Biosimilar Medicinal Products
Quality Package and Comparability

September 2015
Dr John Purves
Agenda

• Philosophy and scientific approach
  – Holistic understanding and strategic considerations
  – Communications and Consultation
  – Definitions, complexity of molecules and special characteristics

• Quality Package and Comparability - C.M.C. matters
  – Quality Management Systems
  – Overview of development of a biosimilar product
  – Complexity of molecules and the method of manufacture / Good Manufacturing Practice / Manufacture and upscaling of manufacture
  – Definition of Quality Target Product Profile
  – I.C.H. and European guidelines
  – Insight into the review of dossiers over the last 45 years (EU)
    • Importance of Pharmacovigilance and life cycle control

• Take Home Messages
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• Take Home Messages
Starting Point – Philosophy and Scientific Approach
Business of Biosimilars - Communications

The Regulation of Medicinal Products is SCIENCE DRIVEN

How to consider the range of products and data requirements - on spectra?

**Science and Product Types**

- Chemicals
- Recombinant DNA technology
- Blood-derived
- Immunologicals
- Advanced therapy

**Legislation**

- Generic (essentially similar)
- Biosimilar (Not generic)
- Full Dossier

Future?
Philosophy and Scientific approach

- Definitions
- Scientific approach to biological and biosimilar medicinal products
  - Complexity / Heterogeneity
  - Development, manufacture and control plans
  - r-DNA technology products
- Comparability
  - within a company
  - between companies
- Comparability criteria – Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA)
- Philosophy regarding the review of dossiers and the decision making procedures – they have evolved, too
  - Q, S, E, RMPs, Benefit / Risk methodology, Ph.V. and life-cycle control
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- Take Home Messages
Quality Management Systems – Importance!

Mission

Objectives

Processes / Audits

Tasks
Biotechnological products are highly complex molecules
Common features: Complexity of Molecules and Methods of Manufacture

• Products are encoded by genetic information and produced from a biological source
• Complex technology
• Manufacturing steps for proteins and handling under aseptic conditions
• Great variability/complexity of starting materials and process reagents
  • Cells
  • Media
  • Enzymes
• Products are sensitive to conditions and changes within the process
• Products are less well understood due to inherent complexity
Biotechnological products are highly complex molecules

- high molecular weight
- complexity (primary / secondary / tertiary / quartery structure; post-translational modifications)
- heterogeneity (drug substance, drug product)
- process- and product-related impurities
- low stability of drug substance / drug product
- species specificity
- immunogenicity

Monoclonal antibody
Biosimilar Monoclonal Antibodies

PHYSICOCHEMICAL CHARACTERISTICS

VARIABLE REGION
- Deamidation
- Oxidation
- N-term Pyro-Glu
- Glycosylation
- Glycation

CONSTANT REGION
- Deamidation
- Oxidation
- Acetylation
- Glycation
- Glycosylation (fucosylation, sialylation, galactosylation, mannosylation...)
- C-term Lys
- Disulfide bond shuffling/cleavage
- Fragmentation/clipping

BIOLOGICAL CHARACTERISTICS

BINDING
- Affinity
- Avidity
- Immunoreactivity/crossreactivity
- Unintentional reactivity

EFFECTOR FUNCTION
- Complement interaction
- FcRn, FcyR interaction
- Mannan binding ligand interaction
- Mannose receptor interaction

OTHER BIOLOGICAL PROPERTIES
- PK properties
- Epitope/Immunogenicity
- Modulatory region (Tregitope...)

Slide from Peter Richardson
General Method of Manufacture

Typical biotech manufacturing process

- Genetic development
  - Q5A
  - Q5B
  - Q5D
  - Q5E

- Cell banks
  - Q9
  - Q10
  - Q7A

- Production
  - Q5A
  - Q5C
  - Q5E
  - Q6B
  - Q11

- Sterilisation
  - Aseptic filling
  - Q8
  - Q8R

- DRUG SUBSTANCE
- Purification
- Working Cell Bank
- Master Cell Bank
- Expression system (1 clone)
- Expression vector
- Gene of interest
- Host cell
- Wild vector

DRUG PRODUCT
Sterile filtration / Aseptic filling
Common features: Complexity of Molecules and Methods of Manufacture

