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IMPD – regulatory quality requirements

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Content

- Legislation
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- IMPD
- IMPs of chemical origin
- IMPs of biological/biotechnological origin
- Placebo
- Commercial drug products in clinical trials
- Amendments
- GMP
- Labelling

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Abbreviations

*Drug substance (**DS**) = Active Pharmaceutical Ingredient (**API**) = Active substance*

*Drug product (**DP**) = Finished dosage form*

*Investigational medicinal product (**IMP**)*

*Non-investigational medicinal product (**NIMP**) = Auxilliary medicinal products*

*Investigational medicinal product dossier (**IMPD**)*

*Clinical trial application form (**CTA**)*

*Substantial Amendment (**SA**)*

*Non-substantial amendment (**non-SA**)*

*Summary of product characteristics (**SmPC**)*

*Good manufacturing practice (**GMP**)*

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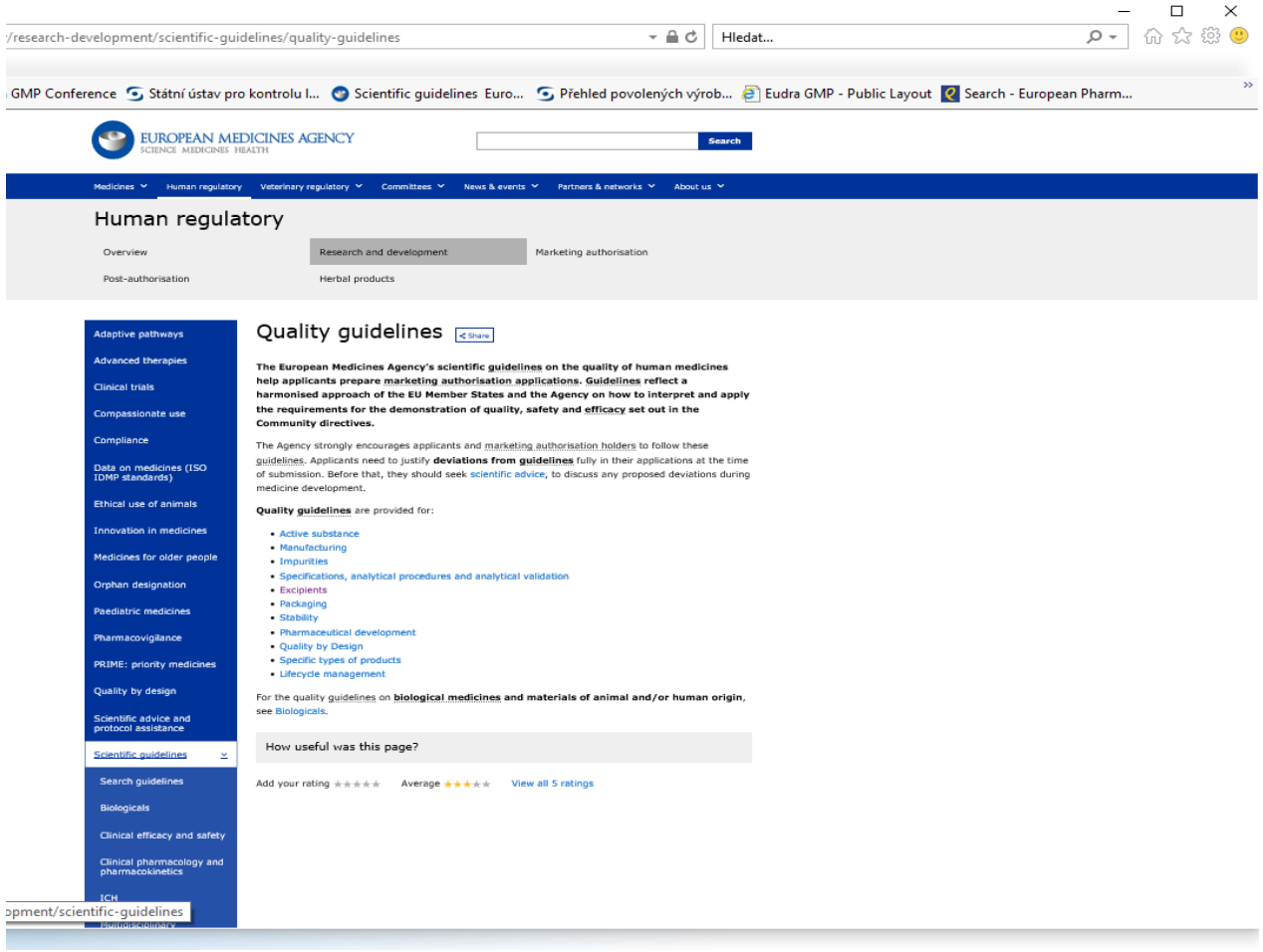
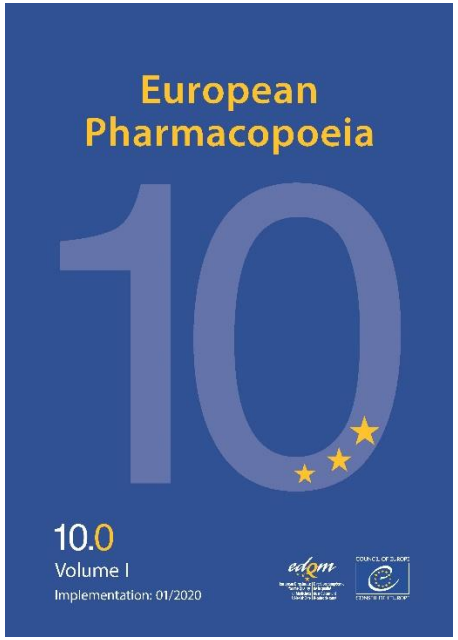
Legislative framework

