# WP1: Regulation

**VALUE**

Regenerative Medicine Value Systems:
Navigating the Uncertainties


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## 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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## 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?



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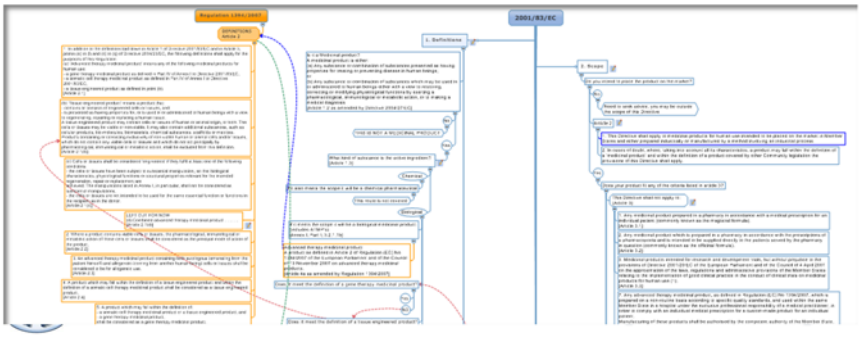
## Outcomes 1: Understanding the regulatory route/s

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



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# 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*



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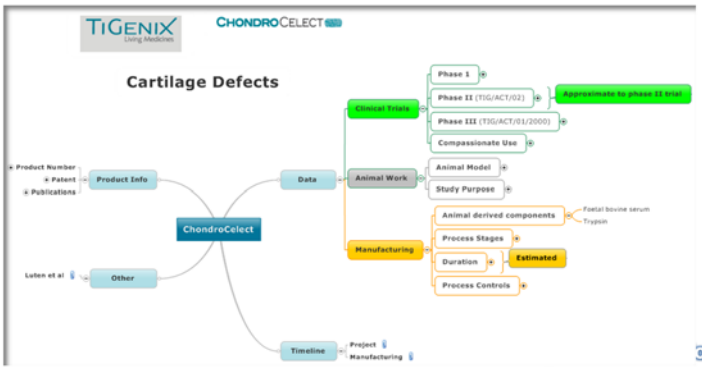
# Outcomes 2: Regulatory road-maps

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



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## 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.





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## 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.



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## 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.



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## 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.



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## 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?



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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*



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## 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*



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## 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*



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# 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





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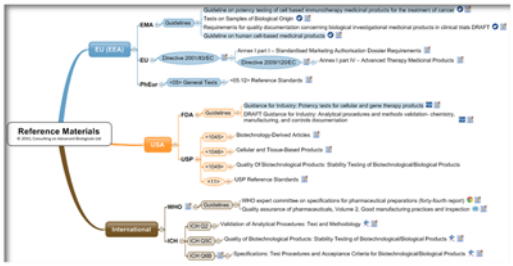
# Web-tools for Cell Therapy

**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*
- Pharmacopoeia
  - PhEur
  - USP
- Regulatory Guidance
  - ICH guidelines
  - EU guidelines
  - US guidelines
  - *Potency (EU/US/ICH)*
  - *Reference materials guidance (EU/US/ICH/WHO)*



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# 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.


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