EDQM: 50 YEARS OF LEADERSHIP IN THE QUALITY OF MEDICINES

PAVING THE WAY FOR THE FUTURE

6-8 October 2014
Strasbourg, France

WORKSHOP

BIOLOGICALS
Advanced Therapies and the RCG Working Party – Preliminary Aspects

EDQM: 50 years of leadership in the quality of medicines, International conference
7.10.2014, Strasbourg

Paula Salmikangas
CAT Chair

Gene Therapy
Medicinal Products

Somatic Cell Therapy
Medicinal Products

Tissue Engineering
Products

Genetically modified cells

medical device + ATMP → combined ATMP

Severe burn victim before and 6 months after treatment with Dermaplast.
The EU legal / regulatory framework

- **Blood**
  - 2002/98/EC

- **Clinical Trials**
  - 2001/20/EC

- **Paediatrics**
  - 1901/2006

- **‘Annex I’**
  - 2003/63/EC
  - 2009/120/EC

- **Advanced Therapy**
  - 1394/2007

- **Medicinal Products**
  - Community Code Dir. 2001/83/EC
  - Medicinal Products Centralised procedure Reg. 726/2004

- **PhVig legislation**
  - Dir. 2010/84/EU Reg. 1235/2010

- **Other starting materials**
  - Medical Devices 93/42/EC, 90/385/EC

- **GMP**
  - 2003/94/EC

- **Orphans**
  - 141/2000

- **Variations**
  - 1084(5)/2003
  - 1234/2008

- **Other starting materials**
  - Medical Devices 93/42/EC, 90/385/EC

- **GMP**
  - 2003/94/EC

- **Orphans**
  - 141/2000

- **Variations**
  - 1084(5)/2003
  - 1234/2008

A new class of medicinal products with a dedicated regulation

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**EMA Committees for ATMPs**

- **CAT**
  - Chair: P. Salmikangas
  - 5 "double members"

- **CHMP**
  - Chair: Dr. T. Salmonsson

**Overview of CAT expertise**

- Ethics
- PhVig Med Day Surgery
- Gene Therapy
- Cell Therapy
- Tissue Engineering
- Biotech

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3
## Marketing authorization applications / CAT 2009-2014 (September)

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### Approved:
- **ChondroCelect** for cartilage repair
- **MACI** for cartilage repair
- **Glybera** for treatment of LPL deficiency
- **Provenge** for treatment of advanced prostate cancer

### Currently
- 5 ATMPs currently under evaluation, 4 withdrawals

## ATMP Classifications 2009-2014 (September)

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- > 250 ATMPs in clinical trials during 2004-2010 (EudraCT)
- 189 ATMPs discussed in scientific advice (Sept 2014)
- 38 PIPs for ATMPs
ATMPs as pharmaceuticals?

- Aspirin
- Filgrastim, G-CSF
- Eucaryotic cell
- Recombinant virus

Special issues for ATMPs

- ATMPs are complex pharmaceuticals, for which traditional approaches may not be possible
- ATMPs are in the frontline of fast evolving science
  - A product maybe already “old”, when a new standard is available
- Manipulation of cells and use of recombinant nucleic acids may bear unknown risks, which may not be solvable through standardisation or quality control
- ATMPs mostly meant to cure diseases/tissue defects, for indications where satisfactory therapies do not exist
- Special challenges concerning manufacturing/quality, safety and efficacy studies
  - Need to balance risks and benefits and use flexible approaches (risk-based approach)
Scientific challenges

- Manufacturing constraints
  - GMP requirements for production
    - starting and raw materials, continuity of material supply
  - Immature production technologies, comparability
  - Variability and process validation, sterility

- Characterisation, potency testing (related to clinical outcome)

- Non-clinical challenges
  - Availability of relevant animal models
  - Proof of concept, safety aspects (species specificities)

- Clinical aspects
  - Possibilities for blinding, availability of comparators
  - Feasibility of dose finding and biodistribution studies in humans, concomitant medication/surgical procedures, efficacy!

- Product-related challenges:
  - Safety: dose, tumourigenicity, biodistribution, integration
  - Efficacy: inter-individual variability, administration

Starting materials

- Genes, cells, tissues, but also other components when present in the final product (e.g. matrices, scaffolds, biomolecules)

- Risk profile of the product: autologous vs. allogeneic, animal-derived materials vs. animal-free, for immediate use vs. frozen, etc.

- What components are part of active substance, what are considered impurities and why?

- Transportation and storage conditions – impact on the final product?