- Products are encoded by genetic information and produced from a biological source
- Complex technology
- Manufacturing steps for proteins and handling under aseptic conditions
- Great variability/complexity of starting materials and process reagents
  - Cells
  - Media
  - Enzymes
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- Products are less well understood due to inherent complexity
Complexity of Manufacture

Typical antibody manufacturing process

QTPP Position and Comparability
Drug Substance Quality Link to Drug Product - 1

• The intended quality of the **drug substance** should be determined through consideration of its use in the drug product as well as from knowledge and understanding of its physical, chemical, biological, and microbiological properties or characteristics, which can influence the development of the drug product.

• The Quality Target Product Profile (QTPP), potential Critical Quality Attributes (CQAs) of the **drug product** (as defined in ICH Q8) and previous experience from related products can help identify potential CQAs of the drug substance.

• Knowledge and understanding of the CQAs can evolve during the course of development. QTPP - A prospective summary of the quality characteristics of a **drug product** that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. (ICH Q8)
Drug Substance Quality Link to Drug Product - 2

• The development of a similar biological medicinal product (biosimilar) relies in part on the scientific knowledge gained from the reference medicinal product, provided that the active substance of the biosimilar has been demonstrated to be similar, in physicochemical and biological terms, to the active substance of the reference medicinal product.

• Biosimilars are manufactured and controlled according to their own development, using state-of-the-art approaches and taking into account relevant and up-to-date information. The product development should be performed in accordance with relevant ICH and CHMP Quality guidelines.

• Consequently, an extensive comparability exercise with the chosen reference medicinal product will be required to demonstrate that the biosimilar product has a similar profile in terms of quality, safety and efficacy to the reference medicinal product.
Drug Substance Quality Link to Drug Product - 3

• **A full quality dossier** (CTD Module 3) is required as detailed in current EU legislation and this should be *supplemented by the demonstration of biosimilar comparability*. Applicants should note that the comparability exercise for a biosimilar product versus the reference medicinal product is an additional element to the normal requirements of the quality dossier. It should be *discussed separately in section 3.2.R when presenting the data in Module 3*.

• There is a need to comply with guidelines, as follows:
  – EMA / CHMP and
  – I.C.H.

• **Manufacturing process** of a similar biological medicinal product - The development and documentation for biosimilars should cover two distinct aspects:
  – i) molecular characteristics and quality attributes (QA) of the target product profile should be comparable to the reference medicinal product;
  – ii) performance and consistency of the manufacturing process of the biosimilar on its own.
Drug Substance Quality Link to Drug Product - 4

- The quality target product profile (QTPP) of a biosimilar should be based on data collected on the chosen reference medicinal product, including publicly available information and data obtained from extensive characterisation of the reference medicinal product.

- The QTPP should form the basis for the development of the biosimilar product and its manufacturing process. This QTPP should be considered as a development tool for which some target ranges may evolve during development, as further information on the reference medicinal product becomes available.

- A biosimilar is manufactured and controlled according to its own development programme, taking into account state-of-the-art information on manufacturing processes and consequences on product characteristics. As for any biological medicinal product, the biosimilar medicinal product is defined by the molecular composition of the active substance resulting from its manufacturing process, which may introduce its own molecular variants, isoforms or other product-related substances as well as process-related impurities.

- As a consequence, the manufacturing process should be appropriately designed to achieve the QTPP.
Drug Substance Quality Link to Drug Product - 5

• The **stability of the biosimilar product** should be determined according to ICH Q5C. Any **claims** with regard to stability and compatibility must be supported by data and **cannot be extrapolated from the reference medicinal product**.

• When changes to the manufacturing process (active substance and/or finished product) are introduced during development, a **comparability assessment** (as described in ICH Q5E) should be performed.

• **For the purposes of clarity**, any comparability exercise(s) for process changes introduced during development should be clearly identified in the dossier and **addressed separately from the comparability exercise performed to demonstrate biosimilarity versus the reference medicinal product**.
• Process changes may occur during the development of the biosimilar product, however, it is strongly recommended to generate the required quality, safety and efficacy data for the demonstration of biosimilarity against the reference medicinal product, using product manufactured with the commercial manufacturing process and, therefore, representing the quality profile of the batches to be commercialised.
Comparability exercise versus reference medicinal product – quality aspects - 1

• The **reference medicinal product** used in the biosimilar comparability exercise at the quality level **must be clearly identified** (e.g. brand name, pharmaceutical form, formulation, strength, origin of the reference medicinal product, number of batches, lot number, age of batches, use).