- Clinical Trial Directive (EC) No 2001/20/EC and national legislation that was put in place to implement the Directive
- Clinical Trial Regulation EU No. 536/2014 will replace the existing EU Directive after implementation (EU CT database and CT portal)
- EudraLex Volume 10: Clinical trials guidelines
- EudraLex Volume 4: Principles and detailed guidelines of GMP for medicinal products

EMA guidelines



PHARMACOPOEIA
(European Pharmacopoeia, United States Pharmacopoeia – National Formulary, Pharmacopoeia of each member state)



- Provide common quality standards throughout the pharmaceutical industry
- Collection of monographs describing both the individual and general quality standards for substances, dosage forms, medicines and analytical methods
- Legally binding and apply throughout the entire life-cycle of a product
- CEPs (certificates of suitability) – quality of a given substance can be suitably controlled by the PhEur monograph
  - active substance
  - TSE

What is a drug product?

- Directive 2001/83/EC:

  Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

  Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis

- FDA:

  The finished dosage form that contains a drug substance, generally, but not necessarily in association with other active or inactive ingredients

What is an active substance?

- Directive 2001/83/EC:

  Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.

- FDA:

  A substance recognized by an official pharmacopoeia or formulary
  A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease
  A substance (other than food) intended to affect the structure or any function of the body
  A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device

Clinical trial application form (CTA, Annex 1)

Annex 1: Clinical trial Application Form

REQUEST FOR AUTHORISATION OF A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE COMMUNITY

To be filled in by the applicant
The questions in this form for the request for authorisation from the Competent Authority are also relevant for the opinion from an Ethics Committee (it represents module 1 of the form for applying to an ethics committee) and can be used as part of that application. Please indicate the relevant purpose in a box below.

REQUEST FOR AUTHORISATION TO THE COMPETENT AUTHORITY: **Yes •**

- Has to be completed in the EudraCT database
- Necessary part of the dossier
- Provides basic information on each CT
  - Sponsor
  - Information on IMPs and placebo
  - Site responsible for QP release
  - Medical condition under investigation
  - Phase of the trial
  - Population of trial subjects

IMPD

Investigational Medicinal Product Dossier

- One of several pieces of IMP related data necessary for clinical trial approval but also forms basis for the CTD to support future marketing authorisation

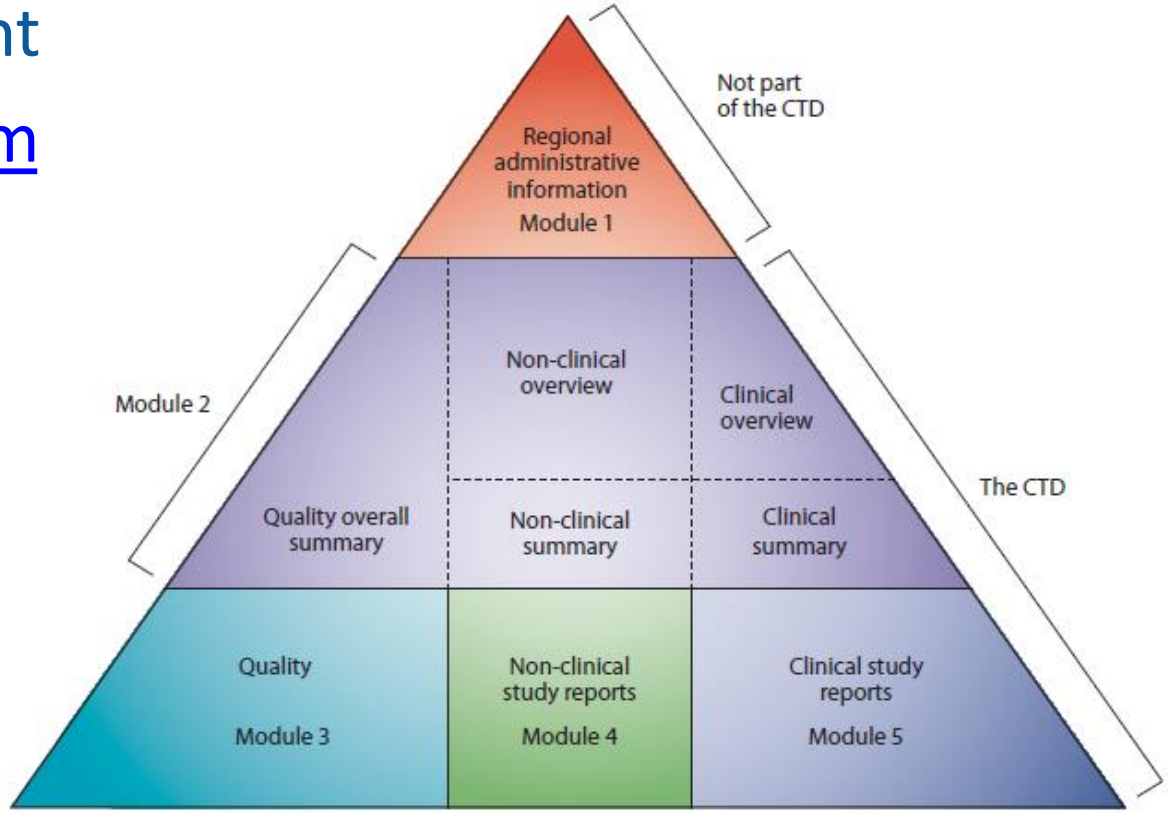
- Information on quality, manufacture and control of IMPs
  - Adapted to the existing level of knowledge and phase of development
  - Most up-to-date information
  - Different amount of information for each product (limited data should be justified)

