ACADEMIC TO COMMERCIAL TRANSLATION

(Ex-) EU Regulators Perspective

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Introduction

- Early stage development in academia
- Tech transfer during development
- Transfer to SME
- Transfer to Large Pharma

Please Note

- I will make sweeping generalisations in the interest of time and to try and simplify endlessly diverse developers, products and situations.
- Please don't take offense
- Feel free to challenge them

Basic Research to Early Development

- Research shows that something can work = proof of concept (PoC)
- Development is an iterative process that attempts to take a research PoC and show it can be repeated time and time again with the same outcome
  - Uncertainty remains with cell-based products as to how much variability is acceptable.
  - Objective to demonstrate risk/benefit is positive

Basic Research to Early Development

- Commercialisation not only needs to consider development of the PoC but also that the idea/product can be commercially viable (i.e. you can make money from it)
  - Demonstrate cost effectiveness (will vary with different markets, indications etc)

Roles played by Academia, SME and Large Bio/Pharma

Early Stage Development
Preclinical PoC to FIM (clinical PoC)

Consulting on Advanced Biologicals

Academia and SME

- development limited to that needed to demonstrate PoC in clinic
  - tendency for '***Artisan manufacturing processes***'
- Understanding of development highly variable
- Understanding of commercialisation highly variable
- Most academic clinical trials restricted to FIM studies
- Regulators focus for FIM is safety (of the study subjects) and demonstration of some expectation for benefit (since not healthy volunteer trials)
  - Regulation is (relatively speaking) light touch

Roles played by Academia, SME and Large Bio/Pharma

Late Stage Development
Phase 2 to Pivotal Studies

Academia

- Generally out of the picture

Small and Medium Size Enterprises (SME)

- Under pressure to deliver quickly on tight/limited budget
- Tendency to cut corners
  - Process development continuous with clinical development
  - Insufficient resources devoted to manufacturing and quality
  - Comparability weak due to weak characterisation
  - Entering pivotal before ready
- Regulatory review of process changes etc during clinical development necessarily high-level
  - Leading to issues at market authorisation (long review time, many follow-up measures)

Large Bio/Pharma

- Generally, well-funded
- Variable strategies
  - Some taking methodical step-wise development
  - Some more aggressive (akin to biotech)
- Development experience – considerable, but obviously not with ATMP's
- Commercialisation experience considerable but again ATMP's have novel issues
- Whether they can be more successful than those to date – TBD.
  - Approach to development and commercialisation not necessarily that different from SME

Are there differences between SME's and Big Bio/Pharma?

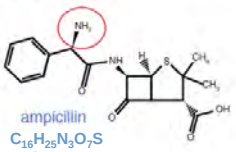
- Yes and no
- Developers with experience (products on the market) generally have a better understanding of what is needed for comparability
- Well-funded, experienced developers likely to understand risks of weak characterisation and comparability and undertake more thorough evaluations
  - But highly variable since what is needed is not yet well understood.

Biologicals are Complex

Grampp and Ramanan 2013 DOI 10.1007/s40259-013-0018-5

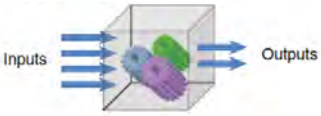
b Chemically synthesized drug
Defined process-structure-function

- Complete knowledge of chemistry and physics



ampicillin
$C_{16}H_{25}N_3O_7S$
52 atoms

- Knowledge and measurement of all relevant inputs and outputs



- One, defined active ingredient linked unambiguously via its identity to the safety and efficacy (S&E) profile

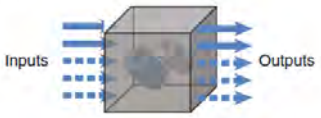
Chemical Process → Defined Structure → Function (Defined S&E)

c Biologic
Correlated process-structure-function

- Partial knowledge of biology and chemistry

Erythropoietin
>4000 atoms

- Impossible to identify or measure all inputs and outputs



- Heterogeneous, partially defined active ingredient correlated to the safety and efficacy profile – contingent on process consistency

