Evaluation and Requirements of the Common technical data CTDs for the Biological drugs

Lorenzo Montrasio

Beirut, 24 January 2018

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Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

*Lorenzo Montrasio, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.

N.B. The compensation received is based on the collective bargaining agreement

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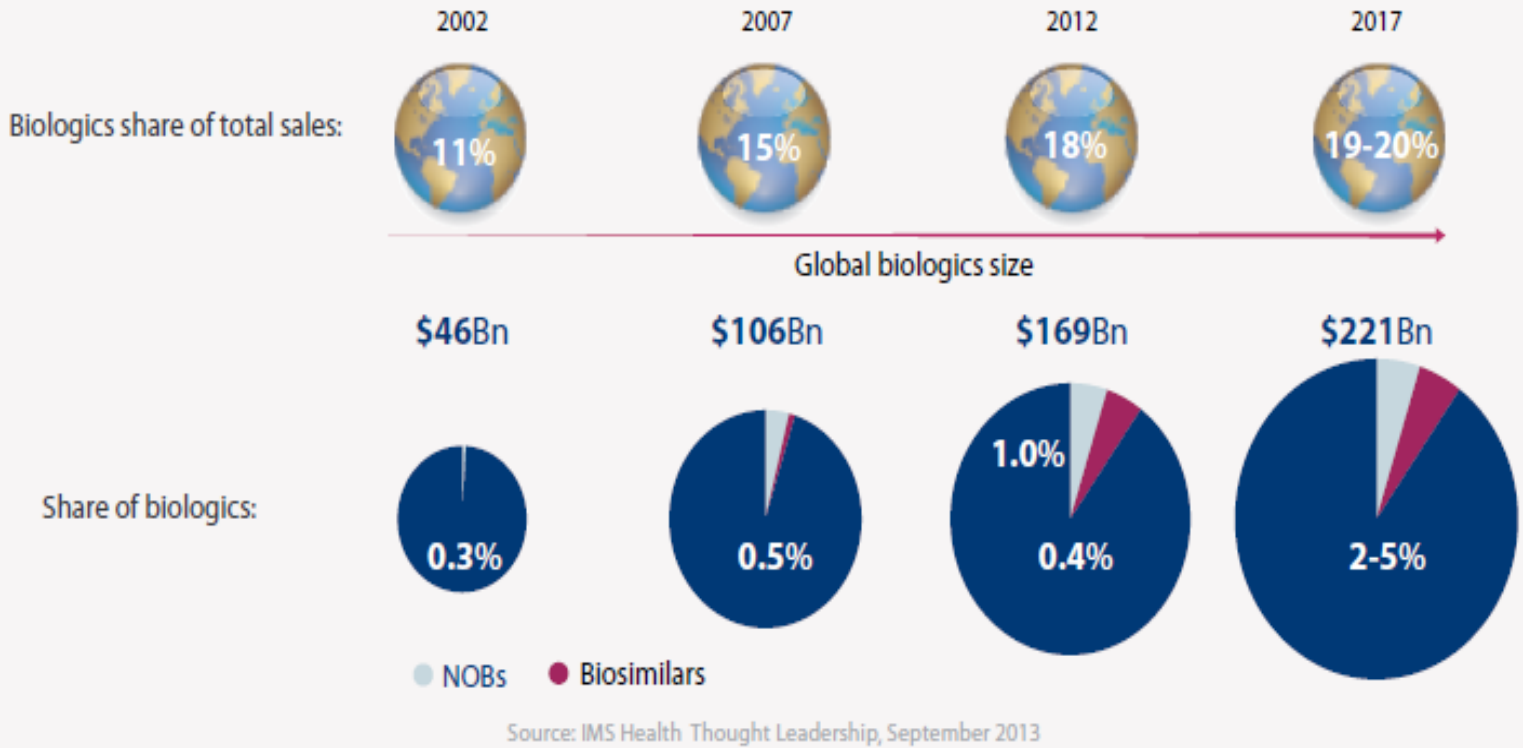
Biological medicinal products