- Full IMPD vs. Simplified IMPD
  - Cross-reference to different clinical trial or marketing authorisation
  - SmPC may be sufficient in some cases

CTD

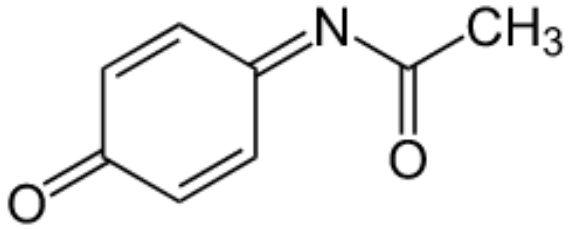
- M4: The Common Technical Document
- https://www.ich.org/products/ctd.html
- Quality – Module 3 (M4Q(R1))
  - Clearly structured format

CTD Triangle



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Investigational medicinal products of chemical origin



IMPs of chemical origin

- **CHMP/QWP/545525/2017**
- Requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials
  - only illustrative not an exhaustive list of requirements
  - trial type related requirements (e.g. Bioequivalence studies)

„It is a responsibility of the sponsor to ensure protection of the CT subjects using a high quality IMP that is suitable for its intended purpose, and to appropriately address those quality attributes that may impair patient safety.“

Drug substance section

- **Reference to ASMF or CEP**
- **Full data**

2.1.S Drug substance

- 2.1.S.1 General information
- 2.1.S.2 Manufacture
- 2.1.S.3 Characterisation
- 2.1.S.4 Control of the drug substance
- 2.1.S.5 Reference standards or materials
- 2.1.S.6 Container closure system
- 2.1.S.7 Stability

2.1.S.4 Control of DS	Phase I	Phase 2	Phase 3
2.1.S.4.1 Specification	Batch results may be acceptable	Preliminary specification	Specification
2.1.S.4.3 Validation of analytical procedures	Table of acceptance criteria for validation	Tabulated summary of validation results	
2.1.S.4.4 Batch analyses	All batches used so far	Current batches	

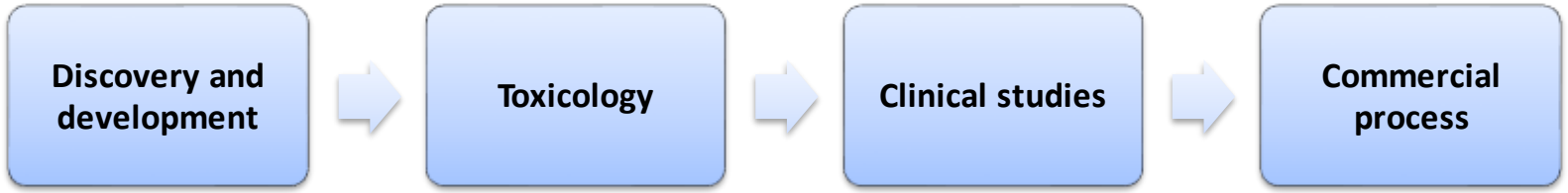
Drug product section

2.1.P Drug product

- 2.1.P.1 Description and composition
- 2.1.P.2 Pharmaceutical development
- 2.1.P.3 Manufacture
- 2.1.P.4 Control of excipients
- 2.1.P.5 Control of the IMP
- 2.1.P.6 Reference standards or materials
- 2.1.P.7 Container closure system
- 2.1.P.8 Stability

2.1.P Drug product	Phase I	Phase 2	Phase 3
2.1.P.2 Pharmaceutical development	Short description where applicable	Brief summary (changes of clinical relevance)	Summary (changes of clinical relevance)
2.1.P.3.4 Control of critical steps and intermediates	Data for non-standard processes and sterile products		Control of critical steps and intermediates
2.1.P.5.1 Specification	Batch results may be acceptable	Preliminary specification	Specification
2.1.P.5.3 Validation of analytical procedures	Table of acceptance criteria for validation	Tabulated summary of validation results	

