



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



GMP, Quality by Design and validation

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An agency of the European Union





Introduction

- EU GMPs – what and why?
- GMP for biologicals
- Quality by design
- Process validation



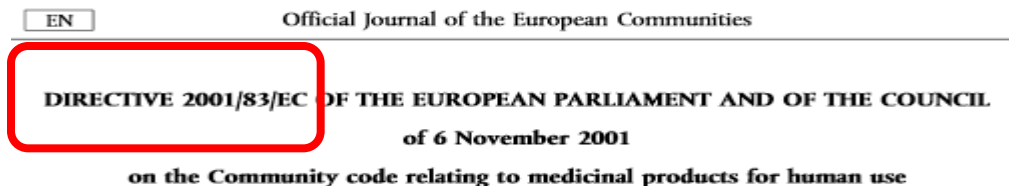
GMP – what it is?



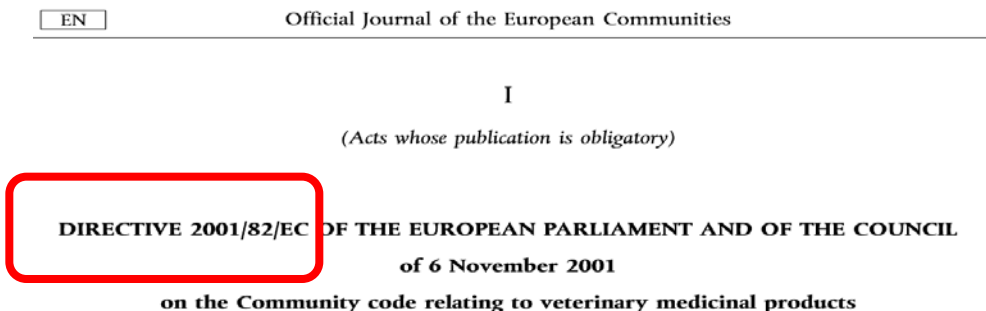
GMP shall mean the part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use



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.

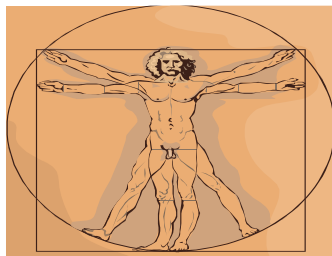


GMP – what is it?

The rules governing medicinal products in the European Union contains guidance for the interpretation of the principles and guidelines of **good manufacturing practices** for medicinal products for human and veterinary use laid down in Commission Directive 2003/94/EC, and 91/412/EEC respectively.

EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines

http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm





GMP – what is it?

Good Manufacturing Practice

Part I	Part II	Part III	Annexes
Basic Requirements for Medicinal Products	Basic Requirements for Active Substances used as Starting Materials	GMP related documents	Substance specific documents
9 Chapters	1 Chapter(49pg)	5 documents	19 annexes



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.**

Type and source of material	Example product	Application of this guide to manufacturing steps shown in grey			
2. Virus or bacteria / fermentation / cell culture	Viral or bacterial vaccines; enzymes, proteins	Establishment & maintenance of MCB, WCB, MVS, WVS	Cell culture and/or fermentation	Inactivation when applicable, isolation and purification	Formulation, filling
3. Biotechnology - fermentation/ cell culture	Recombinant. products, MAb, allergens, vaccines Gene Therapy (viral and non-viral vectors, plasmids)	Establishment & maintenance of MCB ² and WCB, MSL, WSL	Cell culture and / or fermentation	Isolation, purification, modification	Formulation, filling
6. Human sources	Urine derived enzymes, hormones	Collection of fluid	Mixing, and/or initial processing	Isolation and purification	Formulation, filling
7. Human and / or animal sources	Gene therapy: genetically modified cells	Donation, procurement and testing of starting tissue / cells ⁷	Manufacture vector and cell purification and processing,	Ex-vivo genetic modification of cells, Establish MCB, WCB or cell stock	Formulation, filling
	Somatic cell therapy	Donation, procurement and testing of starting tissue / cells	Establish MCB, WCB or cell stock	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, fill
	Tissue engineered products	Donation, procurement and testing of starting tissue / cells ⁷	Initial processing, isolation and purification, establish MCB, WCB, primary cell stock	Cell isolation, culture, purification, combination with non-cellular components	formulation, combination, fill



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)

Q10: Pharmaceutical Quality System (2008)

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



GMP, Quality by Design and validation

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



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25 April 2014
EMA/CHMP/BWP/187338/2014
Committee for Medicinal Products for Human Use (CHMP)

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

Draft

Draft Agreed by Biologics Working Party	April 2014
Adoption by CHMP for release for consultation	25 April 2014
Start of public consultation	1 May 2014
End of consultation (deadline for comments)	31 October 2014

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

Keywords	<i>active substance, biologics, process validation, process evaluation, process verification, lifecycle</i>
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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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