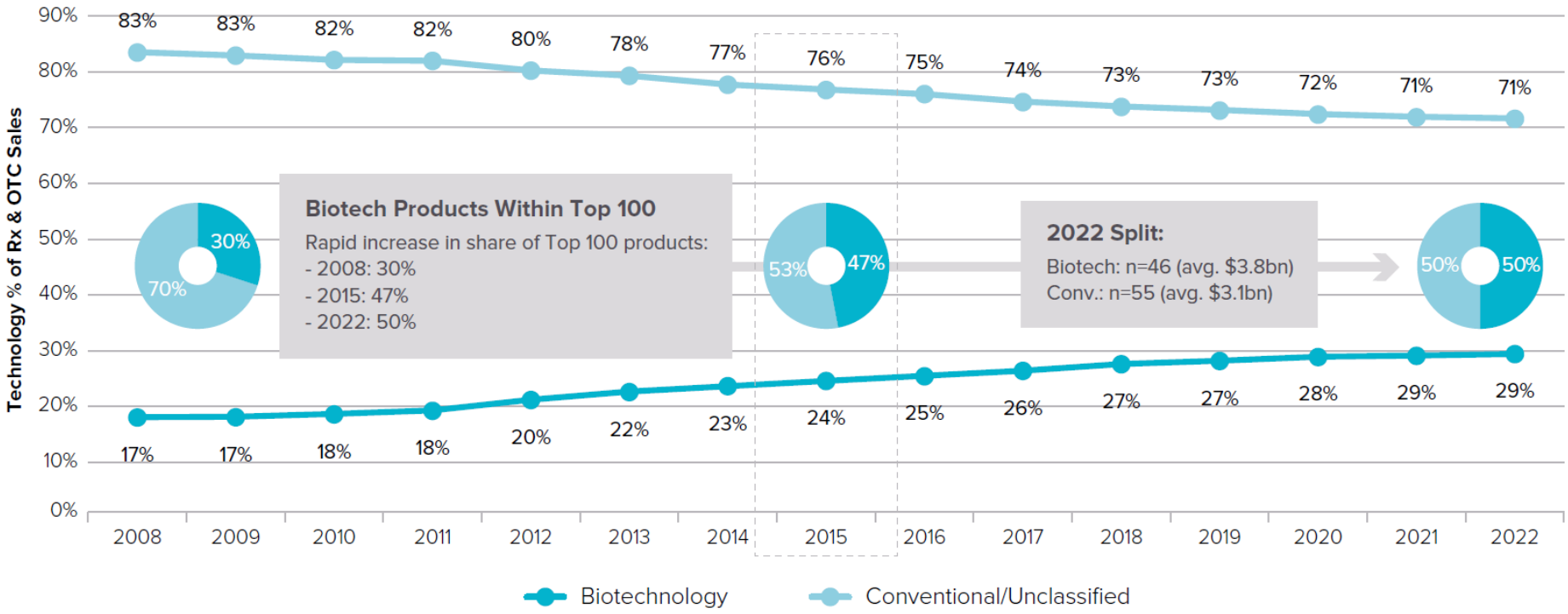
Successful record in treating many life-treatening and chronic diseases

Cost limits their access to patients

The biologics market



Source: IMS Health Thought Leadership, September 2013



Worldwide Prescription Drug & OTC Pharmaceutical Sales: Source: EvaluatePharma® August 2016 - Biotech vs. Conventional Technology

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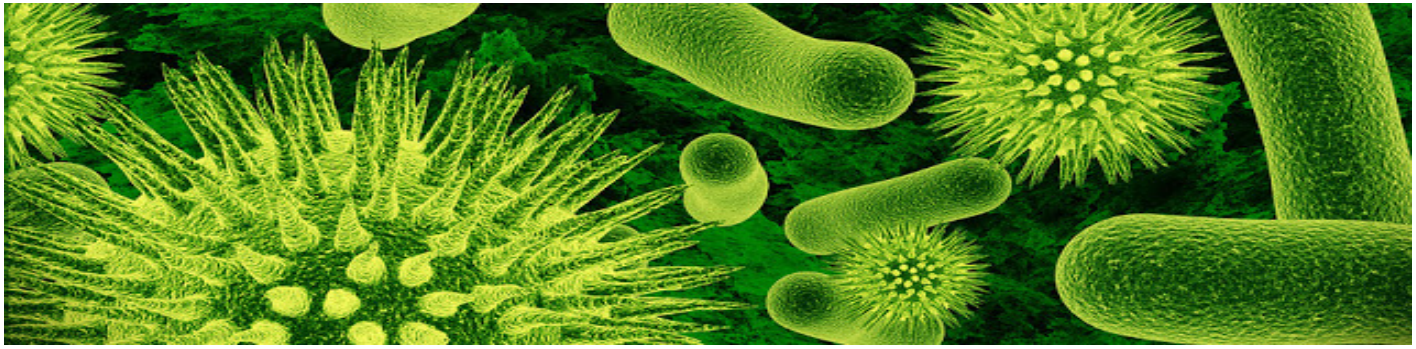
Biological medicinal Products

Directive 2001/83/CE



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

[.....]

Biological substances

Human sources

Animal sources (including *transgenic animals*)

Micro-organisms

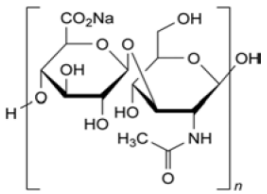
Recombinant products

Different biological sources for the same active substance

01/2011:1472

SODIUM HYALURONATE

Natrii hyaluronas

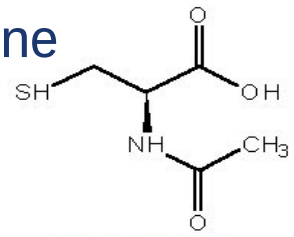


$(C_{14}H_{20}NNaO_{11})_n$
[9067-32-7]

DEFINITION

Sodium salt of hyaluronic acid, a glycosaminoglycan consisting of D-glucuronic acid and *N*-acetyl-D-glucosamine disaccharide units. It is extracted from cocks' combs or obtained by fermentation from *Streptococci*, Lancefield Groups A and C.

N-Acetylcysteine



Coagulation Factor

PLASMA DERIVED PROTEIN
BIOLOGICAL ORIGIN

Single donation
Plasma pool
Manufacturing process (extraction/ purification..)

RECOMBINANT PROTEIN
BIOTECH PRODUCT

Production of protein in genetically modified cells
Purification
Recombinant protein

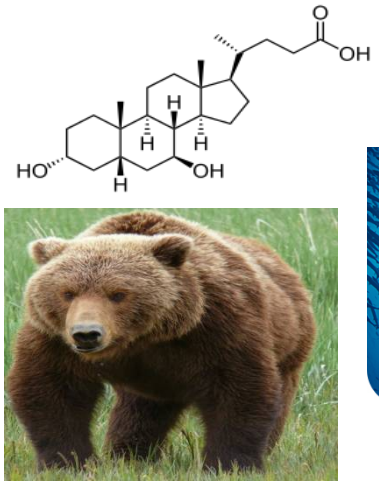
Biological medicinal Products

Directive 2001/83/CE

[.....]

