EMA /US FDA Workshop on

support to quality development in early access approaches

ATMP comparability challenge case study

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Bio Biotechnology Innovation Organization

ebe european biopharmaceutical enterprises

efpia European Federation of Pharmaceutical Industries and Associations

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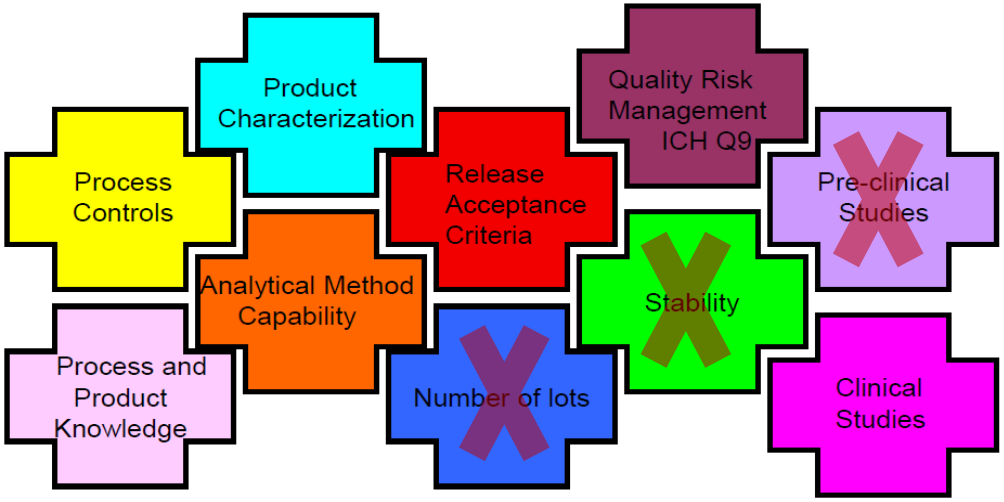
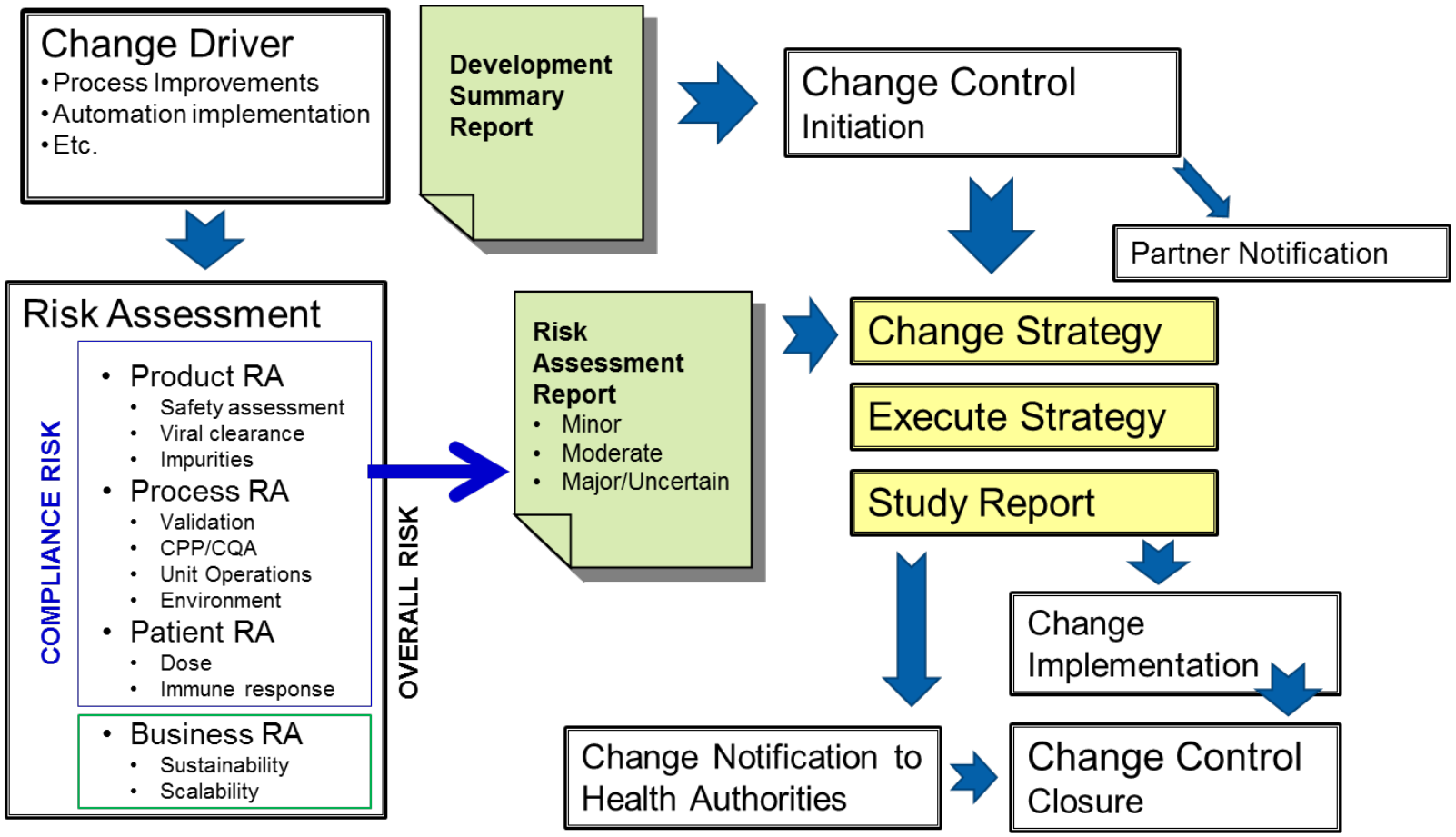
Problem Statement