• **Multiple different batches** of the reference medicinal product should be used to **provide robust comparability data in order to generate a representative quality profile**.

• The **age of the different batches** of reference medicinal product (relative to the expiry dates) should also be considered **when establishing the target quality profile**. This will evolve as more data are collected.
Comparability exercise versus reference medicinal product – quality aspects - 2

• An extensive comparability exercise will be required to demonstrate that the biosimilar has a highly similar quality profile when compared to the reference medicinal product.

• This should include comprehensive analyses of the proposed biosimilar and reference medicinal product using sensitive and orthogonal methods to determine not only similarities but also potential differences in quality attributes.

• These analyses should include side-by-side comparative studies unless otherwise justified. Any differences detected in the quality attributes will have to be appropriately justified with regard to their potential impact on safety and efficacy.

• The aim of the biosimilar comparability exercise is to demonstrate that the biosimilar product and the reference medicinal product chosen by the applicant are similar at the level of the finished medicinal product.
Comparability exercise versus reference medicinal product – quality aspects - 3

• Particular attention should be given to quality attributes that might have an impact on immunogenicity or potency, or that have not been identified in the reference medicinal product.

• The applicant should demonstrate that the desired product (including product-related substances) present in the finished product of the biosimilar is similar to that of the reference medicinal product. Process-related impurities may differ; but, they should be minimised.

• Quantitative ranges should be established for the biosimilar comparability exercise, where possible. These ranges should be based primarily on the measured quality attribute ranges of the reference medicinal product and should not be wider than the range of variability of the representative reference medicinal product batches, unless otherwise justified.

• It should be noted that acceptable ranges used for the biosimilar comparability exercise versus the reference medicinal product should be handled separately from release specifications.
Analytical Considerations - 1

• It is the responsibility of the applicant to demonstrate that the selected methods used in the biosimilar comparability exercise would be able to detect slight differences in all aspects pertinent to the evaluation of quality (e.g. ability to detect relevant variants with high sensitivity). Methods used in the characterisation studies form an integral part of the quality data package and should be appropriately qualified for the purpose of comparability.

• For some analytical techniques, a direct or side-by-side analysis of the biosimilar and reference medicinal product may not be feasible or give limited information (e.g. due to the low concentration of active substance and/or the presence of interfering excipients such as albumin). Thus samples could be prepared from the finished product (e.g. extraction, concentration, and/or other suitable techniques). In such cases, the techniques used to prepare the samples should be outlined, and their impact on the samples should be appropriately documented and discussed (e.g. comparison of active substances before and after formulation/de-formulation preparation).
Analytical Considerations - 2

• Methods
  – Physico-chemical properties
  – Biological activity
  – Immunochemical properties
  – Purity and impurities
  – Quantity

• As for any biotechnology-derived product, the selection of tests to be included in the specifications (or control strategy) for both drug substance and drug product is product specific and should be defined as described in ICH Q6B. The rationale used to establish the proposed range of acceptance criteria for routine testing should be described.

• The claimed shelf life of the product should be justified with full stability data obtained with the biosimilar medicinal product. Comparative real-time, real-condition stability studies between the biosimilar and reference medicinal product are not required.
Testing of Biosimilars

How much of the Iceberg is visible?

Release Tests (Specifications)

Extended Characterization (Process & Product)

Process Control
- Procedures
- Materials
- In-process testing
- Monitoring
- Validation

Unknown
Learned over time – update control strategy

Consistency
Similarity
Comparability
In-Process Controls
End-Product only


London July 2, 2009
Slide from Steven Kozlowski FDA

G.-B. Kresse / CMC
1. It is well established that biotechnological products are more complex than small molecules, since they are often typically composed of a mixture of isoforms. Any change in this mixture of different glycosylated forms may impact on bioavailability (efficacy) or alter immunogenicity (safety).

