

WP1: Regulation

VALUE

Regenerative Medicine Value Systems:
Navigating the Uncertainties

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Consulting on Advanced Biologicals

VALUE
Regenerative Medicine Value
Systems:
Navigating the Uncertainties

High Level Objectives #1

- 1) Understand the regulatory routes for selected product-types e.g. ATMPs (cell-based only), unmodified cells etc.
 - Focus EU and US
- 2) Create generic roadmaps and options for different RM product-types (e.g. autologous, allogeneic, combination products, non-medicines).
 - Route maps will be developed for case-led examples (e.g. CS1-4) that highlight the relative time-scales and cost implications to complete selected roadmaps.

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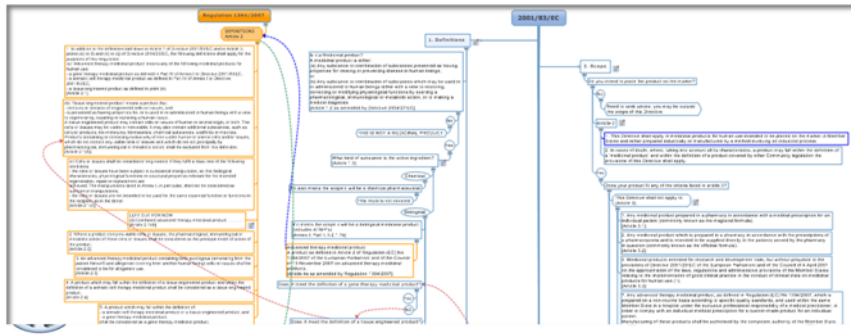
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High Level Objectives #2

- 3) Options to improve the regulatory environment for RMs, will be investigated to facilitate approval of complex RM products.
 - Point-of-care manufacturing
- 4) Other topics identified during project for further study:
 - Cell banking strategy
 - Impact of multiple manufacturing sites
 - Are biosimilar cell therapies possible?

Outcomes 1: Understanding the regulatory route/s

- 1) Understand the regulatory routes for selected product-types e.g. ATMPs (cell-based only), unmodified cells etc.
 - Methodology
 - Analysis of legal framework, guidelines and literature, discussions with experts and stakeholders
 - Mind-mapping EU legal structure

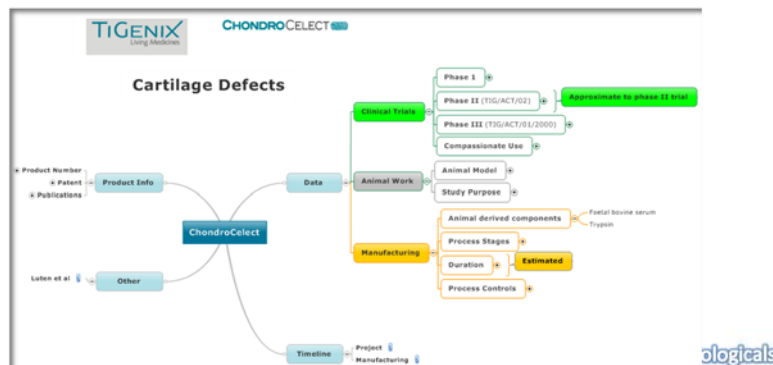


Outcomes 1: Understanding the regulatory route/s

- 1) Understand the regulatory routes for selected product-types e.g. ATMPs (cell-based only), unmodified cells etc.
 - **Output: High Level Analysis**
 - PAS 83:2012 Developing human cells for clinical applications in the EU and US.
 - *Cell therapy regulatory primer*
 - PAS 93:2011 Characterization of human cells for clinical applications
 - PAS 84:2012 Regenerative medicine and cell therapy glossary
 - **Output: Detailed Analysis**
 - EU: RSIJ article; Regulating interface science Healthcare products: myths and uncertainties.
 - Regulatory wisdom database (proprietary)
 - EU: *Regulatory classifier web-tool*

Outcomes 2: Regulatory road-maps

- 2) Create generic roadmaps and options for different RM product-types (e.g. autologous, allogeneic, combination products, non-medicines).
 - **Methodology**
 - Data from Case studies
 - Mind-mapping of development route to date



Outcomes 2: Regulatory road-maps

- 2) Create generic roadmaps and options for different RM product-types (e.g. autologous, allogeneic, combination products, non-medicines).
- Conclusions
 - Regulatory route is clear, with few options
 - Data requirements are obscure and can only be determined case-by-case
 - The differences between different products are so significant generic route maps are not possible.

Outcomes 3: Options to improve regulatory system

- 3) Options to improve the regulatory environment for RMs, will be investigated to facilitate approval of complex RM products.
- Methodology
 - As objective 1
 - Discussions with many stakeholders
 - Online discussion forums, meetings (e.g. Innogen) etc.
 - Results
 - Point-of-care manufacturing devices identified as good commercial solution for certain cell therapy products
 - not envisaged by the current regulatory framework
 - doesn't seem to fit the current regulatory framework.