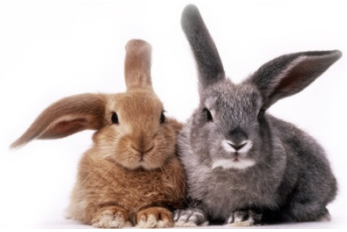
and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.

Biological and Non-biological products derived from animal sources

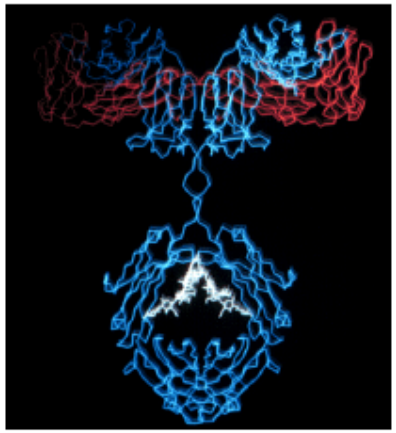


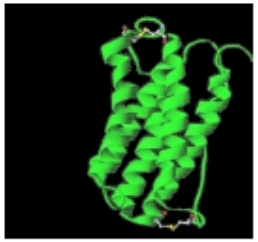
Ursodeoxycholic acid,
Fish Oil rich in omega-3 acids

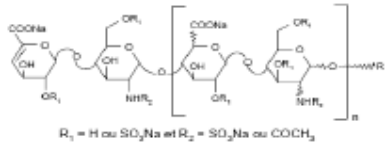
Heparin, LMWH, Protamine,
Anti T-lymphocyte immunoglobulin for human use,
Pepsin, Trypsin

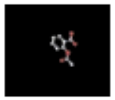


Molecular mass









Mab (IgG)
~660AA, MW: ~150 KDa

Interferon alfa,
165AA, MW: 19.6 KDa

Low molecular mass heparin,
MW: 4.5 KDa

Aspirin,
MW: 180 Da

Molecular mass scale

Regulatory Framework for Marketing Authorization of Medicinal Products

Legislations

Good Manufacturing Practice (GMP)

The European Pharmacopoeia

Guidelines

Scientific Advice

EUDRALEX

https://ec.europa.eu/health/documents/eudralex_en

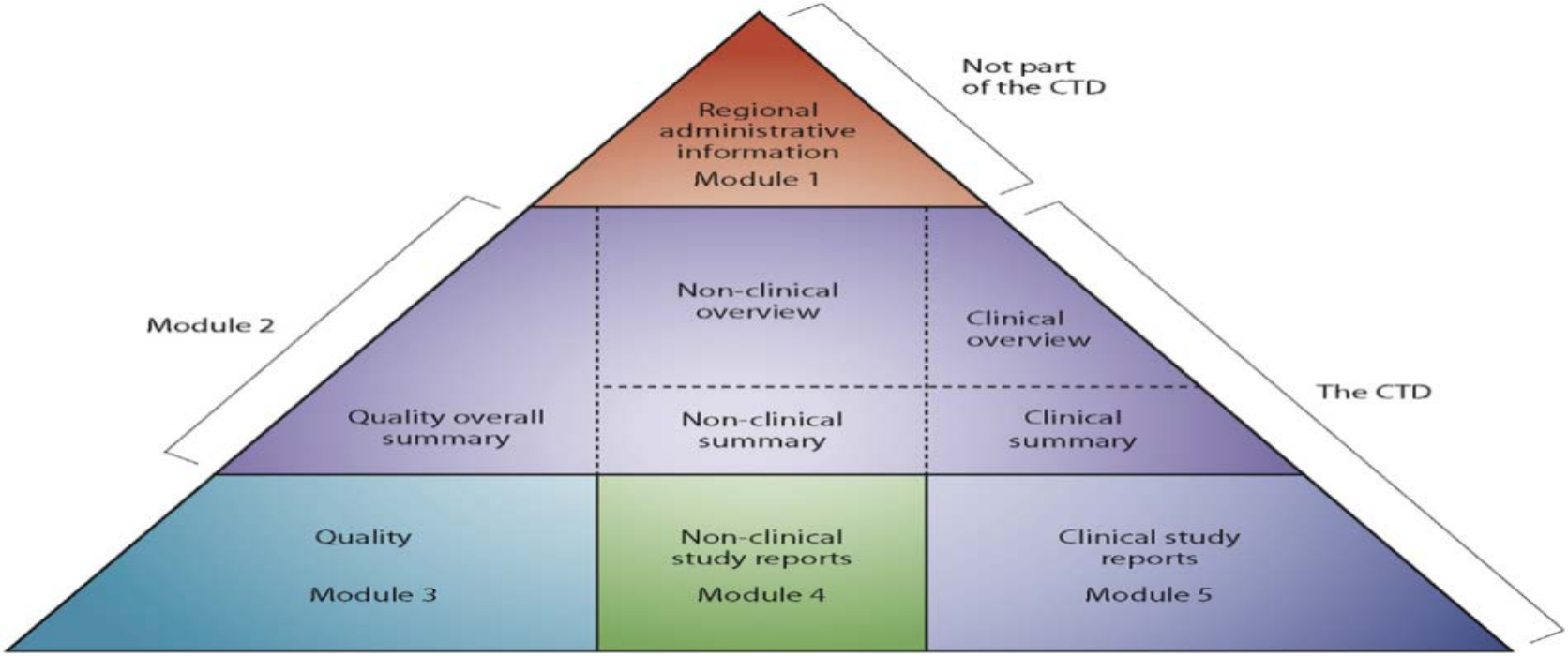
Volume 2 - Pharmaceutical legislation on notice to applicants and regulatory guidelines for medicinal products for human use