Drug product – Pharmaceutical development



From basic dosage forms to more complex

- Considerations: route of administration

Functional aspect of each excipient are basis for development rationalization

Impact stability of DS
Impact physical charcteristics
Impact in-vivo absorption
Impact manufacturability

- Characterization of critical quality attributes of excipients → formulation development (compatibility studies, preformulation studies)

Manufacturing process development

Small scale ⟹ ⟹ pivotal clinical studies ⟹ ⟹ full scale (prior to process validation)

The level of detail is dependent on complexity of the dosage form

Drug product – dosage forms

- Designed for easy and accurate administration
- Classification:
  - Based on route of administration
  - Based on the physical form
- Requirements for different dosage forms are specified in the European Pharmacopoeia

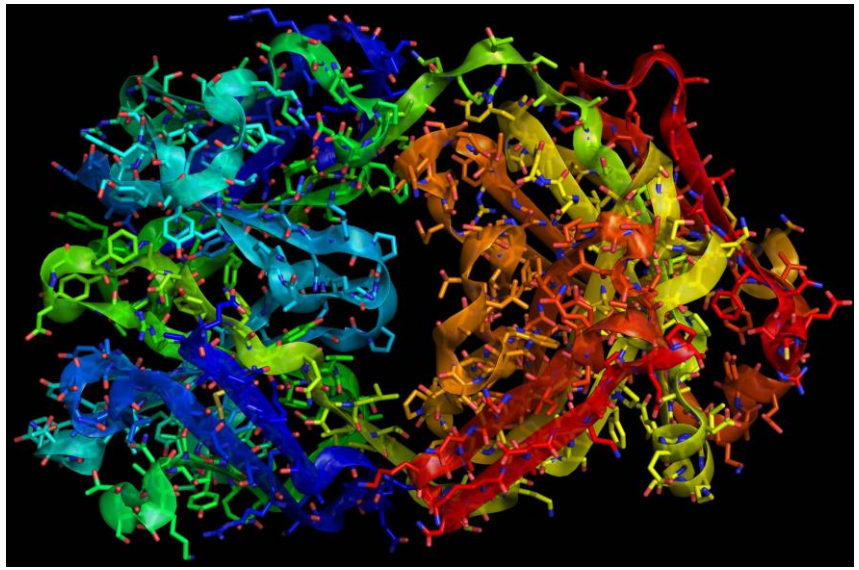
- Additional requirements for dosage forms that need to be reconstituted prior to administration (e.g. powder for solution for infusion)
  - Diluents (sometimes separate IMPD for diluent may be necessary)
  - Compatibility with diluent and material used for administration
  - In-use stability studies

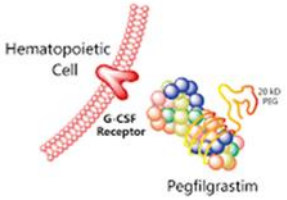
Stability studies

- Provide evidence of how the quality of DS or DP varies with time under the influence of variety of environmental factors
  - Stress testing
  - Long-term testing
  - Accelerated testing
- Representative for the storage conditions, formulation, batch size, manufacturer, and container closure system
- Retest period vs. Shelf-life

- Common mistakes
  - Insufficient discussion of results and trends
  - Not all stability indicating parameters are included
  - Missing stability protocol
  - Data is provided in such a way that assessment of trends is impossible

Regulatory perspectives on quality requirements of biological products





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Legislative Framework - General Definitions – Part I of Annex I of Directive 2001/83/EC

- biological medicinal product: a product which contains a biological active substance

- biological active substance: a substance that is produced by or extracted from a biological source and that needs a combination of physical – chemical - biological testing together with the production process and its control for its characterization and the determination of its quality

“The process is the product.“ – current paradigm

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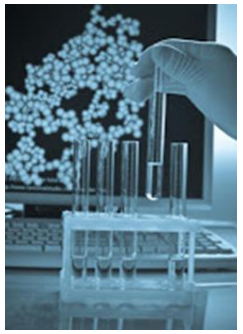
Biological Medicinal Products („biologicals“)



- Blood products (plasma – derived products)
- Immunological products (vaccines, sera, allergens, toxins)
- Biotechnological products (recombinant proteins, monoclonal antibodies, fusion proteins,..)
- Advanced therapy medicinal products – ATMPs (gene therapy, somatic-cell therapy, tissue-engineered products)
- other biological substances classified by the CMDh (non-recombinant origin) - overview (Rev. January 2016)

https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Questions_Answers/CMDh_321_2014_Rev02_2016_01.pdf

Relevant EMA guidelines for biological medicinal products

Biological products:
www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm

CHMP/BWP/534898/2008 Rev.1 (Requirements for quality documentation concerning biological investigational medicinal products in clinical trials)
- Last update 26/04/2018
- ATMPs were excluded from scope

CHMP/BWP/398498 (Virus safety evaluation of biotechnological investigational medicinal products)

