GMP, Quality by Design and validation

Mats Welin, Member of BWP and EMA PAT team
Introduction

• EU GMPs – what and why?
• GMP for biologicals
• Quality by design
• Process validation
GMP – what it is?

GMP shall mean the part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use.
GMP- what is it

Article 40 - Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to the holding of an authorization. This manufacturing authorization shall be required notwithstanding that the medicinal products manufactured are intended for export.

Article 44- Member States shall take all appropriate measures to ensure that the manufacture of veterinary medicinal products in their territory is subject to the holding of an authorization. This manufacturing authorization shall likewise be required for veterinary medicinal products intended for export.
GMP – what is it?


**EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines**

# GMP – what is it?

**Good Manufacturing Practice**

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<th>Part I</th>
<th>Part II</th>
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<th>Annexes</th>
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<tr>
<td>Basic Requirements for Medicinal Products</td>
<td>Basic Requirements for Active Substances used as Starting Materials</td>
<td>GMP related documents</td>
<td>Substance specific documents</td>
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<tr>
<td>9 Chapters</td>
<td>1 Chapter (49pg)</td>
<td>5 documents</td>
<td>19 annexes</td>
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</tbody>
</table>
GMP for SME- Basic requirements

- Pharmaceutical quality system
  - Management of changes, deviations
- Premises / Equipment / Materials
  - Facility designed (process flow, equipment, air flows etc)
  - Reagents / Materials
- Documentation
  - Need to have process and procedure defined and documented
  - Means to control this
- Production
- Personnel
  - Adequate numbers, training and roles etc
- Quality control
- Outsourced activities
- Management of complaints & recalls
- Self inspection
Annex 2 Manufacture of Biological active substances and Medicinal Products for Human Use

Scope

The methods employed in the manufacture of biological active substances and biological medicinal products for human use ('biological active substances and medicinal products') are a critical factor in shaping the appropriate regulatory control. Biological active substances and medicinal products can be defined therefore largely by reference to their method of manufacture. This annex provides guidance on the full range of active substances and medicinal products defined as biological.
Principles

The level of GMP increases in detail from early to later steps in the manufacture of biological substances but GMP principles should always be adhered to. The inclusion of some early steps of manufacture within the scope of the annex does not imply that those steps will be routinely subject to inspection by the authorities.

Guidance for medicinal products derived from fractionated human blood or plasma is covered in Annex 14 and for non-transgenic plant products in Annex 7.

In certain cases, other legislation is applicable to the starting materials for biologicals: e.g. GMOs, blood or blood components that are used as starting materials for ATMPs, cell components for ATMPs.
### Table 1 (excerpt). Illustrative guide to manufacturing activities within the scope of Annex 2.

<table>
<thead>
<tr>
<th>Type and source of material</th>
<th>Example product</th>
<th>Application of this guide to manufacturing steps shown in grey</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Virus or bacteria / fermentation / cell culture</td>
<td>Viral or bacterial vaccines; enzymes, proteins</td>
<td>Establishment &amp; maintenance of MCB, WCB, MVS, WVS</td>
</tr>
<tr>
<td>3. Biotechnology - fermentation / cell culture</td>
<td>Recombinant. products, MAb, allergens, vaccines Gene Therapy, viral and non-viral vectors, plasmids</td>
<td>Establishment &amp; maintenance of MCB² and WCB, MSL, WSL</td>
</tr>
<tr>
<td>6. Human sources</td>
<td>Urine derived enzymes, hormones</td>
<td>Collection of fluid</td>
</tr>
<tr>
<td>7. Human and / or animal sources</td>
<td>Gene therapy: genetically modified cells</td>
<td>Donation, procurement and testing of starting tissue / cells⁷</td>
</tr>
<tr>
<td></td>
<td>Somatic cell therapy</td>
<td>Donation, procurement and testing of starting tissue / cells</td>
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<tr>
<td></td>
<td>Tissue engineered products</td>
<td>Donation, procurement and testing of starting tissue / cells⁷</td>
</tr>
</tbody>
</table>

**Increasing GMP requirements**
Quality by Design

“Develop a harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to quality risk management and science.”

