CMC considerations from development through registration of an Autologous CAR-T Therapy

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Agenda

Introduction

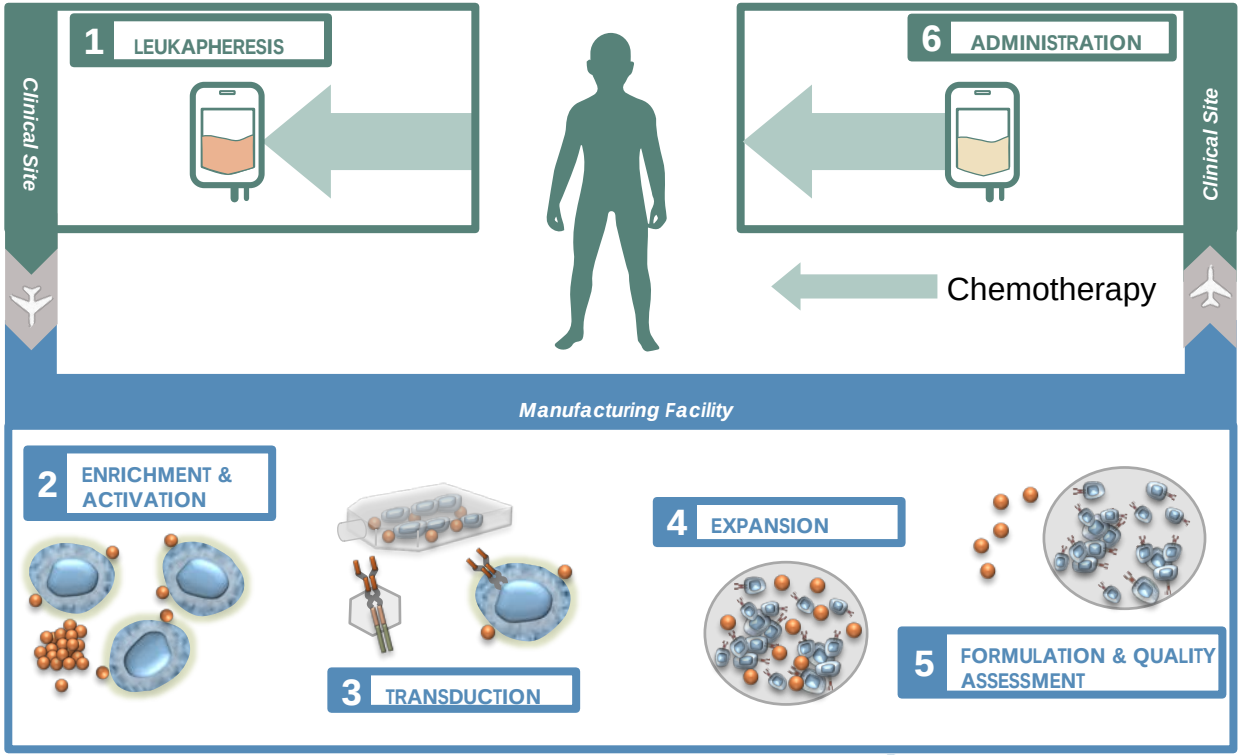
I. Differences between clinical and commercial registration