EMA/CAT/852602/2018 DRAFT (Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials)

+ it is possible to use specific ICH guidelines:
ICH Q5D Derivation and characterisation of cell substrates used for production of biotechnological/biological products
ICH Q6B Specifications: test procedures and acceptance criteria for biotechnological/biological products

European Pharmacopoeia: is mandatory

- Collection of monographs that describe both the individual and general quality standards for ingredients, dosage forms and methods of analysis for medicines
- Provides common quality standards throughout Europe to control the quality of medicines and the substances used to manufacture them
- **Active Substance**
  - Monographies for some biological substances (allergens, filgrastim, infliximab, …)
- **Pharmaceutical Form**
  - Pharmacopoeia tests should be included in the specification
- **Methods which are use for testing of biological DS/DP (2.06…) or 6. General Monographs**
  - Allergen products; Immunosera for human use; Monoclonal antibodies for human use; Recombinant DNA technology products; Vaccines for human use; Host-cell proteins (2.6.34); Host-cell DNA (2.6.35); Monocyte-activation test (2.6.30); …etc

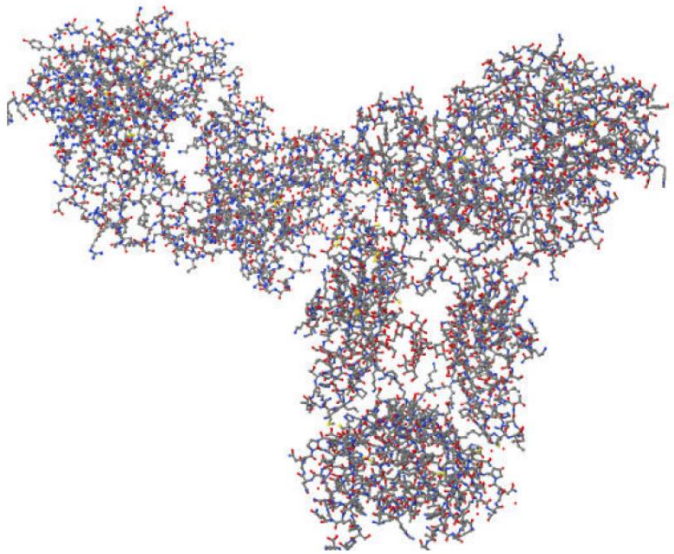
Summary: How are Biological Products Different?

Biological active substance is defined by its manufacturing process

Small Molecule Products	Biological Products
Generally low molecular weight	Generally high molecular weight
Usually organic or chemical synthesis	Made with/from live cells/organisms → *inherent and contamination risk*
Fewer critical process steps	Many critical process steps
Well-characterized	Less easily characterized
Known structure	Structure may or may not be completely defined or known

Size and Complexity of Biological Products

Aspirin 180 Da



Monoclonal Antibody ~150,000 Da

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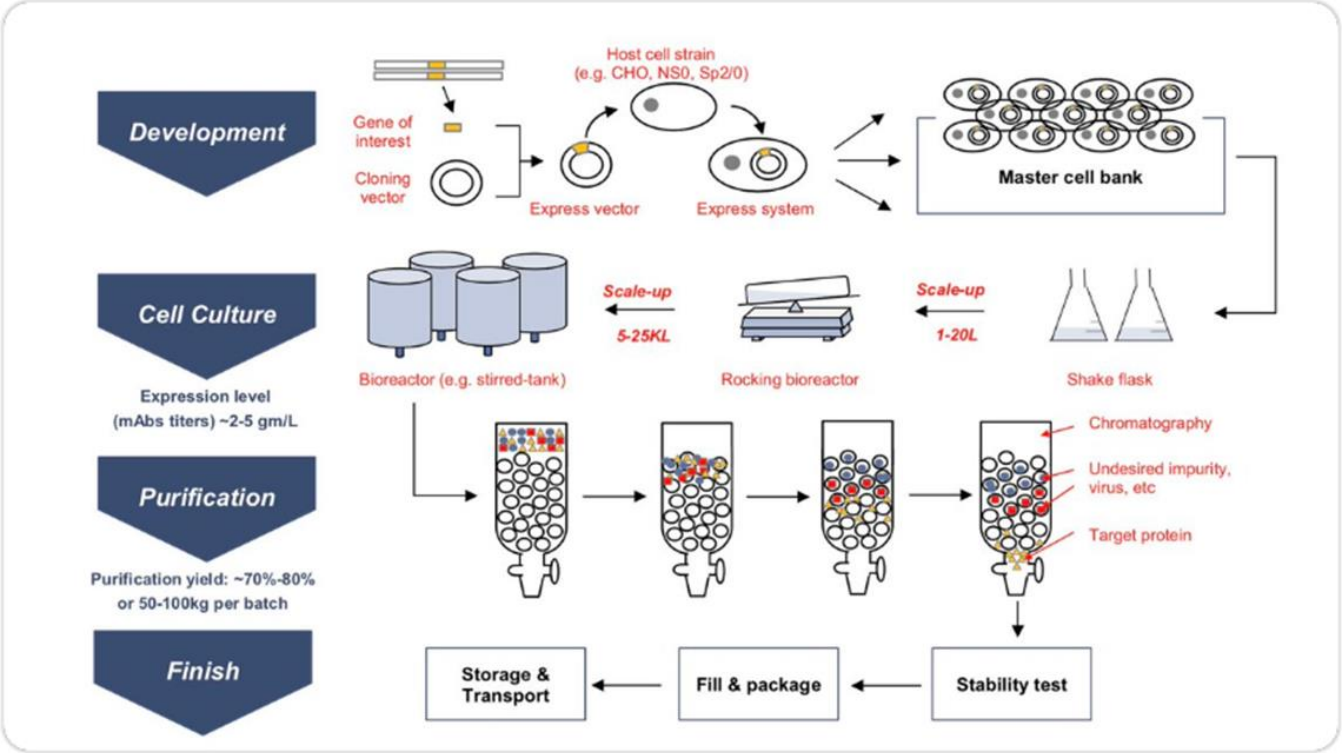
Differences in the requirements to biological medicinal products dossier

