Comparability: Regulatory Perspective

Louise Bisset PhD

Pharmaceutical Assessor – Biological Medicinal Products (Drug Product Licensing)

PSCP workshop
Outline

• Introduction to the MHRA and Medicines Licensing
• Regulatory context for PSC (ATMP)
• Introduction to the assessment process and ‘Module 3’ (Quality)
• Guidelines and written standards
• Manufacture and Comparability: concepts, stages and strategies
• Conclusions
Executive agency

• Executive agency of the Department of Health

Size

• 1225 staff

Location

• Head office at 151 Buckingham Palace Road, London
• NIBSC based at South Mimms, Hertfordshire
• A regional office at York
• British Pharmacopoeia and MHRA laboratories based at LGC in Teddington
Medicines and Healthcare products Regulatory Agency (MHRA)

- Regulates medicines and medical devices, ensures that they work, and are acceptably safe; focuses on the core activities of product licensing, inspection and enforcement, and pharmacovigilance
Key stages for a medicinal product

**Discovery Research**
- Basic research to understand disease

**Pre-clinical Research**
- Synthesis
- Biological testing and pharmacological screening

**Clinical Trials**
- Phase I
- Phase II
- Phase III

**Marketing Authorisation**

**Monitoring**
- Phase IV

**Licensing**

**Inspection, Enforcement & Standards**

**Pharmacovigilance**
Licensing – Authorisation and Advice

- Assess applications for marketing authorisations (Product licences)
- Assess non-safety variations (changes to existing licences)
- Assess and grant clinical trial authorisations
- Key Involvement in the EU medicines framework (EMA)
- Provide scientific and regulatory advice (National and EU)
- EU and National guidelines/legislation
Advanced Therapy Medicinal Products (ATMP)

- PSC-based medicinal product is classed as an Advanced Therapy Medicinal Product.

- ATMP’s are ‘regulated’ at a European level: i.e. the main Medicinal Product legislation is issued by the European Commission which is applicable to all EU/EEA Member-States.

- Main ‘overarching’ legislation for ATMPs:
  - Directive 2001/83/EC (main medicinal product legislation) and Part IV of Annex I.
  - Regulation (EC) No 1394/2007 (‘The ATMP Regulation’).

- Four ‘types’ of ATMP: somatic cell therapy medicinal product; gene therapy medicinal product, tissue engineered product and combination product (includes device)
The Assessment process and ‘Module 3’ (Quality)

• Drug product manufacturer submits ‘dossier’ for ‘Approval’ (assessment).

• Assessment/Approval: current regulations/guidelines/best practice.

• Overall positive benefit/risk balance = Product Approved (MAA).

• Dossier: Quality, Non-clinical and Clinical ‘modules’ assessed by specialist assessors (Pharmacists/PhD’s/MD’s with academic/industrial experience).

• ‘Module 3’ is the EU equivalent of the American term ‘CMC’.
Marketing Authorisation: ‘The Dossier’

Volume 2B - Presentation and content of the dossier
Notice to Applicants, Volume 2B (2 MB)
incorporating the Common Technical Document (CTD) (May 2008)

Manufacturing process described in Module 3
Module 3: ‘Quality’

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Comparability
Quality Guidelines and Standards

Main sources:
- ICH
- European and National Compendia: European Pharmacopoeia (Ph.Eur.)
- EMA (CHMP)
- WHO Guidelines

ICH – International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for human Use (EU/USA/JP)
- Quality, Safety, Efficacy and Multidisplinary guidelines
- Q5A-Q5E Quality of Biotechnology Products

European Pharmacopoeia (Ph.Eur. Or E.P.) ‘provides common quality standards to control the quality of medicines and of substances used in the manufacture of medicines (human and veterinary use)’
- Legally binding in European member states.
- E.g. Individual monographs for products, analytical methods, general monographs applying to all parenteral products.

Also National Pharmacopoeia standards e.g. BP and USP
Comparability: Key Principles

- Main regulatory requirement: ICH Guideline Q5E
  - Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process

- Changes always occur in the manufacturing process of a DP pre- or post MAA (or Clinical Trial).