II. Special considerations on comparability

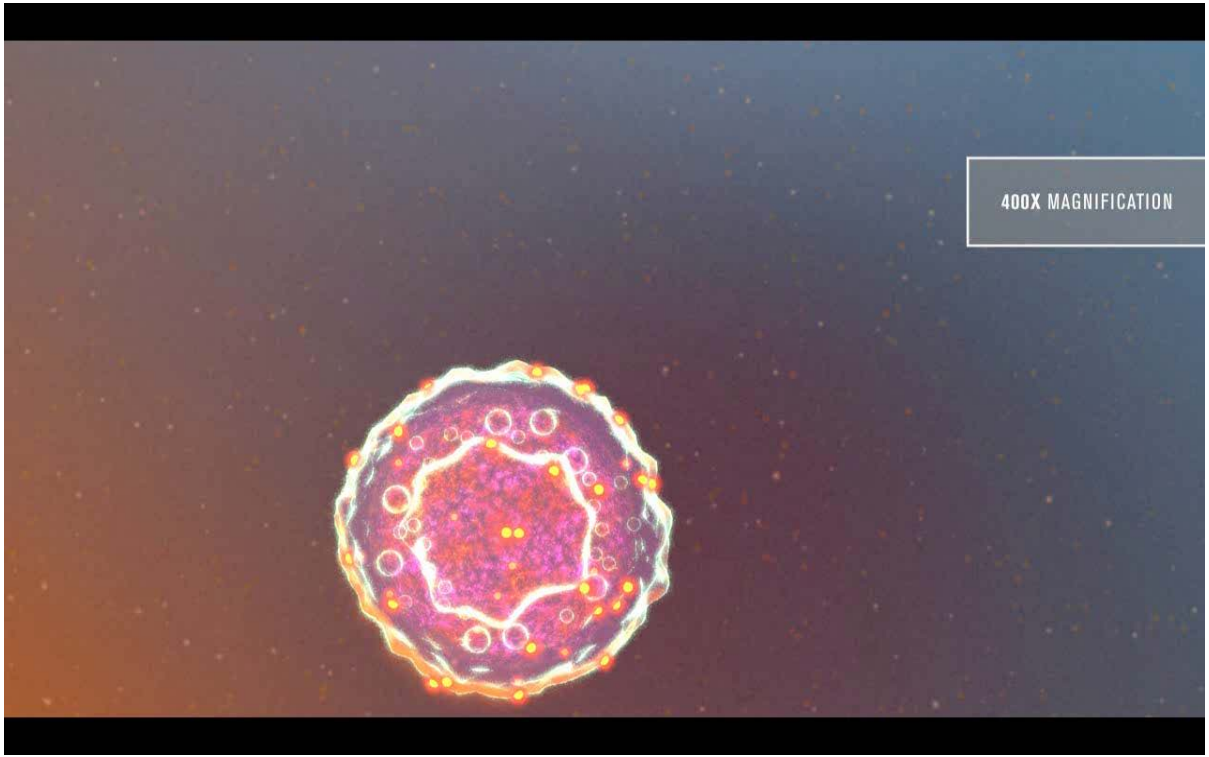
Conclusion

Introduction

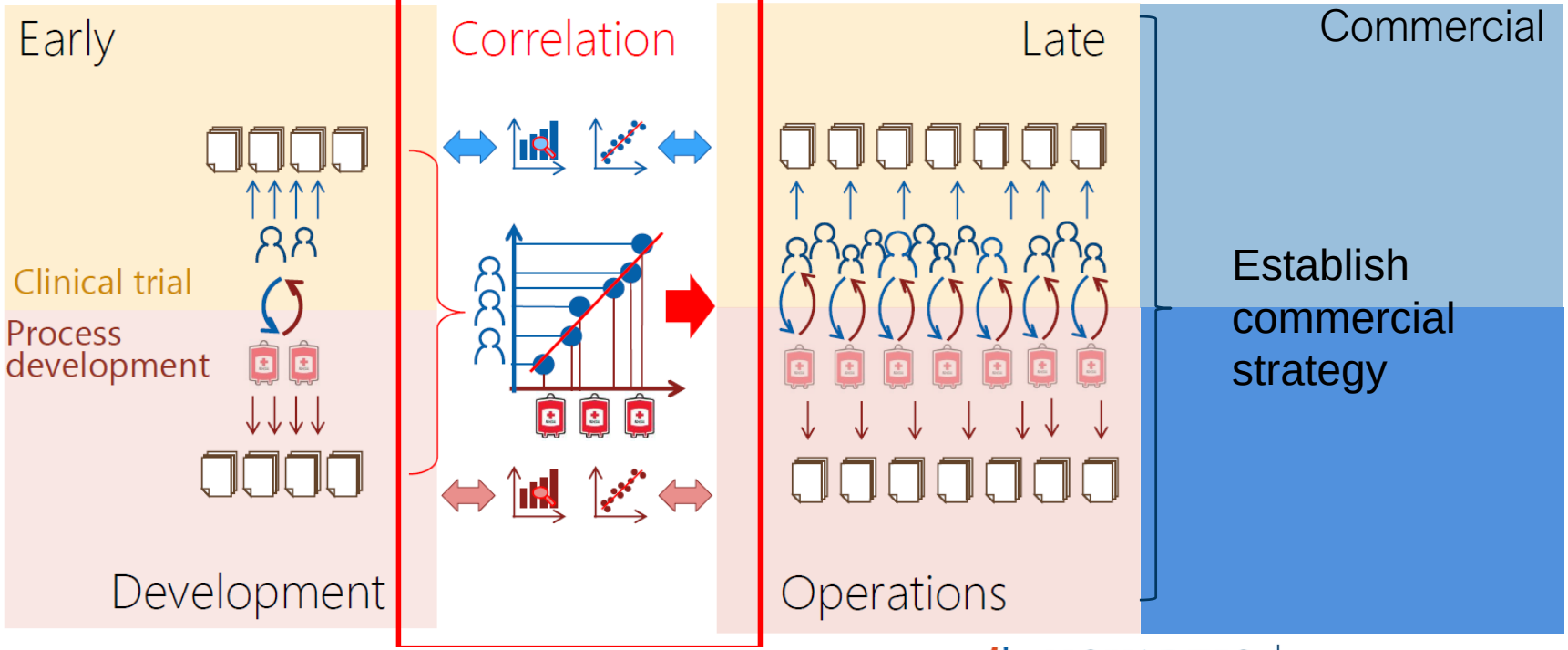
Example of an autologous CAR-T therapy for blood cell cancer