- the CEP procedure (Certification of Suitability of the European Pharmacopoeia) does not apply for biologicals
- due to the complexity of biologicals substances, it is also not possible to use the ASMF (Active Substance Master File) procedure

⟹ in line with Guideline on ASMF Procedure (CHMP/QWP/227/02 Rev.04). Manufacturer of biological medicinal product should take responsibility for the medicinal product, it means to have full and transparent access to the quality related data.

The process is the product

= small change of manufacturing proces can have an impact on the QUALITY DS/DP



Requirements to the dossier – biological active substance

- **Manufacture and manufacturer(s):** …, flow chart, control strategy focused on critical in-process controls (IPC) - acceptance criteria, any reprocessing described and justified
- **Control of materials:** detailed information on critical materials and their control (raw and starting materials), summary of source, history and generation of cell substrate/virus seed, clonality for mammalian cell lines, characterization and testing, cell substrate stability (ICH Q5D), compendial and non-compendial raw materials, materials of human or animal origin (adventitious agents ICH Q5A, TSE safety provided in A section)
- **Control of Critical Steps and Intermediates:** complete information may not be available at early stages (phase I/II)
- **Manufacturing process development:** comparability exercises may be necessary (change of manufacturing process), introduction of a WCB may potentially impact the quality profile of the active substance (comparability study is required)
- **Characterization:** physical-chemical properties, primary, secondary and higher-order structure, post-translational modifications (e.g. glycoforms, oxidized variants), biological activity (appropriate, reliable and qualified method), purity

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Requirements to the dossier – biological active substance

- **Impurities:** **process related impurities** (e.g. HCP (2.6.34.), HC DNA (2.6.35.), antibiotics, free PEG, protein A,…) and **product related impurities** (e.g. precursors, degradation products, aggregates…)
- **Specifications:** tests and acceptance criteria defined – quantity, identity (2 methods), purity, **biological activity (potency assay)** - 'record' or 'report results' limits are not acceptable
- **Description and validation of analytical procedures:** phase I/II – the suitability of the analytical methods should be confirmed, phase III – validation of the analytical methods used for release and stability testing (tabulated summary of pre-defined criteria and validation results)
- **Reference standards:** each in-house working standard qualified against primary reference material (in-house primary reference standard where international/Ph.Eur. is not available)
- **Stability:** testing interval follows ICH Q5C, shelf-life and storage conditions should be provided, **re-test period is not possible for biological DS**

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Requirements to the dossier – biological medicinal product

- **In principle, statements for chemical products apply also for biologicals**
- **Sterile biological products:** sterile filtration is critical step (terminal sterilization is not applicable)
- **Process validation:** following EudraLex Vol. 4, annex 13 the validation of
- sterilising processes should be the same as for product authorized for marketing; validation demonstrated by media fill runs (statement in dossier is required, actual data audited by GMP inspectors), proposed batch scale range – should be covered by media fill validation studies
- **Drug device combinations (DDC):** CE certificate or compliance with the relevant essential requirements of medical devices with regards to safety and performance related device features needs to be demonstrated

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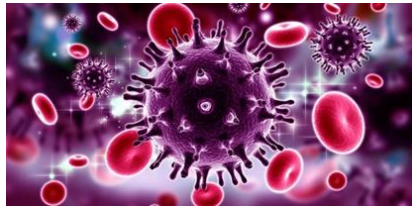
Differences in the requirements to biological medicinal products dossier – Appendices

Adventitious Agent Safety Evaluation

- *Guideline: Virus safety evaluation of biotechnological investigational medicinal products EMEA/CHMP/BWP/398498/2005*
- *Guideline ICH Q5A: Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin*
- testing of cell line and raw materials of human/animal origin
- virus clearance studies (results should be provided, at least 2 representative model viruses)– if it is relevant
- TSE relevant materials (note for guidance on minimizing risk of TSE EMA/410/01)

