any **substance of biological origin** such as
  - micro-organisms,
  - organs and tissues of either plant or animal origin,
  - cells or fluids (including blood or plasma) of human or animal origin, and
  - biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells).
Considered as biologicals

Acc to Directive 2001/83/EC Annex I and CMDh

- Immunological medicinal products.
- Medicinal products derived from human blood and human plasma as defined, respectively in Art 1 (4) and (10) of Directive 2001/83/EC.
- Medicinal products developed by recombinant DNA technology.
- Medicinal products developed by controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells.
- Medicinal products developed by hybridoma and monoclonal antibody methods.

CMDh’s Overview of biological active substances of non-recombinant origin
## Legal Bases for MAA of biologicals

According to Directive 2001/83/EC and Austrian Medicinal Products Act

<table>
<thead>
<tr>
<th>Type of application</th>
<th>Directive 2001/83/EC</th>
<th>Austrian Medicinal Products Act</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full application</td>
<td>Art 8 (3)</td>
<td>Art 9a</td>
</tr>
<tr>
<td>Generic application</td>
<td>Art 10 (1)</td>
<td>§ 10 (1) Z1</td>
</tr>
<tr>
<td>Hybrid application</td>
<td>Art 10 (3)</td>
<td>§ 10 (9)</td>
</tr>
<tr>
<td>Similar biological application</td>
<td>Art 10a</td>
<td>Art 10 (8)</td>
</tr>
<tr>
<td>Well-established use application</td>
<td>Art 10a</td>
<td>Art 10a</td>
</tr>
<tr>
<td>Fixed combination application</td>
<td>Art 10b</td>
<td>Art 10b</td>
</tr>
<tr>
<td>Informed consent application</td>
<td>Art 10c</td>
<td>Art 10 (1) Z2</td>
</tr>
</tbody>
</table>

Contact RMS first for abridged application.
### Specific conditions for variations

**Acc to Guidelines on the details of the various categories of variations** ...

<table>
<thead>
<tr>
<th>B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier</th>
<th>Conditions to be fulfilled</th>
<th>Documentation to be supplied</th>
<th>Procedure type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a)</strong> The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer</td>
<td>1, 2, 3</td>
<td>1, 2, 3, 4, 5, 6, 7</td>
<td>IAIN</td>
</tr>
<tr>
<td><strong>b)</strong> Introduction of a manufacturer of the active substance supported by an ASMIF</td>
<td></td>
<td></td>
<td>II</td>
</tr>
<tr>
<td><strong>c)</strong> The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability</td>
<td></td>
<td></td>
<td>II</td>
</tr>
<tr>
<td><strong>d)</strong> New manufacturer of material for which an assessment is required of viral safety and/or TSE risk</td>
<td></td>
<td></td>
<td>II</td>
</tr>
<tr>
<td><strong>e)</strong> The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product</td>
<td></td>
<td></td>
<td>II</td>
</tr>
</tbody>
</table>
Specific conditions for variations

Acc to Guidelines on the details of the various categories of variations ...

<table>
<thead>
<tr>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. For starting materials and reagents the specifications (including in process controls, methods of analysis of all materials), are identical to those already approved. For intermediates and active substances the specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved.</td>
</tr>
<tr>
<td>2. The active substance is not a biological/immunological substance or sterile.</td>
</tr>
<tr>
<td>3. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current <em>Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products</em>.</td>
</tr>
<tr>
<td>4. Method transfer from the old to the new site has been successfully completed.</td>
</tr>
<tr>
<td>5. The particle size specification of the active substance and the corresponding analytical method remain the same.</td>
</tr>
</tbody>
</table>
Batch release by OMCL

Acc to Art 26 Austrian Medicinal Products Act

- **Art 26 (1) Austrian Medicinal Products Act:**
  The following medicinal products for human use **require batch release** by OMCL:
  - Medicinal products produced from human blood or human plasma.
  - Certain immunological medicinal products consisting of vaccines, toxines, sera or allergens.

→ “Charge staatlich freigegeben”
(„Batch released by OMCL“)

Blue Box Requirement
Batch release by OMCL

Acc to Art 26 Austrian Medicinal Products Act

- **Art 26 (4)** Austrian Medicinal Products Act:
  
  **Exemptions** from the obligation to have batches released by OMCL can be issued, with regard to
  
  • special characteristics of a medicinal product,
  • its route of administration or
  • its indication and
  • provided that safety is not impaired.

Exemptions have to be specifically applied for.

→ „Charge verkehrsfähig“
  („Batch marketable“)

Blue Box Requirement
Batch release by OMCL

Acc to Art 26 Austrian Medicinal Products Act

- **Art 26 (4)** Austrian Medicinal Products Act:
- Example: human albumin (as excipient)
  - Human albumin must be authorised in EU/EEA.
  - Human albumin batches must be tested and approved by an OMCL in EU/EEA.
  - Traceability from plasma donor to finished product must be granted until the expiry date of the finished product.
  - If the manufacturer of human albumin differs from the manufacturer of the finished product:
    1. Appropriate contract for traceability is necessary.
    2. In case of recalls of human albumin batches, the manufacturer of human albumin must immediately inform the manufacturer of the finished product about the recall and the reasons for it.
Batch release by OMCL

Acc to Art 26 Austrian Medicinal Products Act

- **Art 26 (4) Austrian Medicinal Products Act:**
  - Example: human albumin (as excipient)
    - Shelf lives of human albumin and finished product should be synchronised. Human albumin’s shelf life shall not exceed 5 years. Human albumin must not be used if already expired at time of addition.
Identification requirements

Acc to Austrian Regulation on identification requirements for certain medicinal products

- medicinal products produced from human **blood** or human **plasma** (except only human albumin as stabilising excipient)
- **vaccines**

→ **self-adhesive label**

**Blue Box Requirement**

- on primary packaging
- one self-adhesive label per unit dose
- information on self-adhesive label:
  1. product name to unambiguously identify the product
  2. expiry date
  3. batch number
Specific requirements ...