Volume 2A - Procedures for marketing authorisation

Volume 2B - Presentation and content of the dossier (Notice to Applicant, incorporating the Common Technical Document (CTD)

Volume 2C - Regulatory Guideline

Common Technical Document (CTD)



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https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf

CTD format

Internationally agreed format for the preparation of applications to be submitted to regulatory authorities in the three ICH regions of Europe, USA and Japan.

Gives no information about the content of a dossier and does not indicate which studies and data are required for a successful approval

The CTD-format will be applicable for all types of products (chemical active substances, radiopharmaceuticals, biological/biotechnologicals, herbals etc.)

DIRECTIVE 2001/83/EC OF THE Community code relating to medicinal products for human use

Marketing Authorization: authorization to place a medicinal product on the EU market

- ✓Companies apply to EU Competent Authority
- ✓CTD Dossier (art. 8, 10.1, 10.4, 10a)
- ✓A marketing authorization may only be granted to an applicant established in the Community
- ✓EDQM Certificate of European Pharmacopoeia: non applicable to biologics

Type of regulatory procedures for marketing authorization in EU

National (Directive 2001/83/EC)

Mutual Recognition (Directive 2001/83/CE)

Decentralised (Directive 2001/83/CE)

Centralised Regulation Regulation (EC) No 726/2004

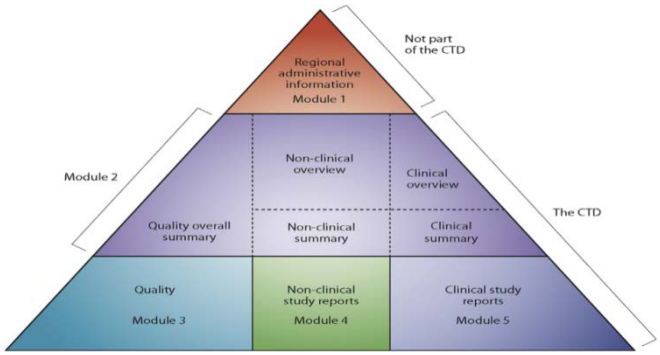
REGULATION (EC) No 726/2004

Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

Medicinal products:

- Developed by biotechnological processes
- Used as performance enhancers (veterinary)
- Containing a new active substance for: HIV, cancer, neurodegenerative disorder, diabetes, auto-immune diseases and other immune dysfunctions, viral diseases.
- Designated as orphan medicinal products (Regulation (EC) No 141/2000)
- If significant therapeutic, scientific or technical innovation

Common Technical Document (CTD)



Module 1: *Administrative and prescribing Information*
Module 2 *Summaries*
Module 3 *Quality (Drug substance and Drug product)*
Module 4 *Nonclinical Study Reports*
Module 5 *Clinical Study Reports*

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https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf

Biologicals Medicinal products

Quality

- Traceability of materials
- Adventitius agents
- Batch to batch consistency

Preclinical and Clinical

- Immunogenicity

Module 3 - Quality

- 3.1 MODULE 3 TABLE OF CONTENTS
- 3.2 BODY OF DATA
- 3.2.S DRUG SUBSTANCE
- 3.2.P DRUG PRODUCT
- 3.2.A APPENDICES
- 3.2.R REGIONAL INFORMATION
- 3.3 LITERATURE REFERENCES OTHER INFORMATION

All procedures need to be validated and the results of the validation studies must be provided

Analytical test procedures described in sufficient detail to be repeated (e.g. by an official laboratory).

3.2.S DRUG SUBSTANCE

3.2.S.1 General Information Scientific

3.2.S.1.2 Structure (name, manufacturer)

- The schematic amino acid sequence indicating glycosylation sites or other posttranslational modifications and relative molecular mass

3.2.S.2 Manufacture Manufacture

3.2.S.2.1 Manufacturer(s) (name, manufacturer)

- Name, address, and responsibility of each manufacturer, including contractors, involved in manufacturing and testing (linked to QP Declaration)

3.2.S DRUG SUBSTANCE

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer):

- From vial(s) of the cell bank, through cell culture, harvest(s), purification and modification reactions, filling, storage and shipping conditions.
- Batch scale, numbering system, pooling of harvests/intermediates
- Critical steps and critical intermediates for which specifications are established (as mentioned in 3.2.S.2.4).
- Culture media and other additives (details provided in 3.2.S.2.3);
- Major equipment (details provided in 3.2.A.1);
- Process controls with acceptance criteria (details provided in 3.2.S.2.4).

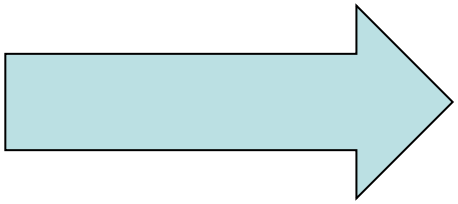
3.2.S DRUG SUBSTANCE

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer):

- Procedures used to transfer material between steps, equipment, areas, and buildings.
- Shipping and storage conditions should be provided. (details in 3.2.S.2.4.)
- Purification and modification reactions: from the crude harvest(s) up to the step preceding filling of the drug Substance.
    - Use and reuse of materials such as membranes and chromatography resins: Equipment details in 3.2.A.1; validation studies in 3.2.S.2.5.
    - Reprocessing procedures in 3.2.S.2.5.