Raw Material of Animal Origin

- safety of the animal sourced materials



BioSummary…

The MOST important is: to DEFINE active substance

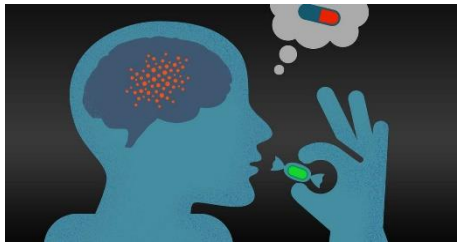
BIO vs. **CHEM**

- Possibility to use Scientific Advice procedures in EMA …
- Innovation in medicines (EMA) – Innovation Task Force …

Placebo

- Should be identical to the DP in physical form, sensory perception, packaging and labelling but has no pharmaceutical activity
- Full IMPD vs. Simplified IMPD
  - For authorised products SmPC may be sufficient

- Maintaining the maximal level of blinding is crucial
  - Sometimes partial blinding is necessary



Authorised drug products

EU/EHP, MRA, ICH countries

NON-MODIFIED

SmPC from country that granted the marketing authorisation

MODIFIED

SmPC from country that granted the marketing authorisation

Relevant chapters of the IMPD concerning the changes

- Different appearance
- Encapsulation for blinding purpose

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Amendments to Clinical Trials

Through subsequent modifications and amendments an additional knowledge on the DP is gained

Substantial

Significant impact on:

-the safety or mental integrity of patients

-the scientific values of the trial

-the conduct or management of the trial

-the quality and safety of any IMP used in the trial

May be implemented after approval by competent authority

Non-substantial

Documentation should be recorded within the company

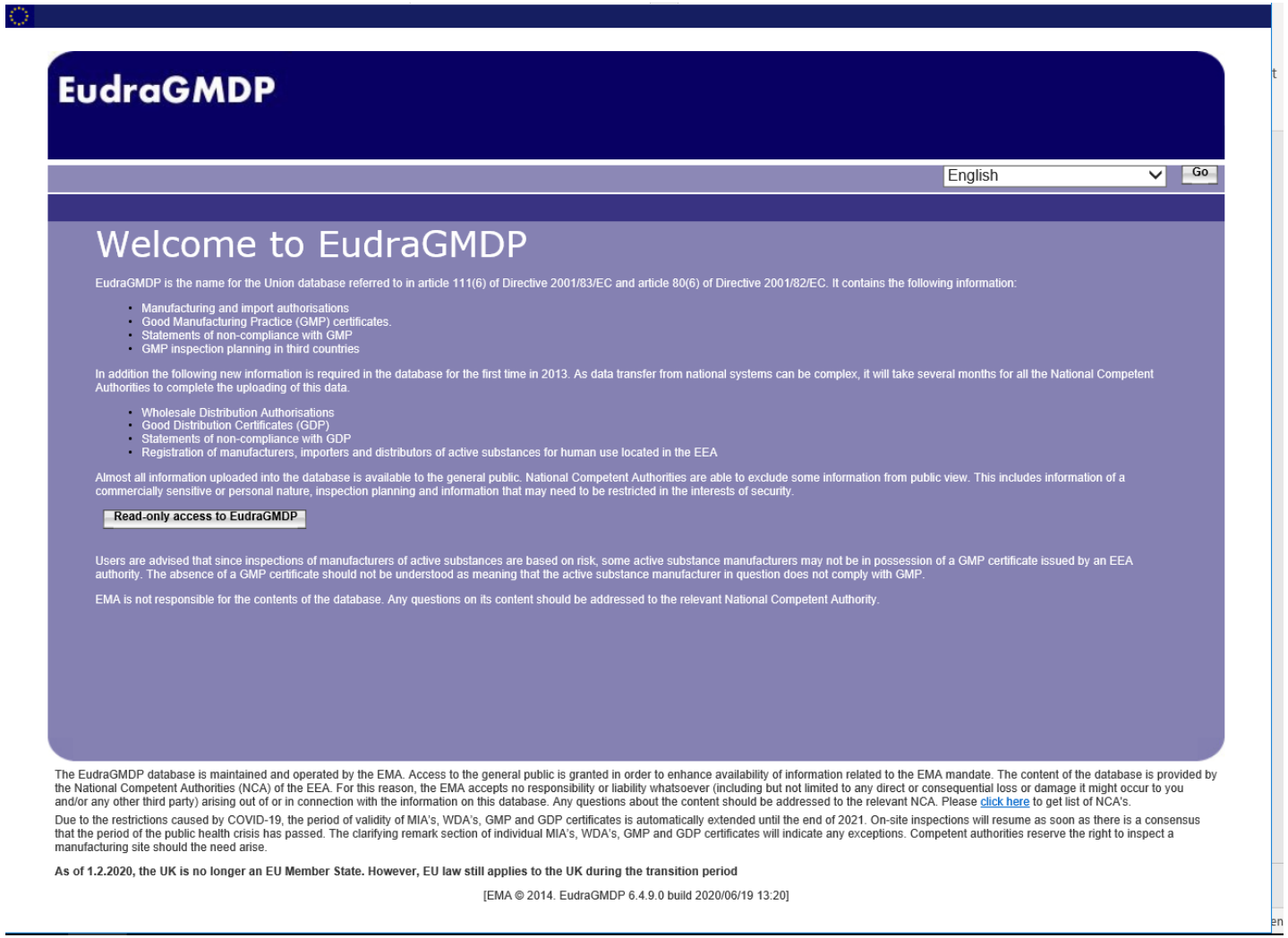
Should be submitted with IMPD update or substantial modification