2. The control of degradation products is extremely important since it is not always easy to distinguish between

2.1. **product related substances** which are active and safe and, therefore, not CQAs and

2.2. **product related impurities**, which may be either inactive or have safety concerns, when they would be important CQAs.

2.3. Because of the complex nature of the starting materials and the manufacturing process itself, it is not always easy to identify all CQAs. During development and scale up of manufacture to commercial stage new CQAs may be identified. Furthermore, changes in the manufacturing process may affect product quality, exemplifying the need for detailed in-process controls of all steps in the manufacturing procedures.

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product. (I.C.H Q8 quotation)
3. It is important to define the quality target product profile (QTPP) at the onset as it relates to the quality, safety and efficacy of the product to be used in patients and to be marketed.

4. As shown in slide 1, there are detailed controls over the production facilities, individual detailed process steps leading to the product, recognising the needs of the patient. Throughout production there must be a control strategy covering all process parameters, process model and design space (QbD option), identification of a list of CQAs and the QTPP established, based on knowledge of the reference product. Risk assessments should be performed to cover all of these parameters.

5. The CQAs will be dependent upon the specific manufacturing processes for the products concerned, to ensure they do not compromise the safety and efficacy of the product.
Common Features: Fragile Nature of the Molecule

• Limited stability – cold chain storage and transport
• Denatured proteins may:
  • Precipitate
  • Have reduced / no potency
  • Have increased immunogenicity
    • Side effects e.g. rash
    • Autoimmune response e.g. Erythropoietin
  • Have changed pharmacokinetics
• Even an apparently ‘innocent’ material used in the manufacture of a biopharmaceutical product (a syringe stopper) may cause unexpected deleterious effect or could impact stability
10 years in ... and still evolving to allow for the introduction of highly complex molecules

The EMA has developed a robust regulatory pathway for biosimilars...

Slide cited with permission from Virginia Acha, Amgen
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• Take Home Messages
Take Home Messages – Starting Points

• The availability of the E.U. Centralised Procedure, provides information on the clear pathway to obtain a Marketing Authorisation (MA) for a biosimilar medicinal product, taking into account the:
  – Evolution of the legislation, science and review of data submitted in support of applications for MAs
  – Strengthening of the review of dossiers to include not only Quality, Safety and Efficacy; but, also, Risk Management Plans and Pharmacovigilance – life-cycle control
  – Evidence of the robust procedures put in place at the EMA shown by the numbers of MAAs either granted / refused / withdrawn
  – Implementation of the Quality Management Systems put in place within, and across, Regulatory Agencies within the European Community, which are key to supporting the robust procedures
Take Home Messages – Evolution

• Regional Experience has been gained within the E.U. regarding the
  – Implementation of legislation
  – Provision of guidelines to convey the Regulators understanding of the data requirements arising from the legislation
  – Provision of Scientific Advice
  – Review of dossiers – Quality, Safety and Efficacy and Risk management Plans: then, the granting of Marketing Authorisations and life-cycle control
  – Implementation of pharmacovigilance to strengthen product life-cycle control
• W.H.O. has undertaken discussions on data requirements for biosimilar medicinal products
Take Home Messages – Progress and Harmonisation

• Account needs to be taken of efforts undertaken already, by a wide group of International and other bodies
  – Nationally, Regionally and Globally
  – Established guidelines and experience
    • E.U.
    • I.C.H.
    • W.H.O.
  – The need for clear regulatory pathways
  – The need to maintain and progress scientific and regulatory debate

• Such harmonisation should further facilitate the development of not only Regional but, also, Global approaches, to help strategic planning
Take Home Messages – Challenges

• Regional and global progress in the development of biosimilar medicinal products – harmonisation?

• Review by regulatory authorities?

• Communications
  – Awareness / Education about this class of products / Physicians / Healthcare workers
  – Societal Implications – growing healthcare costs / budget difficulties

• Market access?

