

Process Specifications in Biomanufacturing: Case Studies

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Scope of the Presentation

- Biopharmaceuticals – the central paradigm
- Changes to an original process or product
 - Principles for assessing changes
 - ICH Q5E, ICH Q6B guidelines
 - Case studies from the CMC perspective
 - Regulatory issues associated with comparability

Recognised Paradigm

for biotechnological/biological products

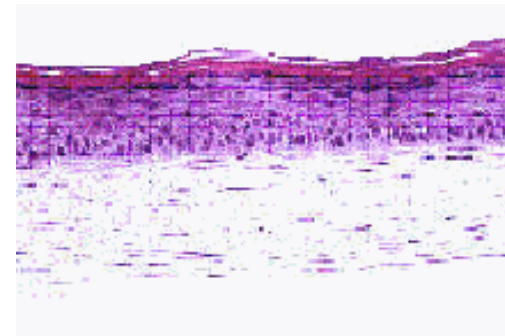
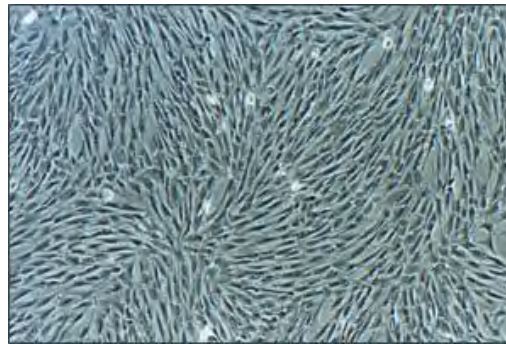
Product



Process

Degree of Product Complexity

- Impact of process changes and degree of complexity of comparability exercises increase as follows:
 - *Well-characterised product of recombinant DNA technology*
 - *Gene therapy product*
 - *Less well-characterised biologic (e.g. conventional vaccine)*
 - *Somatic cell therapy product*
 - *Tissue engineered product*



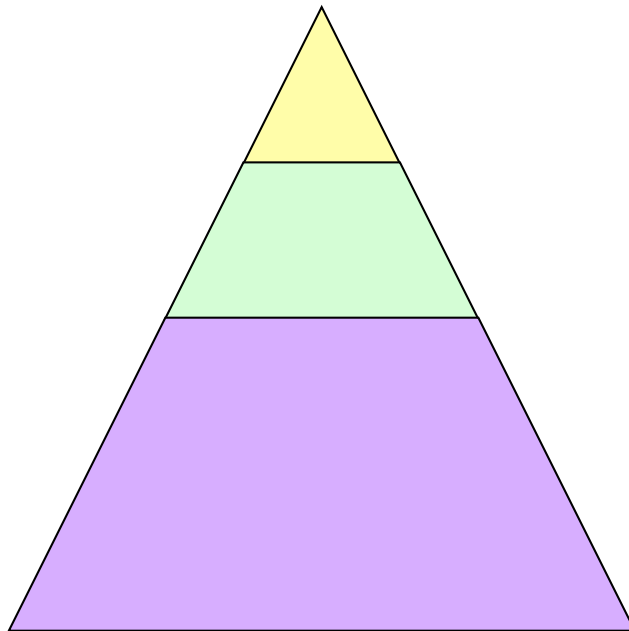
Key Factors Relating to Comparability

- Comparability of material used in pivotal CMC work (e.g. stability) and in clinical trials
 - Quality attributes may be relevant to labelling - have to relate to product intended for the market
- Comparability between material used in nonclinical and clinical studies
 - Nonclinical studies used for risk assessment - results have to be relevant for marketed product
- Comparability between material used in clinical trials with that intended for marketing

Pre-approval and Post-approval Changes

- Principles:
 - Data required in support of a process change are basically the same, pre- or post-approval
 - Sufficient analytical resources to demonstrate and document comparability are required
 - Changes should either be made very early, before embarking on pivotal studies, or else be held back until a much later stage, preferably post-approval
 - Changes in the middle of pivotal clinical studies should be **AVOIDED**

Volume of data in a typical biotech product dossier



← **Drug product data**

← **Drug substance data**

← **In-process data**

Guidelines of Relevance to Comparability

- ICH Q5E
 - Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process
 - Primarily designed for post-approval process changes, but equally useful for process changes during development
- ICH Q6B
 - Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products



Two essential components contribute to product quality, consistency and comparability

- Drug substance/product specifications
 - Supplemented with extended characterisation tests for “trending” and for comparability exercises after process changes during development
- In-process specifications
 - Additional in-process testing provides for better understanding of the process on an ongoing basis and for comparability exercises

*It follows that **availability of appropriate test methods** is essential for the assessment of the impact of a process change*

Experience shows that the single biggest pitfall...

associated with process changes during biotech product development is ...
... an **inability** to assess the impact of the change owing to **lack of, or deficient, analytical methods**



Is the following statement meaningful?

“Product conformed to the same specifications after the process change”

Answer: Not really !!!

Specifications are of direct relevance to a particular process, and do not necessarily apply after a process change

Case Study 1

An example relating to data submitted to justify drug substance release specifications:

Data to justify a specification of ≤ 40 ppm for routine control of an impurity in a biotech product from two different processes, A and B

Process	Batch data [ppm]									Mean	SD
A	20	28	26	11	10	29	16	12	29	20	8
B	31	36	33	38	33					34	3

Example:

Process-related impurities derived from the expression system, such as **host DNA or host cell proteins (HCP)**

Assays for HCP may be challenging to develop, but are viewed as very important from the regulatory perspective

Note: DNA and HCP are useful marker impurities, alongside product-related substances and product-related impurities

Case Study 2

Assays/procedures used to determine residual HCP in drug substance

Immunoassay results for mammalian HCP in drug substance, before and after a process change involving modification of the culture medium

Assay Method	Process A	Process B
"Generic" host cell protein assay	~ 10 ppm	~ 20 ppm
Antibodies generated using antigen from Process A	~ 100 ppm	~ 40 ppm
Antibodies generated using antigen from Process B	~ 20 ppm	~ 80 ppm

In-process Controls and Action Limits

- There is more to understanding a biological production process than just formal in-process controls
 - Gathering other “less critical” information can provide useful insights into general characteristics of the process
 - Action limits are mentioned 5 times in ICH Q6B (hint!)