- Process changes are inevitable in autologous products development, even late or post-approval, as knowledge grows
- Relative to Biopharmaceuticals comparability exercises
  - More frequently required
  - More complex design, require greater resources (full scale)
  - Higher risk for clinical comparabilty



Risk-based change control

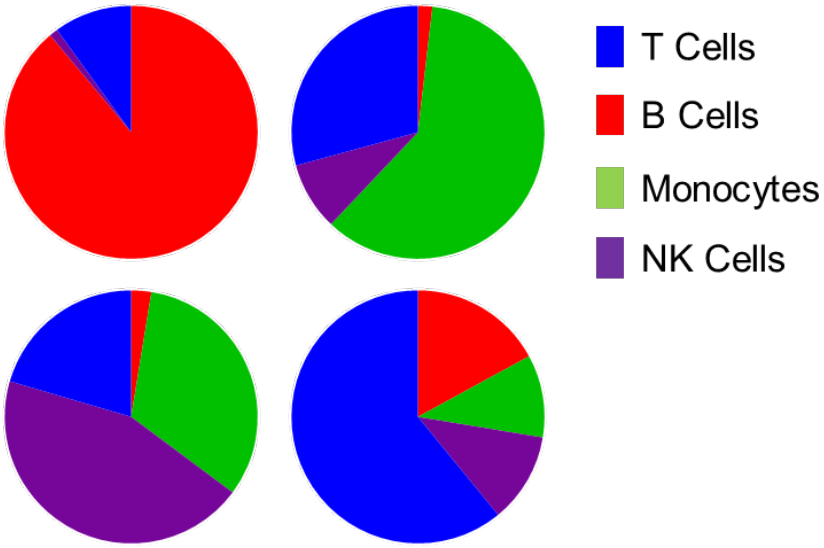


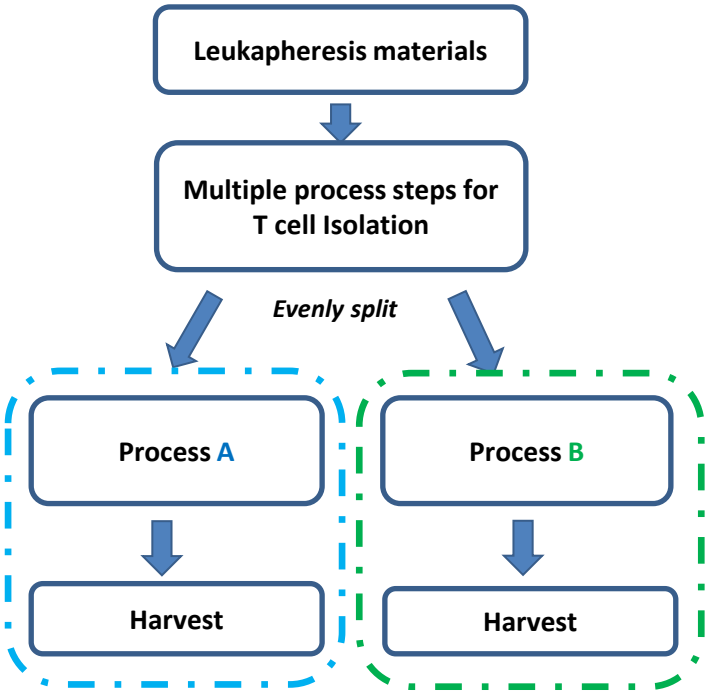
General principles and study design

- Full scale manufacturing, using ‘Split apheresis’ where appropriate
- Scientifically sound and qualified analytical methods suitable to assess product quality attributes that might be affected by the process changes
- Pre-defined in-process control acceptance criteria and final product release specifications