3.2.S DRUG SUBSTANCE

Flow diagrams: relevant information for each stage as described in the relevant sections



i.e. population doubling levels, cell concentration, volumes, pH, cultivation times, critical processing time, holding times, and temperature, elution profiles and selection of fraction, storage of intermediate.

3.2.S DRUG SUBSTANCE

3.2.S.2.3 Control of Materials (name, manufacturer)

- Raw materials, starting materials, solvents, reagents, catalysts (including: media components, monoclonal antibodies, enzymes)
- Listed and identified in the process
- Qualifyed ad controlled
- Specification of source, manufacture, and characterisation
- Demonstration that they meet standards (including clearance and control of adventitious agents: details in 3.2.A.2.)

3.2.S DRUG SUBSTANCE

3.2.S.2.3 Control of Materials (name, manufacturer)

- Cell substrate
- Source, history, and generation
- Analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone
- used to develop the Master Cell Bank
- Cell banking system, characterization, and testing
- quality control activities, and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s))

3.2.S DRUG SUBSTANCE

3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

- Stability data supporting storage conditions should be provided.

3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

- Demonstration of manufacturing process suitability
- Selection of process controls and limits for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification)
- Analytical procedures and validation should be cross-referenced (e.g., 3.2.S.2.4, 3.2.S.4.3) or provided as part of justifying the selection of critical process controls and acceptance criteria.
- Protocols & Results

3.2.S DRUG SUBSTANCE

3.2.S.2.6 Manufacturing Process Development (name, manufacturer)

- Description and rational of change(s) made to the manufacture process
- Evaluating of the potential impact on quality and nonclinical & clinical studies
- Data from comparative analytical testing on relevant drug substance batches
- Cross-reference to the location of these studies in other modules and section 3.2.S.4.4.

3.2.S DRUG SUBSTANCE

3.2.S.3 Characterisation (name, manufacturer)

3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

- Details of desired product and product-related substances
  - primary, secondary and higher-order structure, post-translational forms (e.g., glycoforms), biological activity, purity, and immunochemical properties
- Impurities from the manufacture and/or degradation:
  - acceptance criteria for impurities
  - justification
  - qualification
  - cross reference between commercial and non-clinical & clinical batches

3.2.S DRUG SUBSTANCE

3.2.S.4 Control of Drug Substance (name, manufacturer)

3.2.S.5 Reference Standards or Materials (name, manufacturer)

3.2.S.7 Stability (name, manufacturer)

- Measure how a pharmaceutical product maintains its quality attributes over time
- Carried out under various stress conditions (e.g. temperature, light, humidity, mechanical agitation).
- Accelerated stability studies: can reveal otherwise-hidden properties and the degradation pathways of product.

3.2.P DRUG PRODUCT

3.2.P.1 Description and composition of the drug product Composition and container

3.2.P.2 Pharmaceutical Development

3.2.P.3 Manufacture Method of Preparation

3.2.P.4 Control of excipients Excipients(s)

3.2.P.5 Control of drug product Control Tests on the Finished Product

3.2.P.6 Reference Standards or Materials Batch analysis: Reference material

3.2.P.7 Container Closure System Packaging Material (Immediate Packaging)

3.2.P.8 Stability Stability Tests on the Finished Product

3.2.P DRUG PRODUCT

- 3.2.P.2.2.3 Physicochemical and Biological Properties (name, dosage form)
- Parameters relevant to the performance of the drug product: pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity.
- 3.2.P.4.5 Excipients of Human or Animal Origin (name, dosage form)
- 3.2.P.5.3 Validation of Analytical Procedures (name, dosage

3.2.P DRUG PRODUCT

- 3.2.P.2.2.3 Physicochemical and Biological Properties (name, dosage form)
- Parameters relevant to the performance of the drug product: pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity.
- 3.2.P.4.5 Excipients of Human or Animal Origin (name, dosage form)
- 3.2.P.5.3 Validation of Analytical Procedures (name, dosage

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment (name, manufacturer)

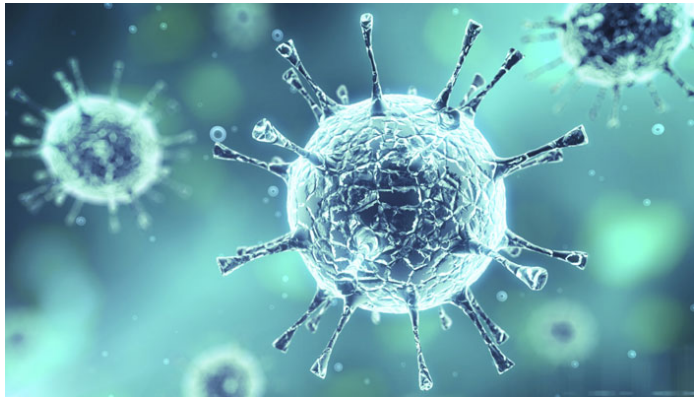
3.2.A APPENDICES

3.2.A.1 Facilities and Equipment (name, manufacturer)

- Diagram illustrating the manufacturing flow (movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas).
- Information on other products manufactured in the same areas
- Product-contact equipment, and its use (dedicated or multi-use)
- Information on preparation, cleaning, sterilisation, and storage of specified equipment and materials
- Information on procedures and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination.