Biological Process → Complex Structure → Function

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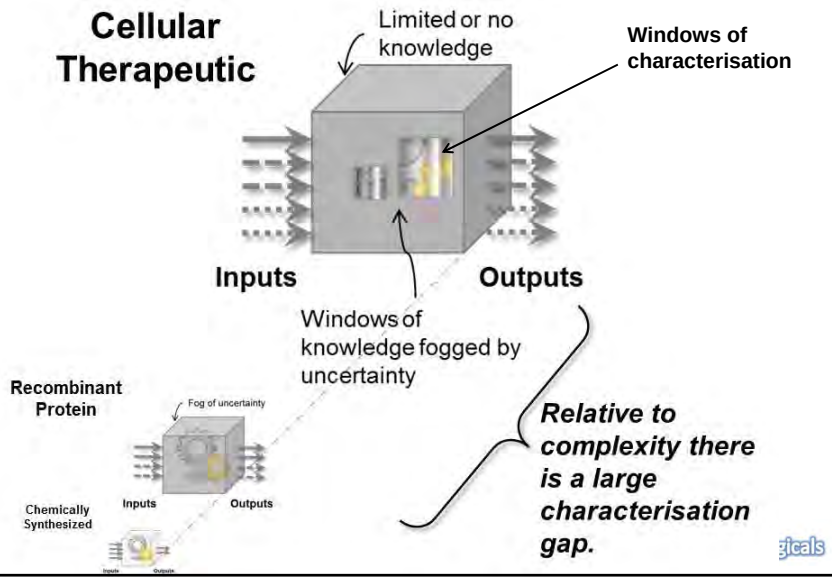
Cell Therapy Products even more so



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Comparability is more difficult for cell-based products

- The structure of a cell (cellular active substance) cannot be determined
  - Only small parts of the structure can be determined
  - In figure: *windows of characterisation*
- Furthermore, cells are heterogeneous populations
  - Have to compare patterns of gene/protein expression (similar to glycosylation patterns for therapeutic glycoproteins)
  - In figure: *fogged by uncertainty*

These bring considerable uncertainty when assessing comparability

Identifying critical quality attributes (CQA) is uncertain

- Full knowledge of the structure and function of a cell will not be known
- Mechanism/s of action (MoA) will be uncertain
  - MoA is also dependent on the disease to be treated
  - Disease mechanism/s will not be fully understood
- Identified/claimed CQA are therefore (at best) educated/informed guesses.
  - They may not be CQA
  - You may never be certain

These bring considerable uncertainty when assessing comparability

Likely most important methods for comparability

Given the structure cannot be fully determined:

- Methods that measure cell functions
  - Related to (assumed) MoA
  - One or more of which will be considered ‘potency’ assays
  - Can be in vitro
  - Can be in vivo (many limitations, but can be reassuring)
- Don’t forget stability (reconfirmation) is an important part of comparability

The Need for Change

There are many reasons why changes are required:

- During development:
  - Transfer of research process to GMP
  - Materials changes
  - Process improvements
  - Change in presentation (e.g. fresh to frozen)
- Once on the market:
  - Materials changes
  - Process improvements
  - To comply with changing regulatory requirements
  - Scale up/out
  - Manufacturing site changes

Common Mistakes with Comparability

Meeting Current Specifications is NOT Sufficient!

- Characterisation of the product and process identifies test methods that are useful as IPC/release specifications.
  - Some of these will hopefully be CQA
- Manufacturing experience (and other factors) are used to set specifications for a stable qualified process.
- Changing that process means the validity of these specifications needs to be reconfirmed.
  - Include ‘extended characterisation’.
    - Additional methods
    - Additional samples

Key Methods for Comparability

- Since we can't define the structure of what is being manufactured we need to focus on demonstrating the biological function is comparable.
- Those methods that evaluate relevant biological functions are therefore key
  - Bioassays
  - Ex vivo organ/tissue culture
  - In vivo models (e.g. pharmacology models)

Conclusions

- Commercialisation is different to development
- Getting a clinical trial approved in no way means your development is on track at any stage.
- Comparability is difficult – much uncertainty as to what is needed even late in development (understanding MoA, cQA etc).