May be implemented immediately

GMP Compliance of IMPs

- No specific documents to demonstrate GMP compliance of active substance are required
  - Exception: sterile APIs
- GMP compliance should be demonstrated for all sites responsible for manufacture, testing, packaging, labelling, import and QP release of all non-authorised or modified authorised IMPs in clinical trial
  - Manufacturing authorisation
  - GMP certificate
  - QP declaration

EudraGMP database



EudraGMDP

English Go

Welcome to EudraGMDP

EudraGMDP is the name for the Union database referred to in article 111(6) of Directive 2001/83/EC and article 80(6) of Directive 2001/82/EC. It contains the following information:

- Manufacturing and import authorisations
- Good Manufacturing Practice (GMP) certificates.
- Statements of non-compliance with GMP
- GMP inspection planning in third countries

In addition the following new information is required in the database for the first time in 2013. As data transfer from national systems can be complex, it will take several months for all the National Competent Authorities to complete the uploading of this data.

- Wholesale Distribution Authorisations
- Good Distribution Certificates (GDP)
- Statements of non-compliance with GDP
- Registration of manufacturers, importers and distributors of active substances for human use located in the EEA

Almost all information uploaded into the database is available to the general public. National Competent Authorities are able to exclude some information from public view. This includes information of a commercially sensitive or personal nature, inspection planning and information that may need to be restricted in the interests of security.

Read-only access to EudraGMDP

Users are advised that since inspections of manufacturers of active substances are based on risk, some active substance manufacturers may not be in possession of a GMP certificate issued by an EEA authority. The absence of a GMP certificate should not be understood as meaning that the active substance manufacturer in question does not comply with GMP.

EMA is not responsible for the contents of the database. Any questions on its content should be addressed to the relevant National Competent Authority.

The EudraGMDP database is maintained and operated by the EMA. Access to the general public is granted in order to enhance availability of information related to the EMA mandate. The content of the database is provided by the National Competent Authorities (NCA) of the EEA. For this reason, the EMA accepts no responsibility or liability whatsoever (including but not limited to any direct or consequential loss or damage it might occur to you and/or any other third party) arising out of or in connection with the information on this database. Any questions about the content should be addressed to the relevant NCA. Please click here to get list of NCA's.

Due to the restrictions caused by COVID-19, the period of validity of MIA's, WDA's, GMP and GDP certificates is automatically extended until the end of 2021. On-site inspections will resume as soon as there is a consensus that the period of the public health crisis has passed. The clarifying remark section of individual MIA's, WDA's, GMP and GDP certificates will indicate any exceptions. Competent authorities reserve the right to inspect a manufacturing site should the need arise.

As of 1.2.2020, the UK is no longer an EU Member State. However, EU law still applies to the UK during the transition period

[EMA © 2014. EudraGMDP 6.4.9.0 build 2020/06/19 13:20]

How to demonstrate GMP compliance of IMPs?

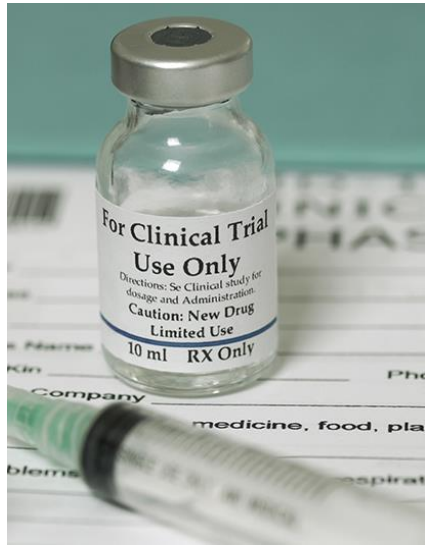
- MIA/GMP certificate:
  - Corresponding scope of manufacturing activities
  - Issued for Investigational medicinal products
  - Valid (in general not older than 3 years)

- QP declaration:
  - Specific for each clinical trial (EudraCT number)
  - Issued by site responsible for final release into EEA
  - Valid (in general not older than 3 years)

Clinical trial labelling

- *The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice, Annex 13, Investigational Medicinal Products*

- Considerations:
  - All information in national language
  - Primary and secondary packaging
  - For all IMPs in the clinical trial
  - Authorised drug products used in clinical trial should also be labelled
  - Any missing information should be justified



Conclusions

- The nature of the product, stage of development, patient population, nature and severity of the illness should be considered for each application
- quality and safety of the DP should be ensured
- Pharmacopoeia and EMA guidelines should be taken into consideration

Recommendations

- Communication with the regulatory authority is important
- Any missing information should be justified

Any questions?

Acknowledgement

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 825881