ICH Brussels July 2003

Joint effort Industry and regulators applicable both to small molecules and biotech

Q8(R2): Pharmaceutical Development Revision (2009)
Q9: Quality Risk Management (2006)
Q11: Development and Manufacture of Drug Substances (chemical/biological entities) (2012)
Q12 Life cycle management (under preparation)
Q8 Pharmaceutical Development
Basic Principles

• Quality cannot be tested into products; i.e. quality should be built in by design.
• The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product.
• Information from pharmaceutical development studies can be a basis for Quality Risk Management.
QbD in a nutshell

Testing in quality

Quality by design
Pharmaceutical Development - Basic Principles

- Basic elements of Pharmaceutical development for all products:
  - defining Quality Target Product Profile
  - identifying critical quality attributes of the drug product
  - determining (critical) quality attributes of the starting materials (drug substance, excipients)
  - selecting an appropriate manufacturing process
  - identifying a control strategy
Pharmaceutical Development: Opportunities

• Depending on the level of development (scientific understanding) achieved and a robust quality system in place, opportunities exist to consider more flexible regulatory approaches, for example, to facilitate:
  – risk-based regulatory decisions (reviews and inspections);
  – manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review;
  – reduction of post-approval submissions;
  – real-time release testing, leading to a reduction of end-product release testing.
Pharmaceutical Development: Opportunities cont.

- But
  - the main driver may be a better understanding of the process and higher predictability of the outcome. If I know my process well this means that what goes in is likely to come out as a product that can be released to the market. This limits risk for shortages and lower costs due to less rejections. In addition easier to make future changes.
Pharmaceutical Development (QbD): Demystification

• A systematic approach will facilitate the process to achieve quality and should automatically generate more knowledge.

• Not necessarily new requirements:
  – Pharmaceutical development has anyhow to be done
  – QbD does not require the establishment of e.g., design space or real time release testing: a company might decide based on full scientific understanding not to establish a design space or RTR testing.
  – The level of development will depend on the complexity of the process and product and on the opportunities chosen or wanted by the applicant.
Process validation

- **PV** develops during product lifecycle. Process validation studies should normally be completed and included in the Marketing Authorisation Application (MAA) or a variation application, where relevant.

- Successful process validation should **demonstrate that the design of the manufacturing process and its control are appropriate for commercial manufacturing**.

- Studies should include process evaluation of **all steps in the manufacture**. All in-put and out-put should be described.

- The applicant should base the **inputs and outputs** studied on their **potential criticality** and justify their selection.
Process Validation, cont.

Contribution of data from small scale studies to the overall validation package is expected and acceptable.

Successful demonstration of the suitability of the small scale model could reduce data requirements for process verification in large scale (e.g. reduced number of batches) and/or impact on control strategy.

Where prior knowledge or platform manufacturing experience is utilised, the contribution of these data to the overall validation package will depend upon justification that the data is representative of the proposed commercial process.
QWP Guideline on Process Validation for Finished Products-Scope

• “This document is intended to provide guidance on the process validation information and data to be provided in regulatory submissions for the finished dosage forms of chemical medicinal products for human and veterinary use.....The general principles also apply to active substances.”

• .... The principles described are also applicable to biological medicinal products. However, these should be considered on a case by case basis in view of the complex nature and inherent variability of the biological substance.....

.....“clarifies how companies can take advantage of the new possibilities given when applying enhanced process understanding coupled with risk management tools under an efficient quality system as described by ICH Q8-Q10.”,
Draft BWP guideline PV biological active substances

Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission

Draft

<table>
<thead>
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<tbody>
<tr>
<td>Draft Agreed by Biologics Working Party</td>
<td>April 2014</td>
</tr>
<tr>
<td>Adoption by CHMP for release for consultation</td>
<td>25 April 2014</td>
</tr>
<tr>
<td>Start of public consultation</td>
<td>1 May 2014</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>31 October 2014</td>
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</tbody>
</table>

Comments should be provided using this [template](#). The completed comments form should be sent to BWPSecretariat@ema.europa.eu

**Keywords**

- active substance
- biologics
- process validation
- process evaluation
- process verification
- lifecycle
Contents

Scope primarily recombinant proteins. Principles may apply to other biologicals as well

General aspects in (Development)- Evaluation – Verification

More specific points to consider
• Upstream processing
• Downstream processing
• Multifacility production

Circulated for comments Q2-3 2014. Work ongoing to update
GMP Annex 15
The Annex describes the principles of qualification and validation which are applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal products

Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed.

The relevant concepts and guidance presented in ICH Q8, Q10 and Q11 should also be taken into account

• Focus overall validation activities, not only what to put in file.
• Describes traditional validation and continuous process verification as well as on going process verification
Thank you for your attention

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