3.2.A APPENDICES

3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)



3.2.A APPENDICES

3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

- Information assessing the risk with respect to potential contamination with adventitious agents
  - For non-viral adventitious agents:

    e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi.
  - For viral adventitious agents:

    e.g. HIV, HCV, HBV, HAV, PB19

Viral Safety (Ph. Eur. 5.1.7). NfG on Minimising the Risk of TSE

- Product-specific risk assessment based on:
- Species of origin
- Organ, tissue, fluid of origin
- Potential contaminants (including epidemiological data)
- Infectivity and pathogenicity of the potential contaminants
- Amount of material used to produce a dose of medicine
- Controls carried out on the donor(s), on the raw material, during production and on the final product;
- Capacity of manufacturing process to remove/inactivate viruses.

DIRECTIVE 2002/98/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC

DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

Animals derived medicinal products

Batch to batch consistency is triggered by manufacturing process and supply chain.

Animals should fit for human consumption following ante-and post mortem inspection.

Viral and TSE Risk Assement for potential adventitious agents (viral and non-viral).

Biological/Biotech products

Production requires specifically designed:

- Expression system
- Production system and purification system
- Analytical methods for quality control

Biotechnological/biological products subject to changes in their manufacturing process

Scaling up

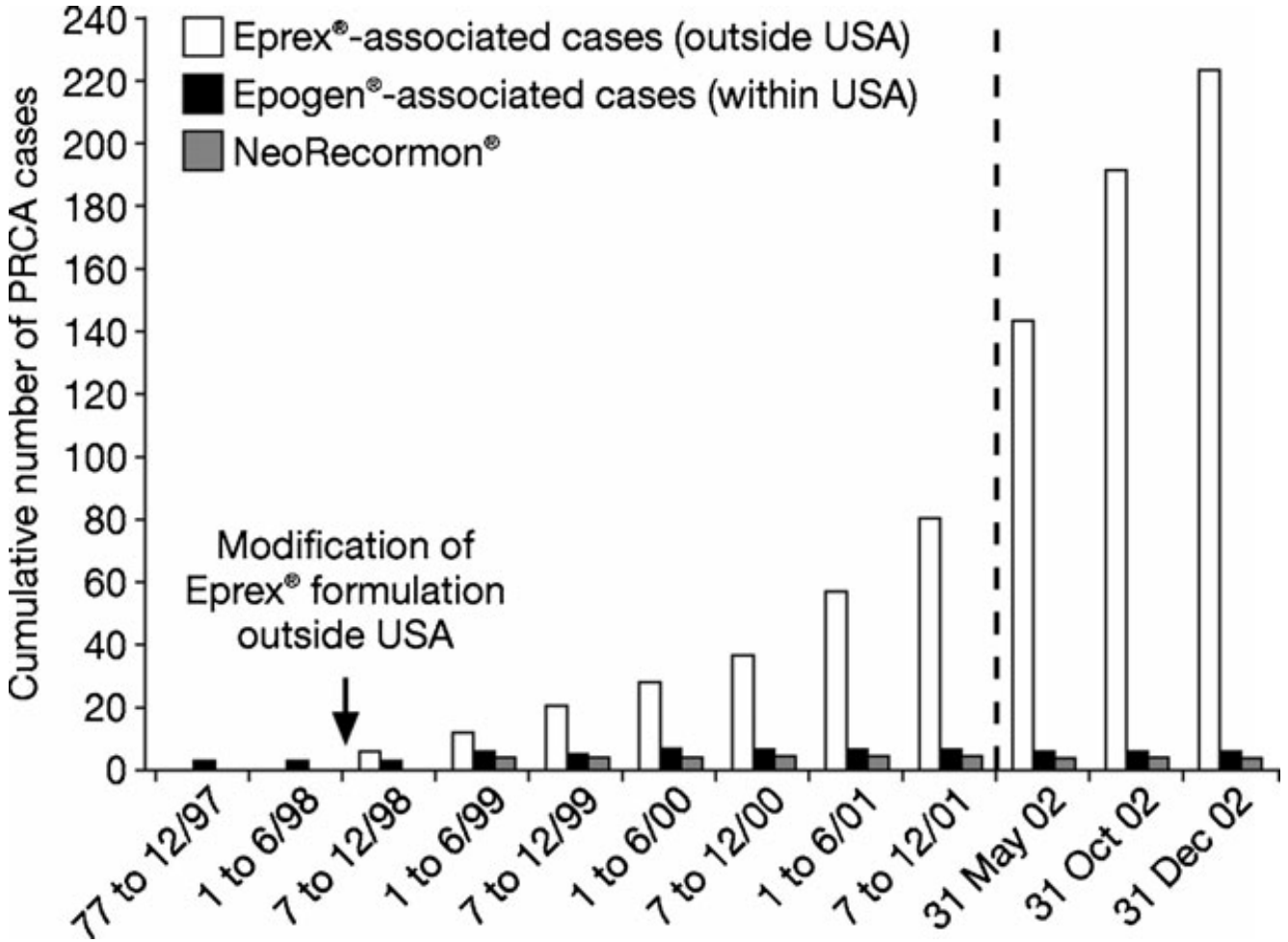
Transfer to alternative manufacturing sites

Manufacturing process

Methods of control

Change in the starting material and supply chain.

Comparability exercise: product attributes within the variability prior to change.


