Regulatory requirements for early stage clinical trials with cell-based medicinal products

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Opening Remarks

- Cell-based medicinal products are in themselves diverse, so it's hard to generalise (case-by-case).
- Clinical trial authorisation remains the remit of national competent authorities (NCA), so second-guessing 27 NCA's is difficult.
- As yet no centralised guideline for investigational ATMPs*
- Recommend discussing with NCA prior to submission.
- It's up to you to provide a 'sound' scientific rationale.
  - Its your product you understand it better than anyone.

*DRAFT Guideline on quality of biotech IMPs
http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500075559.pdf

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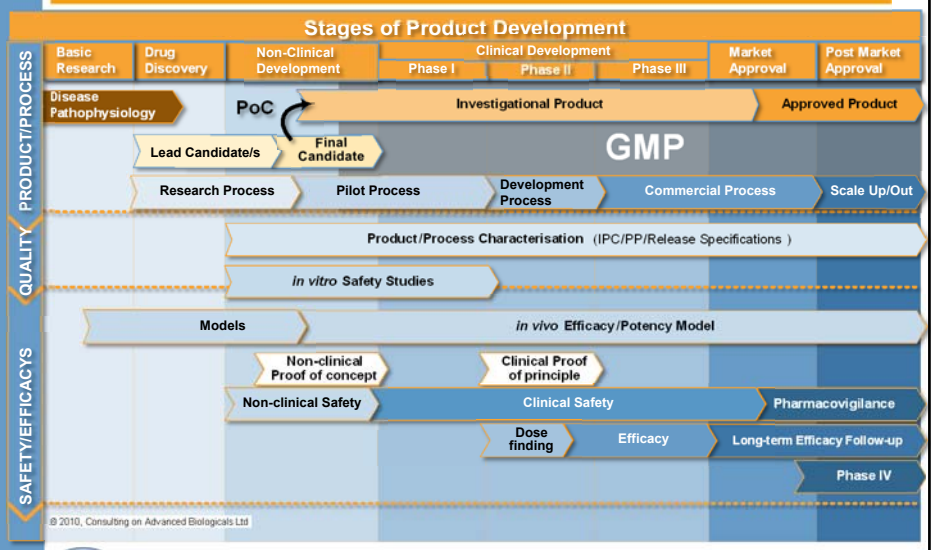
Product Development



CAB

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QUALITY

CAB

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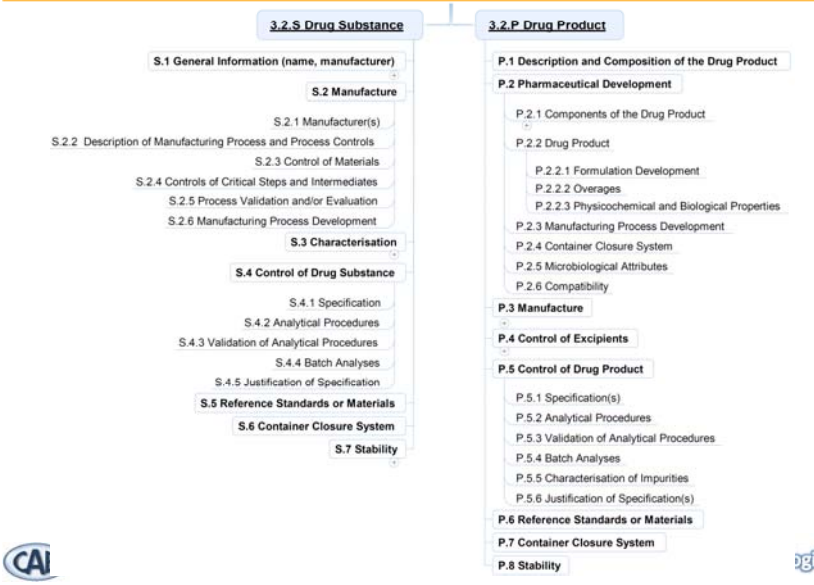
Common Technical Document (CTD)