- For ATMPs, a product is as good as the quality of the starting and raw materials!
Raw materials for production of ATMPs

- key raw materials are high risk biologicals (growth factors, cytokines, MAbs)
- quality of raw materials can affect safety, potency, purity and stability of medicinal products
- availability of high quality raw materials is limited, in many cases ‘for research use only’- materials the only choice; more recently ‘GMP’-grade materials available (price differences)
- GMP-grade does not necessarily mean that there would be all required quality attributes analysed for each material
- product documentation and information e.g. about changes difficult to obtain from suppliers
- qualification of materials by testing and suppliers by auditing is very expensive and time consuming
Scope, purpose and phase

- a meeting with all stakeholders was held to discuss the challenges of ATMP developers and raw material manufacturers
- a working group, RCG, was established to discuss the way forward
- general chapter, i.e. not binding requirements at this stage
- raw materials of biological origin
- requirements both for testing and production of raw materials
- categorised based on risks: animal-derived RM, RM produced using animal-derived materials, animal-free RM
- final draft discussed early June, released for consultation 1.10.2014
European Pharmacopoeia
- applicable for ATMPs!
  - general chapters
  - analytical methods
  - microbiological purity, TSE, sterility
  - specific monographs for gene therapy and cell therapy products
  - monographs on primary packaging materials....

- important and useful for ATMP developers and assessors

- New developments in collaboration with all stakeholders (industry, national competent authorities, external experts, CAT members...)
  ➔ to ensure that all challenges, risks, and limitations are considered when new standards / requirements are established
  ➔ to benefit patients
  ➔ to support development of innovative medicines for unmet medical needs!
Congratulations

Thank you for your attention!
Monographs in the Field of Biologics: Recent experiences and future challenges

Jaana Vesterinen, Fimea

Ph. Eur. Texts

- About 70 Expert Groups and Working Parties
- Over 2500 monographs and 300 general chapters

Ph. Eur. update 2013 courtesy of Dr M. Buda
Examples of biological monographs / texts

Substance specific monographs

- **Groups 6 & 6B**
  - Human insulin
  - Glucagon
  - Somatropin
  - Filgrastim
  - Molgramostim
  - Interferons
  - Erythropoetin
  - Follitropin
  - Calcitonin
  - Human coagulation factors

- **P4Bio WP**
  - Insulin glargine (2571)
  - Human coagulation factor VIIa (rDNA) concentrated solution (2534)
  - Human coagulation factor IX (rDNA) concentrated solution (2522)
  - Teriparatide (2829)

Classes of substances and Analytical methods, eg.
- Recombinant DNA technology, products of (784)
- Monoclonal antibodies for human use (2031)
- Raw materials for the production of cell-based and gene therapy… (5.2.12)
- Peptide mapping (2.2.55)
- Glycan analysis of glycoproteins (2.2.59)

P1 and P4 working procedures

- P1: traditional elaboration by Groups of Experts and Working Parties
- P4: substances still under patent, involving confidential exchange and collaboration between the manufacturer and the EDQM. Therefore, the WP is only composed of representatives of authorities and the EDQM staff. **P4Bio for biologicals.**

Courtesy of Dr E. Charton
**Substance specific biological monographs**

- Defines specifications for the drug substance, based on specifications of the approved products
- Provides analytical methods and system suitability criteria for testing the identity and quality of the substance
- Is used together with a reference substance (CRS or BRP)

**DEFINITION** (amino acid sequence, glycosylation site, assay limits)

**PRODUCTION**: instructions for manufacturers (different host expression systems, truncated/PEG forms not covered)

**IDENTIFICATION** (peptide mapping, bioassay, glycan analysis...)

cross-reference to the test section

**TESTS (purity)** (physico-chemical / chromatographic methods)

**ASSAY** (physico-chemical assay methods, bio/immuno-assays)

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**An ideal monograph for a biological drug substance?**

- **Detailed enough** to facilitate the testing in any laboratory
- **Flexible enough** to allow alterations and case-to-case considerations
- Giving guidance for alternative approaches

- **State-of-the-art** utilising modern methodology
- **Conventional** enough to allow any laboratory to repeat testing
**Detailed or flexible?**

Examples of different levels of flexibility: Glycan analysis

1. Human coagulation factor VIII (rDNA)
   PRODUCTION: Carbohydrates/sialic acid. To monitor batch-to-batch consistency, the monosaccharide content and the degree of sialylation or the oligosaccharide profile are monitored and correspond to those of the manufacturer’s reference preparation.

2. Follitropin
   IDENTIFICATION:
   E. Glycan analysis (2.2.59). Detailed instructions follow.
   **Result:** $Z = 177-233$.