- Data are statistically evaluated where feasible and meaningful (number of batches to be used for the comparability assessment sufficient to derive a statistically significant conclusion).
- In cases where surrogate material is used as a starting material, a justification for its use is provided.
- A side-by-side stability program may be needed. Alternatively, appropriate short-term stress testing (in-use stability).

Use of ‘Split Apheresis’ starting material

- Heterogeneity of Incoming Material





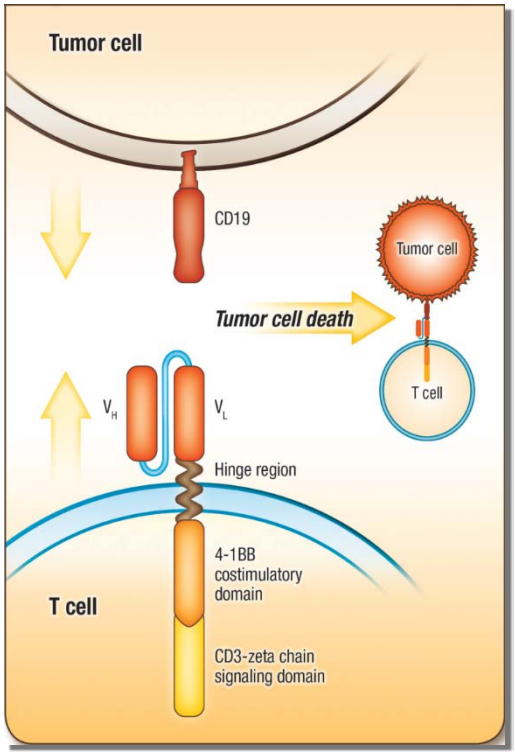
Split donor apheresis is used to minimize unrelated variability which might be caused by different starting material in order to better assess the impact of the change.

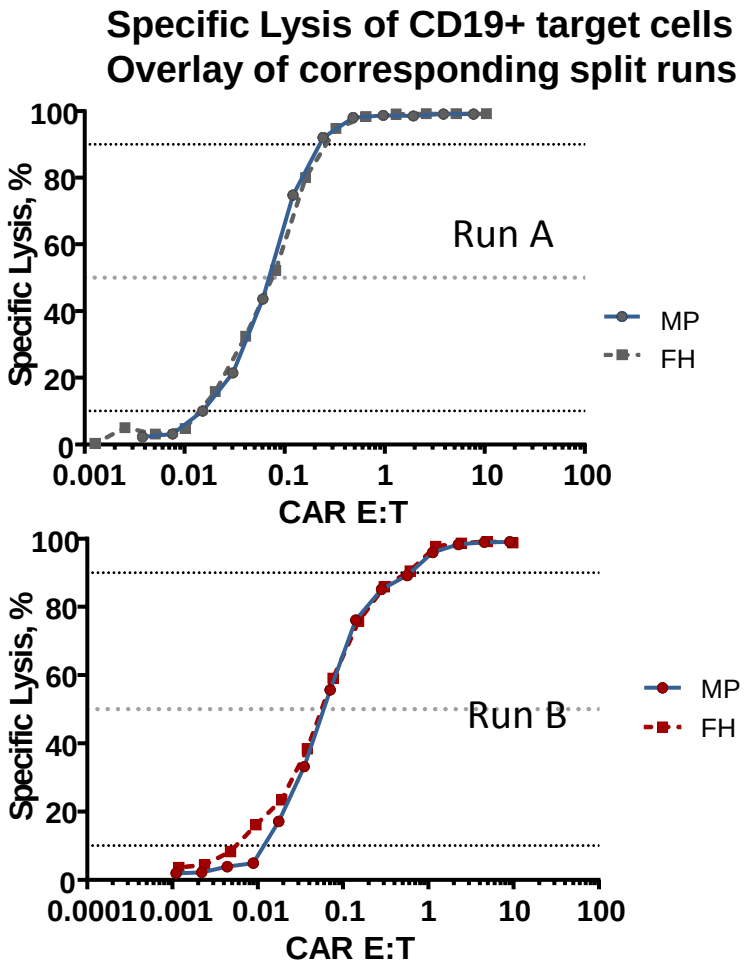
Components of the Comparability Study

The analytical program to show comparability of process performance and the product quality before and after process changes and/or site transfer includes:

- Process performance (growth rate, cell volume, viability...)
- Results of QC release testing (according to Specifications)
- Biological activity (product functionality) measuring responsiveness to target cells, such as cytotoxicity, cytokine profile, proliferation
- Cell characterization (non-GMP) such as cell population analysis / phenotyping
- Statistical comparison of quality attributes of process samples and final product
- Short-term comparative stability study if needed

Comparing functional responses: Cytotoxicity



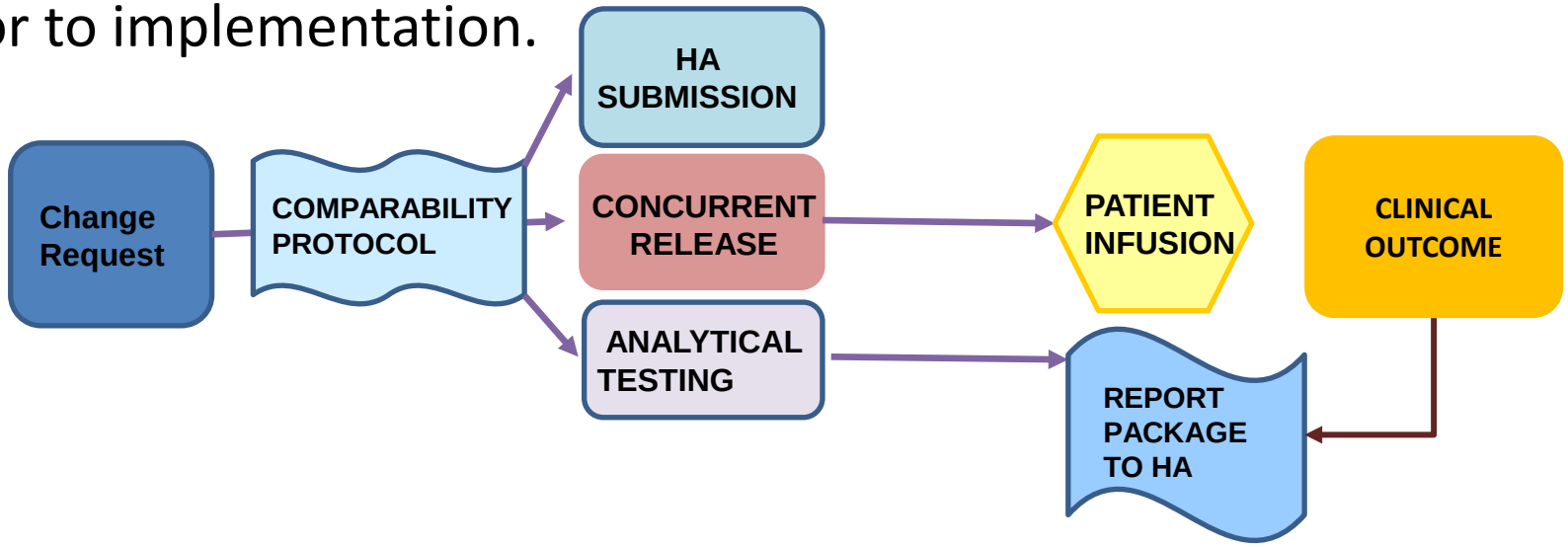


Comparability challenges

- Donor/Patient variability
- Product cannot be fully characterized
- Understanding of CQA's (especially in early development)
- Established matrix of functional assays
- Understanding assay variability to set appropriate acceptance criteria
- Process consistency

Comparability using patient cells

- Based on the assessment of the change it may be necessary to use patient cells to fully evaluate the impact of the change prior to implementation.



If impact assessment requires clinical patient manufacturing (GMP) setting:

a. A comparability protocol is filed as an amendment to the IND/IMPD.
b. Patient gets infused with concurrent release under analytical comparability
c. Submit completed report to agencies