Action limit =

An internal (in-house) value used to assess the consistency of the process at less critical steps

Example:

Changes in process conditions, such as the need for a holding step, can affect product quality

Consider a downstream step, where the column eluate was sometimes not immediately processed, but ***held overnight***

Aggregates were measured to show the drug substance specification of \leq **2.5%** was still met in a series of batches

Case Study 3

Effect of holding times on the generation of product-related impurities

Aggregate levels in 7 sequential batches of bulk drug substance;
proposed specification $\leq 2.5\%$

Batch #1 ^{a)}	Batch #2 ^{b)}	Batch #3 ^{b)}	Batch #4	Batch #5 ^{b)}	Batch #6 ^{a)}	Batch #7 ^{a)}	Mean \pm SD
1.4%	0.6%	0.5%	0.6%	0.6%	1.6%	1.5%	1.0 \pm 0.5

- a) Column eluate held overnight before further processing
- b) Batches being used in clinical trials

Case Study 3: Analysis

- Data appeared to be in 2 groups, but well within specification
 - 0.5 - 0.6% (no holding of column eluate)
 - 1.4 - 1.6% (with overnight hold)
- Degree of the impact not immediately obvious at the level of purified bulk drug substance, since the specification was met
- **HOWEVER**, a significant difference was seen based on in-process testing (next slide)
- **AND**, another product-related species was detected in eluates that were held overnight



Case Study 3: In-process Data

Analysis of column eluate in-process samples

	Batch #4	Batch #5 ^{b)}	Batch #6 ^{a)}	Batch #7 ^{a)}
Aggregates in purified bulk	0.6%	0.6%	1.6%	1.5%
Aggregates in column eluate	~4%	~ 2%	~ 12%	~14%
Species X in column eluate	Not detected	Not detected	~2%	~2%

a) Column eluate held overnight before further processing

b) Batches being used in clinical trials

Case Study 3: Lessons Learned

- In-process testing of the column eluate was crucial
 - These analyses provided greater insight and showed that holding of the column eluate might not be appropriate
 - Even without the holding step, an **action limit** was needed for the column eluate, to ensure the absence of unexpected degradation
- A previously unknown route of degradation was discovered through this in-process testing
 - Implications for stability studies?

Remember:

- Action limits help mitigate risk during manufacturing, but are only meaningful if appropriate actions are associated with them
- Appropriate actions are **not** ...
 - "Report value"
 - "Report to management"
- Examples of appropriate actions **could be** ...
 - "Conduct additional tests X, Y and Z to determine impact"
 - "Monitor parameter again at the next stage"



Case Study 4

Cell viability at the start of mammalian cell fermentation

Viability specification provisionally set at 90%

Run #1	Run #2	Run #3	Run #4
99%	98%	95%	99%

Pre-sterile-filtered medium for production run #3 was held unusually long owing to production fermenter equipment failure

Viability was lower than in other production runs but within specifications, and therefore, was considered to be acceptable

Case Study 4: Analysis and Consequences

- Pre-sterile-filtered medium was subsequently found to be contaminated with Gram-positive bacteria
 - Batch #3 had to be rejected
 - Cell viability was very sensitive to this problem
- The lower limit on viability (90%) was set too low to automatically trigger an investigation
- More microbiological control was required
- Pre-filter holding time needed to be minimised
- New **acceptance criterion** for viability was set at **> 95%**
- **Action limit** introduced for viability at **< 98%**

Consequences of the Paradigm for Biopharmaceuticals

- Since a biopharmaceutical product is defined by its process
 - In-process parameters (upstream and downstream) are as important as release parameters for the definition of the product, its quality and consistency
 - For extensive process changes, re-validation of part or all of the manufacturing process may be required as part of a comparability exercise
- What might be the consequences of less robust CMC comparability data?



Comparability and Refusals/Withdrawals of Marketing Authorisation Dossiers in the EU

- EU committee reached 66 positive opinions in 2008
- But there were 7 negative opinions and 23 withdrawals
 - Non-success rate > 30%
- Most unsuccessful applications involve some serious, unresolved CMC issues including **comparability problems**, as well as clinical deficiencies



Withdrawal of Mycograb Marketing Authorisation Application in the EU

Mycograb (*efungumab*)

- Background information
 - Recombinant *E. coli* human monoclonal antibody to fungal hsp90, for treatment of invasive fungal infections
- **Quality issue** with testing for aggregates, proposed methodology not considered adequate for control of the manufacturing process and for demonstration of stability
 - Deficient methods!
 - Comparability of material used in clinical trials, to that intended for marketing, was therefore uncertain

Concluding Comments

- In-process controls (with acceptance criteria) can be supplemented with additional parameters (action limits) to gain insight into process attributes
 - These will contribute significantly towards the comparability exercises required for process changes
- The paradigm linking biopharmaceutical products to their production processes is reinforced by cases of problems arising after process changes
 - Subtle differences in product quality cannot always be detected at the level of the drug substance
- Therefore, comparability exercises will usually require extensive characterisation and in-process testing
- Such analytical strength supports a robust manufacturing scheme and mitigates the risk of production failure as well as ensuring that products meet their expected attributes of quality and safety

Thank you!