Outcomes 3: Options to improve regulatory system

- 3) Options to improve the regulatory environment for RMs, will be investigated to facilitate approval of complex RM products.
- **Conclusions**
 - Current framework is flexible enough to cope with cellular therapeutics (or almost any medicinal substance)
 - Relies on the developer to determine the data requirements
 - However, certain approaches to manufacturing may not fit the framework very well (e.g. point-of-care devices).
 - Many stakeholders believe regulation could be simpler
 - No one can suggest how.
 - WP1 conclusion: cannot see any real options to alter process.

Outcomes 3: Options to improve regulatory system

- 3) Options to improve the regulatory environment for RMs, will be investigated to facilitate approval of complex RM products.
- **Why significant change isn't required:**
 - Current framework has few 'hard rules'.
 - Asks that you establish safety (S) and efficacy (E) and demonstrate you can consistently manufacture the product to an acceptable quality (Q).
 - Principles conveyed through guidelines
 - Data evaluated against principles – scientific peer review.
 - how you do this doesn't necessarily have to follow the traditional approach so long as you provide adequate evidence for Q/S/E.
 - there is much flexibility in the process.

Outcomes 4: Hot regulatory topics

- 4) Other topics identified during project for further study.
- Methodology
 - As objectives 1 and 2
 - Topics identified that have significant impact on value chain
 - Cell banking strategy
 - Impact of multiple manufacturing sites
 - Are biosimilar cell therapies possible?

Outcomes 4: Hot regulatory topics

- 4) Other topics identified during project for further study.
- Cell banking strategy
 - Allogeneic cell products superficially appear to follow biotech business model – large batches, off-the-shelf
 - Unlike biotech, cell banks in most cases don't last product life-cycle
 - Additional regulatory burden
 - Time and cost of qualifying new cell banks
 - Uncertainty as to how to establish comparability
 - Strategy chosen will impact profitability
 - Decisions need to be made early
 - May be stuck with decision even if situation changes
 - *Publication in preparation*

Outcomes 4: Hot regulatory topics

- 4) Other topics identified during project for further study.
- Impact of multiple manufacturing sites
 - Autologous products in particular can pose logistical challenges
 - Collect donor biopsy, manufacture, deliver product
 - Links to point-of-care manufacturing issue
 - Regulatory burden can be increased
 - Establishing and maintaining comparability between sites
 - Manufacturing process and QC
 - Process/QC changes leading to re-validation on all sites in addition to confirming all sites equivalent
 - *Publication in preparation*

Outcomes 4: Hot regulatory topics

- 4) Other topics identified during project for further study.
- Are biosimilar cell therapies possible?
 - IP for certain cell therapy products is a minefield, and patent protection may be limited.
 - Common assumption that 'data protection periods' provide protection
 - This assumes an abridged (generic, biosimilar, well established use) MAA is possible
 - Only biosimilar is theoretically possible (ATMP's are biological medicinal products)
 - There are multiple reasons why the biosimilar paradigm does NOT work for cell therapy products.
 - *Publication in preparation*

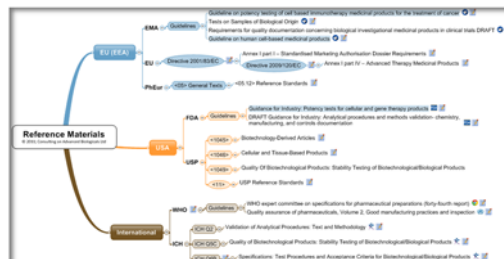
Other Work

- Analysis of industry from a regulatory perspective
 - Analysis of available EMA/NCA data
 - Analysis of regulatory trends and drivers
 - Comparison with biotech trends
- Regulatory teaching and Web-tools
 - Materials to help convey principles to clients
 - Web-tools for clients and others to use
 - Materials for talks/training courses

Web-tools for Cell Therapy

See <http://www.advbiols.com/Resources.php>

- Regulatory principles
 - Product development
 - Importance of Characterisation
 - Comparability
 - Importance of reference materials
 - Tech transfer
 - Regulatory classifier
 - Agency advice (NCA/EMA/FDA)
 - Cell banking strategy
- Regulatory Guidance
 - ICH guidelines
 - EU guidelines
 - US guidelines
 - Potency (EU/US/ICH)
 - Reference materials guidance (EU/US/ICH/WHO)



Conclusions

- Current frameworks in EU and US broadly similar and flexible
 - Few hard rules
 - Data requirements need to be established case-by-case
- If the basic requirements of quality, safety and efficacy are to be maintained, it is difficult to see how the process could be made simpler.
- Certain characteristics of cell therapy products mean they may carry a higher regulatory burden, with implications for profitability.
- Point-of-care manufacturing devices make sense for some autologous products, yet the current framework is not designed to accommodate them.
- Multiple manufacturing sites may increase regulatory burden and manufacturing complexity, with implications for profitability.
- Biosimilar cell therapy products are not possible, hence 'data protection periods' are irrelevant.