Product Comparability: The Challenges for ATMPs

DIA/MHRA Workshop on Advanced Therapy Medicinal Products

PAREXEL CONSULTING

COMPARABILITY VS CONSISTENCY

Consistency:

Product quality from batch to batch

Comparability

Confirmation of comparable product quality characteristics pre- and post-manufacturing process changes

- scale up of process
- move from FBS+ to FBS- process
- addition of new manufacturing facility

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Comparability (1)

Two scenario's:

- Process changes made during product development
- Process changes made post-authorisation

In both cases you need to assess to what extent:

- the quality profile of the product is changed
- the safety and efficacy of the product has been impacted

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Comparability (2)

The comparability study should consider:

- The suitability of the analytical methods to characterise the product
- Safety and efficacy criteria
  - i.e. product release specifications that have been qualified in NC and C studies
- What is the hypothesis is being made:
  - The change does not impact on the quality profile of the product
  - The change will impact on the quality profile of the product

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Hypothesis 1: The change does not impact on the quality profile of the product

Demonstrate IPC and/or release data are not modified when comparing pre- and post-change process

- Analytical methods need to be sensitive enough to detect slight differences in the products quality profile

With the current state of art analytical methodologies is this an achievable goal for ATMPs?

…….. depends on the ATMP in question…. ? ……

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ARE THE ANALYTICAL ASSAYS SUITABLE FOR COMPARABILITY?

Gene Therapy Products

- Vectored products
  - Sequence
  - Transgene expression / biological activity
  - Content (infectivity assays/colony forming unit/particle:infectivity ratio)
  - Protein characterisation (capsid vector)
  - Additional safety issues i.e. confirmation of tissue tropism if this is a feature of the vector is question

On the whole, assuming the assays are suitably validated … yes ….

Physicochemical/biological comparability is achievable.

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ARE THE ANALYTICAL ASSAYS SUITABLE FOR COMPARABILITY?

Cell Therapy Products

- Typical analytical methodologies used
  - Morphology
  - Growth characteristics
  - Cell surface markers
  - mRNA / cytokine expression profiles
  - Potency – functional assays v's surrogate assays
- Added complications for autologous products:
  - Heterogeneity of starting materials
  - If GM cell – heterogeneity of insertion site
    - can you say with certainty if one insertion site is a greater safety risk compared to another?

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Cell Therapy Example: Adipose Derived Stem Cell

Assay	Pre-change acceptance criteria (n=25 batches)	Post change results (n=3)
Morphology	Fibroblast type morphology	Fibroblast type morphology
Identity MSC +ve markers	CD90 98.9 - 99.5% CD73 90.2 - 99.8% CD105 88-4 - 99.2%	CD90 98.9 - 99.4% CD73 95.1 - 99.5% CD105 78.2 - 92.2%
Impurities	CD45 1.1 - 2.9% CD34 10.3 - 27.1% CD14 0.1 - 0.3%	CD45 0.5 - 2.5% CD34 14.8 - 21.2% CD14 0.3 - 0.5%
Identity qRT-PCR for transcription factors	2.5-3.5 fold increase expression relative to mature adipocyte	3-4.5 fold increase
In-vitro Potency Immunosuppression surrogate assay	Rate of Kynurenine formation relative to reference	Rate of Kynurenine formation relative to reference

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Cell Therapy Example: Adipose Derived Stem Cell

Extended Characterisation:

- Functional activity assay
  - inhibition of lymphocyte proliferation in a 2-way MLR
- Demonstration of mulipotency:
  - Differentiation to adipogenic, osteogenic/chondrogenic lineages
- TEM
  - Ultrastructural organisation

Is this, along with known non-clinical and clinical characteristics, sufficient to demonstrate comparability?

Possibly – if you can relate quality attributes, safety and efficacy back to the overall non-clinical and clinical experience

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Hypothesis 2: The change impacts on the quality profile of the product

Additional evidence from non-clinical or clinical studies may be required

The extent and nature of these studies ….

should be covered by other speakers throughout the day!

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Conclusions (1)

- Comparability for GTMPs is likely to achievable on the basis of physico-chemical and biological activity analytical methods
- Cell therapy products are more problematic
  - Assays not always sufficiently sensitive to demonstrate small changes in quality profile do not impact on safety and efficacy
  - Further complicated by heterogeneity in starting materials, which can result in wide acceptance limits for release
  - Potency assays may not be functional, so the relationship between potency and clinical efficacy is more difficult to establish

So maybe comparability is not achievable for CTMPs ….. BUT

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Conclusions (2)

If the manufacturing change is post-authorisation

- the assays used for characterisation and product control have been accepted by the agency
- the relationship between quality and safety/efficacy has, in theory, been established
- So assuming the data is 'similar' pre and post-change, demonstration of comparability should be achievable.

Maybe the best advice is to try to tackle the issue of comparably post-approval, rather than through-out development?

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