Eprex®-associated cases (outside USA)
Epogen®-associated cases (within USA)
NeoRecormon®
Cumulative number of PRCA cases
240
220
200
180
160
140
120
100
80
60
40
20
0
Modification of Eprex® formulation outside USA
77 to 12/97
1 to 6/98
7 to 12/98
1 to 6/99
7 to 12/99
1 to 6/00
7 to 12/00
1 to 6/01
7 to 12/01
31 May 02
31 Oct 02
31 Dec 02

COMMISSION REGULATION (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

Module 3.2.R Regional Information For EU

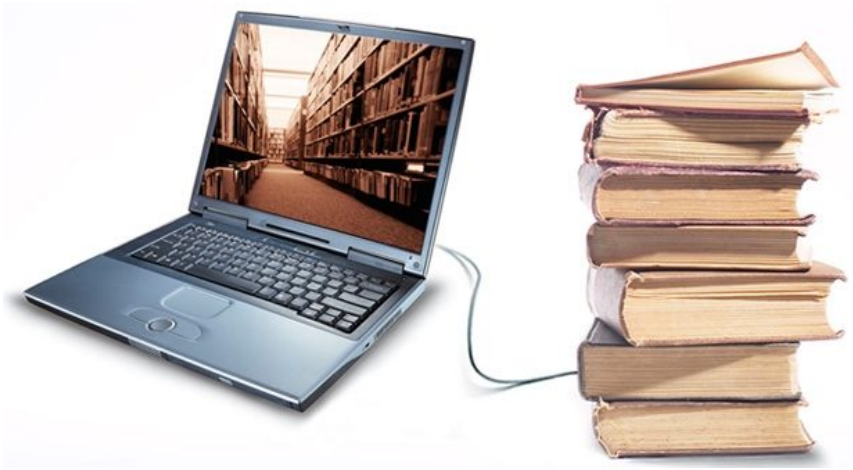
Any additional drug substance/active substance and/or drug product information specific to each region:

- Process Validation Scheme for the Drug Product
- Medical Device
- Certificate(s) of Suitability
- Medicinal products containing/using in the manufacturing process materials of animal and/or human origin
- Table A : Materials of animal origin covered by the NfG on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products
- Table B : Other materials of animal origin
- Table C : Albumin and other human tissue derived materials

Module 3.3 Literature References

A List of references to quality guidelines

B List of references to biotechnology guidelines



Module 4
Nonclinical Study Reports

- 4.1 TABLE OF CONTENTS OF MODULE 4
- 4.2 STUDY REPORTS

The study reports should be presented in the following order:

- 4.2.1 Pharmacology
- 4.2.2 Pharmacokinetics
- 4.2.3 Toxicology
- 4.3 LITERATURE REFERENCES

GLP status of the studies submitted.

Module 5
Clinical Study Reports

5.1 Table of Contents of Module 5

5.2 Tabular Listing of All Clinical Studies

5.3 Clinical Study Reports

5.4 Literature References

GCP compliance

Immunogenicity

Immunogenicity studies correlated with PK, PD, safety, and/or efficacy data

- e.g protein
- e.g. vaccines

Immunogenicity

Description of assays and their performance (e.g., sensitivity, specificity, reliability, validity)

Data regarding the incidence, titre, timing of onset and duration of antibody responses should be described for each type of antibody assay used (e.g., IgG by ELISA, neutralisation).

Relationships of antibody formation to underlying disease, concomitant medication, dose, duration, regimen, and formulation should be explored and summarised.

For drugs intended to be given as chronic, continuous therapy, any data on the impact of interruptions of therapy on antigenicity should be analysed and summarised.

Immunogenicity

Analyses of potential clinically relevant correlates of immunogenicity, e.g., to determine the extent to which the presence of antibodies of a particular type or titer appears to correlate with alterations of PK, changes in PD, loss of efficacy, loss of adverse event profile, or development of adverse events.

Particular attention should be paid to events that might be immunologically mediated (e.g., serum sickness) and events that might result from binding of cross-reactive endogenous substances by antibodies to the administered drug.

Immunogenicity assessment

Analysis of risk factors:
Previous experience of the product/product class
Physicochemical and structural aspects
Route and/or the mode of administration
Patient - and disease - related factors

The overall immugenicity assessment should consider the nature of the immune response (anaphylaxis, neutralizing antibodies), the clinical relevance and severity of consequences (loss of efficacy and other adverse events), the incidence of immune responses, and the population being studied.

Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (Consolidated version : 02/07/2012).

Gene therapy medicinal product

Somatic cell therapy medicinal product

Tissue engineered product

Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use

Clinical trials in Rare disease

Drugs in rare diseases are judged against the same standards as for other products, however, limitations on patient recruitment should be taken into account in the regulatory process.