3. Human coagulation factor IX (rDNA)
   PRODUCTION:
   Flexible, no details

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**Human coagulation factor IX (rDNA), concentrated solution (2522)**

**PRODUCTION**
Produced in mammalian cells by a method based on rDNA technology
Prior to release, the following tests are carried out:
Host-cell-derived proteins, limits as approved
Host-cell- and vector-derived DNA, limits as approved

**Glycan analysis**
Use a suitable method developed according to general chapter 2.2.59. Glycan analysis
- Release the glycans, for example peptide $N$-glycosidase F (PNGase F).
- Label the released glycans, for example 2-aminobenzamide.
- Analyse the labelled glycans by liquid chromatography

Details allowing any laboratory to perform the test are given as an example
System suitability:
- the chromatogram obtained with reference solution (a) is qualitatively similar to the chromatogram supplied with human coagulation factor IX (rDNA) CRS; 5 groups of oligosaccharide peaks corresponding to P0 neutral, P1 mono-, P2 di-, P3 tri- and P4 tetrasialylated...
- no significant peaks are observed in regions P0 to P4 in the chromatogram obtained with blank solution.

Results:
- the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with reference solution (b);
- the tetrasialylated peak area ratio for the test solution is within the limits authorised by the competent authority.

Flexibility is obtained using two standards:
- a) CRS for method performance check-up
- b) In-house reference for analysing results

Cutting edge or easy-to-perform?

• The monographs need to keep pace with methodological development
• The testing must also include methods that are widely available, so that an independent laboratory can verify the quality
• Both cutting edge and conventional methods can be included into monographs to find a balance

For the OMCL network, the methodological demands are challenging and even more active collaboration and planning between laboratories is needed to obtain the best possible use of public resources
**In vitro bioassays in monographs**

1. **Not absolutely necessary**, if the structure of a molecule is simple and it can reliably be determined by physicochemical studies *(Insulin, human, 0838)*
2. Not defined in ASSAY section, but under PRODUCTION it is stated that biological activity must be tested using a suitable validated bioassay approved by competent authorities *(Somatropin concentrated solution, 0950; Glucagon, human, 16635)*
3. **A defined bioassay** with acceptance limits given *(Erythropoietin concentrated solution, 1316)*

**Challenges:**

- Often manufacturers prefer bioassays containing reagents/ components with proprietary right issues → *this forms a challenge* for setting common Ph. Eur. standards for bioassays
- Bioassays need to be calibrated against WHO international standards/ Ph. Eur. standards (BRPs) → *establishing an international requires marked input from the manufacturer and the laboratories participating the establishment study. Expensive and labor-intensive.*

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**Conclusions**

Ph. Eur. monographs play an important role as quality standards for biotech products, as they are considered by manufacturers and regulators

**Test methods**

- Validated analytical methods with suitability criteria (performance verification)
- Useful only if they provide enough details
- Must be scientifically sound, up-to-date

**Specifications**

- Based on approved products
- ‘Flexibility’ can be built into specifications by using common standards for method performance check-up, in-house standards to calculate results

**Reference standards**

- Expensive to establish
- High level international strategy and coordination is needed not to waste resources!

*We need to keep an open mind and exchange opinions!*
BIOPHARM DEVELOPMENT IN THE EUROPEAN PHARMACOPEIA
A Perspective From Industry

Phil Travis
Manager/Team Leader
Global Quality Intelligence and Compendial Affairs

Foundation

- Setting the EDQM Standard
  - Peter Castle (1946 – 2008)
  - Collaboration at all levels of EDQM
  - Good science and Common Sense Solutions
  - Balancing the roles and responsibilities of Compendia, Regulators and Industry
  - Domestic responsibility with global perspective and value

EDQM: 50 Years of Leadership in the Quality of Medicines
6-8 October 2014
Global Quality Intelligence and Compendial Affairs

Foundation

• Public standards can provide a benefit for the process of establishing safe and effective medicines for patients
  – 50th Anniversary of the EDQM
  – Demonstrates a long standing value
  – A flexible BIOPHARM monograph can help provide objective standards encompassing a variety of methodologies without undue restrictions

• Is the compendial process suitable for Biopharmaceuticals?
  – Functional
  – Flexible
  – Timely

To maintain value, public standards need to be contemporary with the established scientific development of the Industry and Regulators
  – Functioning in the present while preparing for the future

The established value in an Excipient or Small Molecule Drug Substance monograph is no different than the potential for a BIOPHARM monograph
  – That does not mean that they must look the same
  – That does not mean every topic is ready for development