- A biological medicinal product cannot be fully characterised (compared to small molecule) = the paradigm ‘the product is the process’

- Show ‘highly similar’ (comparable) product produced after changes are made to the manufacturing process following pivotal clinical trials (also during product development – setting specifications)
Comparability: Key Principles cont’d

• If cannot show at Quality level (i.e. manufacture and final product batch release data/characterisation/stability) then further NC/C studies may be required.

• Regulatory advice: Avoid substantial changes to process before pivotal clinical trial (not always feasible!)

• Comparability highly dependent on a fully characterised product (know your product!)
Path to Comparability

• Changed planned to a manufacturing process

• Develop Comparability strategy/testing plan (Quality)

• Testing

• Analysis of results

• Highlight differences in pre-and post change parameters. Effect on efficacy or safety? Further Non-clinical or clinical studies?

• Comparability report and update M3 manufacturing process development
Examples of manufacturing process changes

• Change to a raw/starting material supplier

• Introduction of new manufacturing process site

• Removal of a key raw material (e.g. FBS, antibiotic)

• Changes to seed stocks (MCB/WCB or VSB)

• Changes to equipment/procedures (e.g. clarification/chromatography)

• Introduction of new unit operations (e.g. purification/viral clearance steps)

• Manufacturing Scale-up/out : 2d to 3d culture

• DP formulation (excipient)
Comparability strategy/testing plan

• Dependent on:
  ➢ nature of the change
  ➢ Step in the manufacturing process
  ➢ Pre- or post- licensing approval or pivotal clinical trial

• Risk-based approach: testing based on effect of change on CQA (justify reduced testing)

• Establish comparability acceptance criteria:
  ➢ Current specification
  ➢ Historical batch data (wider acceptance criteria)
  ➢ Statistical analysis

• Consider if testing beyond current tests is required (extended characterisation)

• Discuss Approach with CA – EMA/CHMP procedure ‘post approval change management protocol’
Testing and Analysis

• Test at level of IPC/Release data/ sterility and characterisation

• For substantial change(s) side-by-side manufacture using Process A and B.

• Side-by-side characterisation testing using representative material from old and new process.

• Compare data

• Comparability at the level of quality where all acceptance criteria are met.
Examples of Non-comparability for Quality

- Different glycosylation pattern
- Physico-chemical: appearance, aggregates, pH, osmolarity
- Different phenotypic or genotypic profile
- New product or process-related impurity
- Existing product or process-related impurity outside specifications limits
- Multiple vs single parameter differences
- Improvements in purity
Approaches to non-comparability for Quality

- Original specifications were not appropriate (based on limited data)
- Impurity removed during manufacture
- Risk assessment for potential impurity (worst-case administration per dose)
- Evidence from literature: no safety concern
- Where analytic difference detected with unpredictable (unknown) effects on efficacy and safety further non-clinical or clinical studies. (establish new proven specs.)
- Manufacturer/developer justifies that further safety and/or efficacy studies are not required.
Further non-clinical and clinical bridging studies

- Animal toxicity studies
- Animal efficacy models
- Bio-equivalence, PD/PK
- Immunogenicity testing
- Human safety and efficacy
- Pharmacovigilance monitoring

Case-by-case, indication and posology dependent...
Conclusions: Keys to regulatory success

- Provide a comparability report (M3: DS: manufacturing process development)

- In manufacturing process development section highlight all changes (with reasons) with considered impact on parameter/CQA (consistent approach)

- Highlight where there are differences at the level of quality.

- ‘Justify’ (explain) why further NC/C studies not required:
  - Initial specifications were not representative –
  - No impact on efficacy/safety expected (minor differences) –

- In the majority of cases only Quality data is required.
More Information

**MHRA:**


Link to regulatory queries on regenerative medicine (‘one-stop shop’) – single point of contact for all regulators (HTA, HFEA,HRA,MHRA)

Regulatory/Scientific advice

**EMA:**

ATMP’s website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&mid=WC0b01ac05800241e0

Thank you for listening
Any questions?

Louise.Bisset@mhra.gsi.gov.uk

www.mhra.gov.uk
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