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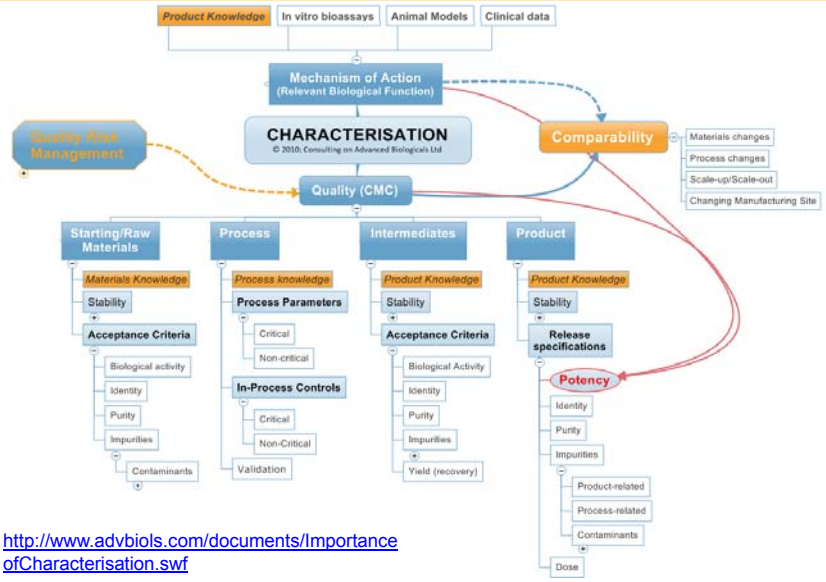
M3

The Importance of Characterisation



http://www.advbiols.com/documents/ImportanceofCharacterisation.swf

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Starting and Raw Materials

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European Tissues and Cells Directive

- Donated Tissues and Cells used to manufacture medicinal products are **starting materials.**
- Starting materials need to be of a suitable quality.
- EUTCD requirements for non-medicinal applications takes into account the intended use.

But

- EUTCD requirements for medicinal product manufacture does not take into account the intended use but only applies to donation procurement and testing.

Directive 2004/23/EC

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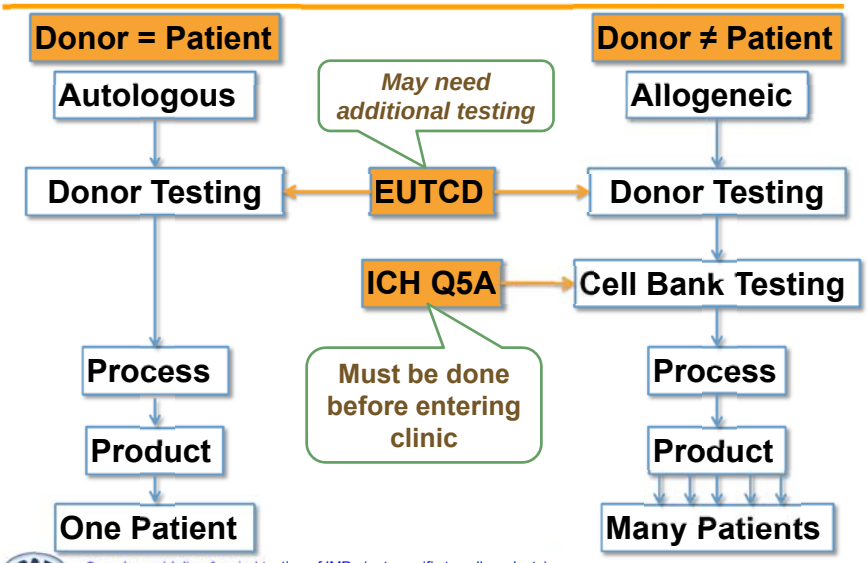
Starting Material Testing



See also guideline for viral testing of IMPs (not specific to cell products)
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003798.pdf

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s.2.3

Selecting Biological Starting and Raw Materials

- Materials of biological origin pose significant concerns for safety and performance.
- Biological materials may harbour bacteria and viruses
- Biological function can be (highly) variable between both batches and suppliers, and is usually highly sensitive to storage and handling conditions
- Consequently you are more likely to need to do in-house testing to supplement the suppliers CoA or confirm suitability for your use, e.g. growth characteristics for serum, biological activity

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s.2.3

My materials are all GMP so that's OK; Right?

- **NO!**
- GMP tells you the facilities are being run in a particular way, but it does not tell you whether the manufacturing process produces a material of a suitable quality
- For biological materials you need to know:
  - Source/provenance
  - What manufacturing steps are included to control, reduce and/or eliminate bacteria and adventitious agents.
  - Whether their are TSE risks and whether they have been managed adequately (e.g. EDQM)
  - Purity/impurities – how much of what.

s.2.3

Non-biological raw materials

- Where there is a pharmacopoeial monograph you should comply
- USP, JP and EU national pharmacopoeias are acceptable for an IMPD.
  - But worth looking to see if there are differences and consider if these matter
  - Note: USP allows water for injections to be made by reverse osmosis – this isn't acceptable in the EU.