e.g. Guidelines for clinical trials in haemophilia A

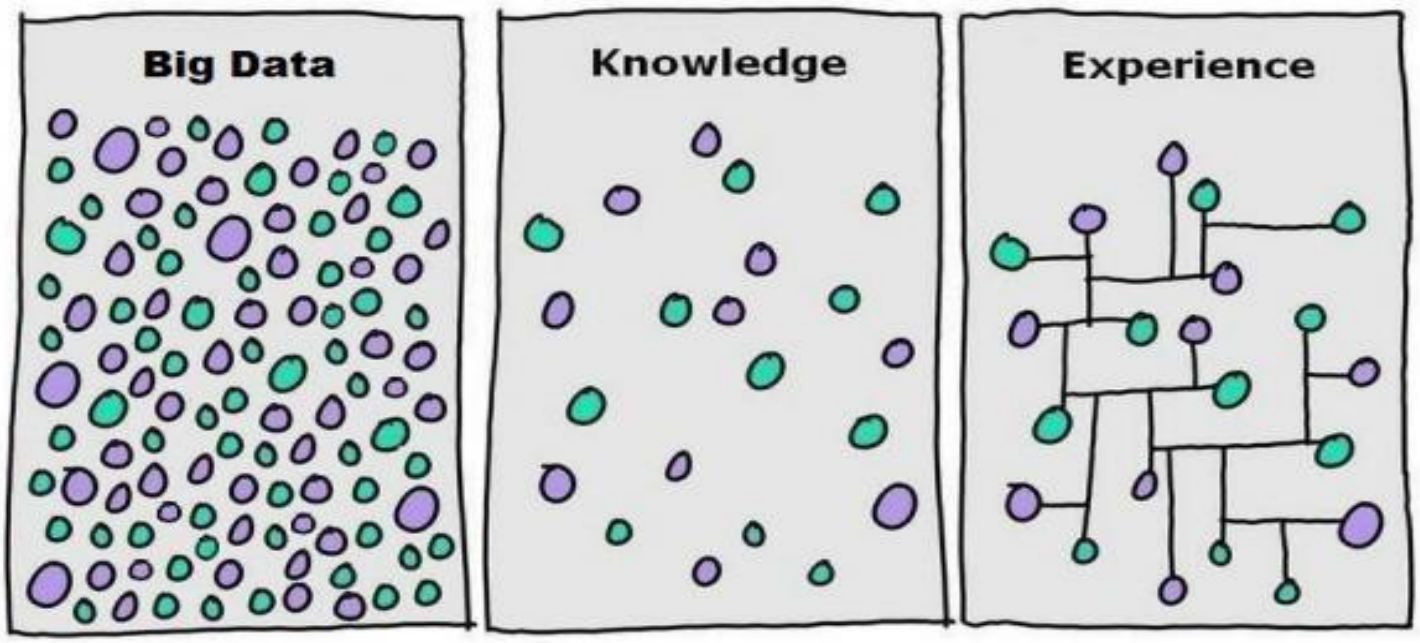
Opportunity for a Scientific Advice


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2011
EMA/CHMP/BPWP/144533/2009
Committee for medicinal products for human use (CHMP)

Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products

Conclusions



R&D CTD

Conclusions

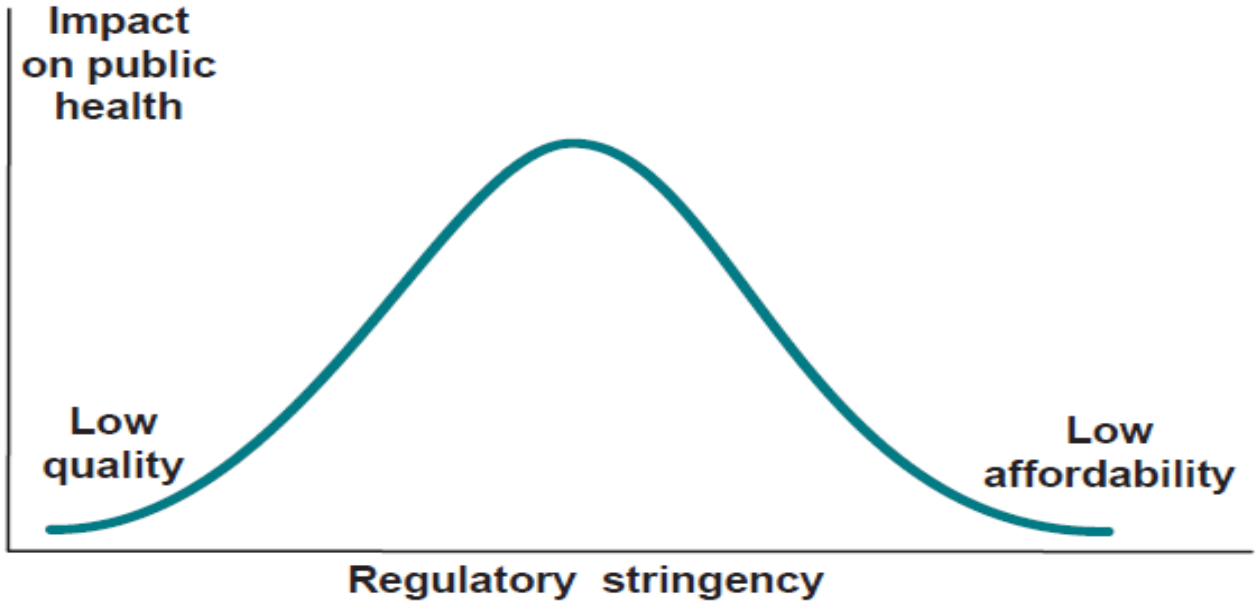
Provide accepted norms and standards for the evaluation

To help applicants obtaining marketing authorisation

To guarantee a harmonised approach of assessment and to support the decision process

Written standards (i.e. legislation and guidelines)
Laboratory standard (i.e. Harmonised Methods; I.S.)

Conclusions



Public health requires quality and coverage

Conclusions

The evaluation process of medicines is based both on trust and detailed controls

Thank you for your attention!

CONTATTI

Lorenzo Montrasio

AIFA

l.montrasio@aifa.gov.it

www.agenziafarmaco.gov.it

Agenzia Italiana del Farmaco

AIFA