... for plasma-derived medicinal products

- Guideline on the warning on transmissible agents in summary of product characteristics (SmPCs) and package leaflets for plasma-derived medicinal products
  
  “Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. ...”
Strain variations
For influenza vaccines

WHO recommendations on the composition of influenza virus vaccines

<table>
<thead>
<tr>
<th>Northern hemisphere influenza seasons</th>
<th>Southern hemisphere influenza seasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-2018</td>
<td>2018</td>
</tr>
<tr>
<td>2016-2017</td>
<td>2017</td>
</tr>
<tr>
<td>2015-2016</td>
<td>2016</td>
</tr>
<tr>
<td>2014-2015</td>
<td>2015</td>
</tr>
<tr>
<td>2013-2014</td>
<td>2014</td>
</tr>
<tr>
<td>2012-2013</td>
<td>2013</td>
</tr>
<tr>
<td>2011-2012</td>
<td>2012</td>
</tr>
<tr>
<td>2010-2011</td>
<td>2011</td>
</tr>
</tbody>
</table>

Archive of recommendations for past seasons from 1998 to 2010

B.I.a.5 Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza

<table>
<thead>
<tr>
<th>Procedure type</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
</tr>
</tbody>
</table>

a) Replacement of the strain(s) in a seasonal, pre-pandemic or a pandemic vaccine against human influenza
Specific guidelines on biologicals

To be considered before application

- EMA’s guidelines on biologicals:

Biologicals: active substance

The European Medicines Agency’s scientific guidelines on biological drug substances help medicine developers prepare marketing authorisation applications for human medicines.

If you have comments on a document which is open for consultation, use the form for submission of comments on scientific guidelines.

For a complete list of scientific guidelines currently open for consultation, see Public consultations.

- Manufacture, characterisation and control of the active substance
- Specifications
- Comparability and biosimilarity
- Plasma-derived medicinal products
- Plasma master file
- Vaccines
- Stability

Biologicals: finished product

The European Medicines Agency’s scientific guidelines on biological medicinal products help medicine developers prepare marketing authorisation applications for human medicines.

If you have comments on a document which is open for consultation, use the form for submission of comments on scientific guidelines.

For a complete list of scientific guidelines currently open for consultation, see Public consultations.

- Pharmaceutical development
- Product information
- Adventitious agents safety evaluation viral safety
- Transmissible spongiform encephalopathies (TSEs) (animal and human)
- Investigational medicinal products
- Genetically modified organisms (GMOs)
- Specifications
Specific guidelines on biologicals

To be considered before application

- WHO’s guidelines on biologicals:
Specific guidelines on biologicals
To be considered before application

- **EMA’s guidelines on Plasma Master File:**

  **Plasma Master File (PMF) procedural guidelines**

<table>
<thead>
<tr>
<th>Document(s)</th>
<th>Language</th>
<th>Status</th>
<th>First published</th>
<th>Last updated</th>
<th>Effective Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline on requirements for Plasma Master File (PMF) Certification</td>
<td>(English only)</td>
<td>adopted</td>
<td>26/02/2004</td>
<td></td>
<td>31/03/2004</td>
</tr>
<tr>
<td>Standard operating procedure for coordinating pre-approval inspections in the</td>
<td>(English only)</td>
<td>adopted</td>
<td>21/07/2004</td>
<td>30/04/2013</td>
<td>29/04/2013</td>
</tr>
<tr>
<td>context of plasma-master-file certification</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Related links**

- Variation guideline and PMF list* (see section D and B.V.a)
- European Medicines Agency Post-Authorisation Guidance (Ref. Variations type I)
- European Medicines Agency Post-Authorisation Guidance (Ref. Variations type II)
- Commission guideline on PMF 2nd step
- *Note: Transfer of PMF to a new Holder and 2nd step procedure since 01.01.2010 are handled as variation procedures.
Sources

For further information

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- Regulation (EC) No 1394/2007
- CMDh’s Overview of biological active substances of non-recombinant origin
- CMDh’s Questions and answers on biologicals
- Variations classification guideline
- Austrian Medicinal Products Act
- BASG/AGES MEA FAQ on batch release
- Verordnung des Bundesministers für Gesundheit, Sport und Konsumentenschutz betreffend Identifizierungserfordernisse für bestimmte Arzneispezialitäten
- Blue Box Requirements
- WHO recommended influenza strains
- Guideline on the warning on transmissible agents in summary of product characteristics (SmPCs) and package leaflets for plasma-derived medicinal products
- EMA’s guidelines on active substances
- EMA’s guidelines on finished product
- WHO’s guidelines on biologicals
- EMA’S guidelines on PMF
Any
Dr. Elisabeth Kiene
Regulatory Expert

BASG -
Bundesamt für Sicherheit im Gesundheitswesen

Traisengasse 5
1200 Wien
T +43 (0) 50 555 36664
elisabeth.kiene@ages.at
www.basg.gv.at