Manufacturing

s.2.2

Manufacturing Process

- GMP even for first-in-man.
- Key toxicity/PoC testing should ideally be with GMP process product (to ensure its representative of what will be used in man)
- Remember to perform comparability between research and GMP process (and following later changes) to ensure the relevant biological function/s of the product are comparable.
- Process qualification data (consistency runs)
- Media fills – sterile filling qualification/validation with final container

s.2.2

Release testing

- Analytical method qualification – fit for purpose
- Specifications – IPC, intermediates, product release
  - Need to make sense, especially if little data (justification)
- As a minimum, quantity, identity, purity and biological activity* (*not just viability*)
  - **Potency* – need to show you are at least thinking about it and have an/some initial method/s
    - FIO usually OK early on
    - OK if it changes later
- Sterility, endotoxin
  - Results later – discuss in clinical protocol

s.2.2

Stability

- Need stability data on product
- Real-time/real conditions usual rule for biotech, may be acceptable to extrapolate a little (≤2x actual), but only if have data to support it (e.g from earlier process)
  - Stability of cryopreserved cells unlikely to be questioned (but does need to be done), but must show freeze/thaw not detrimental to product.
- At least one batch from current process
- Can amend CTA later as new data available if required.

NON-CLINICAL

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Objectives of non-clinical testing #1

- safety (toxicity, including immunogenicity);
- tolerance (local, systemic);
- biodistribution;
- persistence (duration of exposure);
- in vivo proliferation and differentiation;
- tumorigenicity;
- reproducibility;
- biological activity (potency) in vivo and/or in vitro;

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Objectives of non-clinical testing #2

- dose definition including rationale for starting dose in man
- route of administration and schedule;
- study duration to monitor for toxicity.
- Key studies should be GLP compliant where possible; lack of compliance should be well documented and explained.

Note: Genotoxicity studies are not conducted for CBMP unless there is a reason for concern, e.g. in relation to an excipient.

Non-clinical Challenges #1

- Animals are xenogeneic to humans
  - strong immunogenicity
    - Immunocompromised animals, e.g. nude mice
      - Still see clearance limiting study duration
- Homologous models
  - Can be difficult to develop homologous product (differences in phenotype, signalling pathways etc)
- Genetically modified animals
  - KO, Transgenic, huamnised

Non-clinical Challenges #2

- Animals are not humans but other mammals are >90 similar so you should learn something
- Easy to get argue against value of model at molecular level, but may still be valid for other general toxocity
  - Reaction site, systemic effects
  - Provides some indication of what you might expect
- In vitro modelling may also be of value
  - Organ culture
  - Tissue culture
  - Bioassays

Bottom line

- You need some data to support the scientific rationale of the therapy
- You need evidence to support the safety of the proposed initial dose
- You need to identify all possible toxicity so that the clinical protocol can anticipate these
  - What should you do if the patient exhibits acute toxicity (clinical plan)

CONCLUSIONS

- Clinical trials primarily consider the safety of the patients
- The CTA should therefore put a strong focus on mitigating risk
- The CTA should present a scientifically sound rationale supported by data generated with the investigational medicinal product
- Recommendation: Seek advice from the NCA to ensure you are addressing all their concerns prior to submission of the CTA.

Further Reading

http://rsif.royalsocietypublishing.org/content/early/2010/09/14/rsif.2010.0442.focus

Note: Free Access

Further Reading

Chapter 19:
A CATalyst for Change: Regulating Regenerative Medicines in Europe.
C. Bravery

http://www.crcpress.com/product/isbn/9781439836064;jsessionid=mhKy2DXbsRPGj8OFCaw42A**

Further Reading

- Web-tools covering EU, US and ICH guidelines and PhEur and USP chapters relevant to cell-based products
  - www.advbiols.com/resources (free)
- PAS-83 (BSi, 2006) Guidance on codes of practice, standardised methods and regulations for cell-based therapeutics.
  - Currently being updated to include EU and US rules (2011)
  - http://www.bsigroup.com/sectorsandservices/Forms/PAS-83/Download-PAS-83/ (free)
- PAS 84 (BSi, 2008) Regenerative medicine. Glossary
  - Currently being updated (2011)
  - http://www.bsigroup.com/sectorsandservices/Forms/PAS-84/Download-PAS-84/ (free)
- PAS 93 (BSi, *2011*) Characterisation of cells and cell products.
  - http://www.bsigroup.com/sectorsandservices/Forms/PAS-93/Download-PAS-93/ (free)