KEEP AN OPEN MIND IN EXPLORING OPPORTUNITIES AND VALUE THAT CAN BE ATTAINED FROM BIOPHARM DEVELOPMENT
Developing a BIOPHARM Public Standard

- **Industry considerations**
  - Submission timing
    - Opinions Vary: Patents life/loss of exclusivity
    - P4 Process (Innovator) vs P1 Process (Open Market)
  - Status of manufacturing
    - Developing new process / sourcing
    - Developing new methods / specifications
  - Proprietary Knowledge
    - Key methods following patented analytical technology
    - Testing kits – Need basic knowledge to give flexibility
  - Support for RS program
    - Inventory and Cost

Traditional Monograph Evolution

- **Functionality Related Characteristics (FRC)**
  - Recognizes relevant control parameters while providing more flexibility for industry application
  - How can similar flexibility assist BIOPHARM development?

- **Harmonization**
  - Pharmacopoeial Discussion Group
    - 6 Chapters developed to support BIOPHARM applications
      (Capillary electrophoresis, Protein determination, Peptide mapping, etc.)

- **General Notices**
  - Quality by Design / Process Analytical Technology
BIOPHARM Development / Evolution

- Establish a common understanding with general content (notices, chapters and monographs) and then follow with specific monographs
- A monograph only suitable for one manufacturer’s material/process is not a public standard
  - Start with a goal of a functional public standard
- Form and function can be clarified during development
  - Engage the EDQM to find suitable answers
    - Before submission
    - During Ph. Eur. development
    - Open minded debate on different opinions helps challenge traditional thinking and find new solutions

Challenges of Biosimilar Materials

- Finding the right balance in analytical technology for a public standard
  - Established Robust Technology (HPLC, SDS-PAGE)
  - Advanced Technology (Capillary Electrophoresis; 5.1.6 Alternative Methods for Micro)
- Materials are not identical
  - The core monograph content will need more flexibility than a traditional monograph
  - The core monograph content will reflect less of the regulatory filing than a traditional monograph

Compliance with a Ph. Eur. Biopharmaceutical Monograph does NOT Establish Biosimilarity
**Global Quality Intelligence and Compendial Affairs**

**BIOPHARM Monograph content will reflect less of the regulatory filing than a traditional monograph**

**Small Molecule**
- Ph. Eur. Monograph
  - Identification
  - Impurities
  - Additional Quality Attributes
  - Assay

**Biopharmaceutical**
- Material and Application specific attributes:
  - Identification / Impurities / Quality / Functionality
- Regulatory Guidance
- Industry Evolution
- New Technology / Manufacturing

**Regulatory Filing**
- Application specific requirements:
  - Functionality
  - Regulatory Guidance
  - Industry Evolution
  - New Technology / Manufacturing

**BIOPHARM Development / Evolution**

- **Solutions for Biopharmaceutical Monograph Flexibility**
  - Adapt the monograph based on roles and responsibilities of Industry and Regulators
  - Expand the Production section of the monograph (similar to FRC flexibility)

  (Monograph #2322)
  
  “…Use a suitable method developed according to general chapter…”
  
  “…The limit is approved by the competent authority”
  
  “…Use a suitable in-house reference preparation shown to be representative of batches tested clinically and batches used to demonstrate consistency of production…”

  (Monograph #2349)
  
  “…In agreement with the competent authority, and in light of a risk assessment, rapid assays (e.g. multiplex PCR) may be applied as alternatives…”

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21
New Compendial Development

- **Raw Materials for Cell and Gene Therapies / Product Monographs / Etc.**
  - Is there sufficient content and agreement to make a public standard valuable?
    - Appropriate common expectations
    - Supports Industry/Regulatory use without interfering with development
  - Is there a sufficient foundation for development?
    - General notices/chapters/monographs
    - Clear understanding of function and flexibility of public standard

Public standards are most valuable when they reflect a well established topic

Take Home Messages

- **To maintain value, BIOPHARM standards need to be contemporary with the established scientific development of the Industry and Regulators**
- **Keep an open mind in exploring opportunities and value that can be attained from compendial development of BIOPHARM topics**
  - Biopharmaceuticals (Products Monographs, Harmonization, etc.)
  - Ensure there is agreement on suitable content for development of a new topic
  - Respect tradition but do not let it limit you
- **BIOPHARM standards benefit from a strong foundation**
  - General supporting content
  - Functional
  - Flexible
  - Timely
Congratulations on 50th Anniversary

Thank You

Merci