• Patients access?
Thank you for your attention

John Purves
Contact Details:
Telephone - Home: - +44 (0) 1279 657149
Mobile: - +44 (0)
7710307505
E-mail - jpurves845@aol.com
Spectra of Size and, thus, Molecular Complexity

Aspirin
180 Daltons

Insulin
5,700 Daltons

mAb
150,000 Daltons
Definition of a biological product

- A biological substance is one that is produced by, or extracted from, a biological origin/source, and
- Because of its complexity it cannot be fully characterised by physico-chemical means alone, - this applies to the substance / drug substance / finished medicinal product.
- Its quality is determined by a battery, or combination, of physico-chemical and biological tests, together with the details of manufacture and control processes.
- Such products include biotechnology derived, blood or plasma derived products or an immunological, or cells, gene transfer materials, cell therapy materials, r-DNA and biosimilar medicinal products.

But, there are additional, and particular, legal provisions for Biosimilars!

- Biosimilar medicines are “follow-on” versions of original biological medicines. They are independently developed as “copies of the original product” after the patent protecting the original product has expired.

- The biosimilar medicinal product has its own specific route of manufacture; but, it is intended to have the same mechanism of action as the original product.

- Such products are designed to be used in the same indications / diseases as the original product.
Biosimilar Medicinal Products

• Biotechnology-derived: recombinant proteins
  – Product complexity – major factor thus the importance of comparability regarding the Quality Target Product Profile and Critical Quality Attributes
  – Data requirements not always the same for similar products
  – Case-by-case approach is applicable to the generation and review of dossiers

• Application of the “biosimilar approach” to other biological medicinal products
  – Is not ruled out;
  – However, the ability to characterise the product becomes critical
Biological Medicinal Products are Special

• Products have an active substance which is of biological origin

• As such, they are special regarding:
  • Variability, fragility, administration via parenteral use only, possible transmission of pathogenic agents, lacking relevance of animal models for pre-clinical testing, high costs of development, high costs for health systems
  • The accepted approaches to the development of long established pharmaceuticals, often may not be applicable
  • Considerations by the industry and regulators need to treat such products on a case-by-case basis

• Biological medicinal products offer new treatment options and may deliver more innovation for the industry in the future i.e. cell, gene, immunotherapy products etc.
The Process is the Product

Each company has its own unique cell line, process and manufacturing platform

Eli Lilly & Co:
Expression system: *E. Coli*
Expressed molecule:
• Pro-Insulin (35 AA bridge)
• Leader sequence
• Other sequences as needed in *E. Coli*

Novo Nordisk:
Expression system: *S. Cerevisiae*
Expressed molecule:
• Insulin precursor (3 AA bridge)
• Leader sequence
• Other sequences as needed in *S. Cerevisiae*

Source: Talk Inger Mollerup, NovoNordisk A/S
Joint EMEA/DIA Workshop on Biosimilars, Paris 2005
The Process is the Product

And processes are very different!

Eli Lilly & Company:
Unfolding and refolding

Novo Nordisk:
Secreted with correct folding

Different
• HCP’s
• reagents
• solvents
• chrom. resins
• pH ranges
• etc. etc. etc.

Purified Human Insulin

Source: Talk Inger Mollerup, NovoNordisk A/S
Joint EMEA/DIA Workshop on Biosimilars, Paris 2005
The Process is the Product

- Fluctuations in the manufacturing process (e.g., pH, temperature, culture media):
  - Batch inconsistency (glycosylation spectra, aggregates)

- Changes in the manufacturing process (e.g., expression system):
  - New product?

• “One process – one product“ paradigm

Biotechnological medicinal products are „specific products“

Biotechnological medicinal products are more than the drug substance

Small changes in production can have a high impact
Production Processes and Guidelines

Typical biotech manufacturing process:

1. **Wild vector**
2. **Gene of interest**
3. **Host cell** → **Expression vector** → **Expression system (1 clone)**
4. **Master Cell Bank**
5. **Working Cell Bank**
6. **Culture / Fermentation**
7. **Purification**
8. **DRUG SUBSTANCE**
9. **Sterile filtration / Aseptic filling**
10. DRUG PRODUCT

- **Genetic development**
  - Q5A
  - Q5B
  - Q5D
  - Q5E

- **Cell banks**
  - Q7A
  - Q9
  - Q10

- **Production**
  - Q5A
  - Q5C
  - Q5E
  - Q6B
  - Q11

- **Sterilisation Aseptic filling**
  - Q5E
  - Q6B
  - Q8
  - Q8R