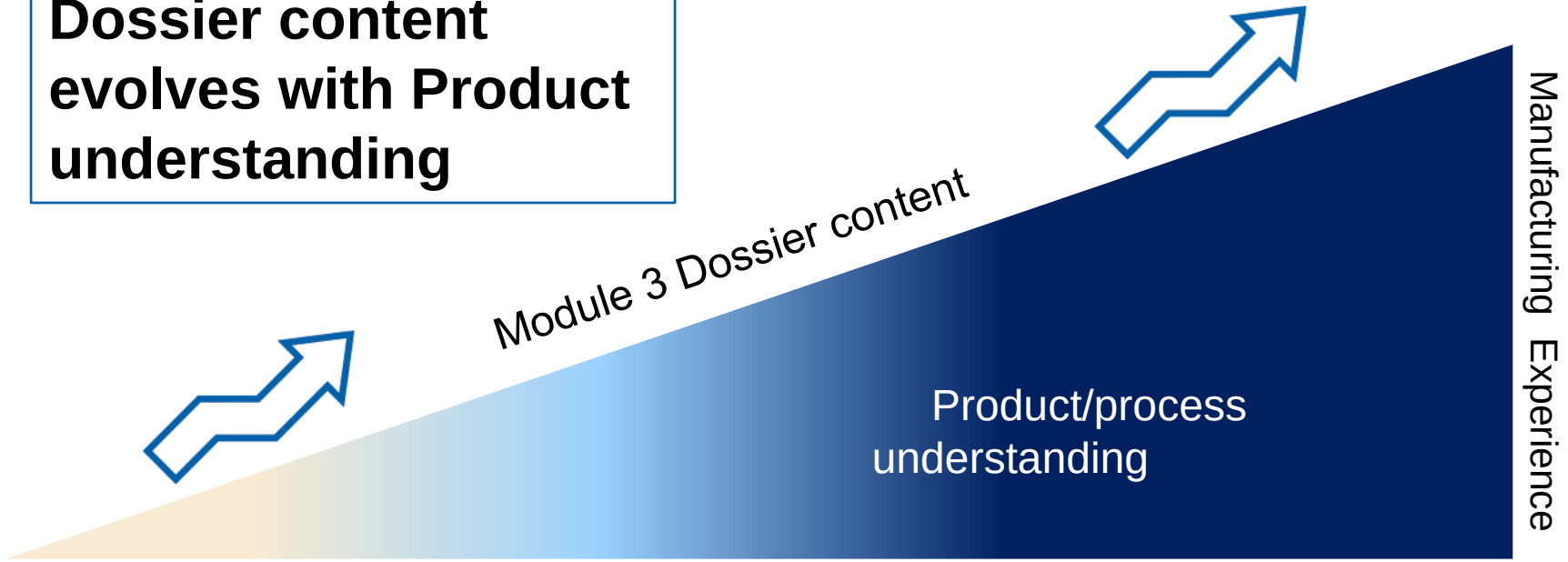
And this is how it works...



I. Differences between clinical and commercial registration



Dossier content evolves with Product understanding



Phase 1 → Pivotal → Registration → Post-approval

Short Development

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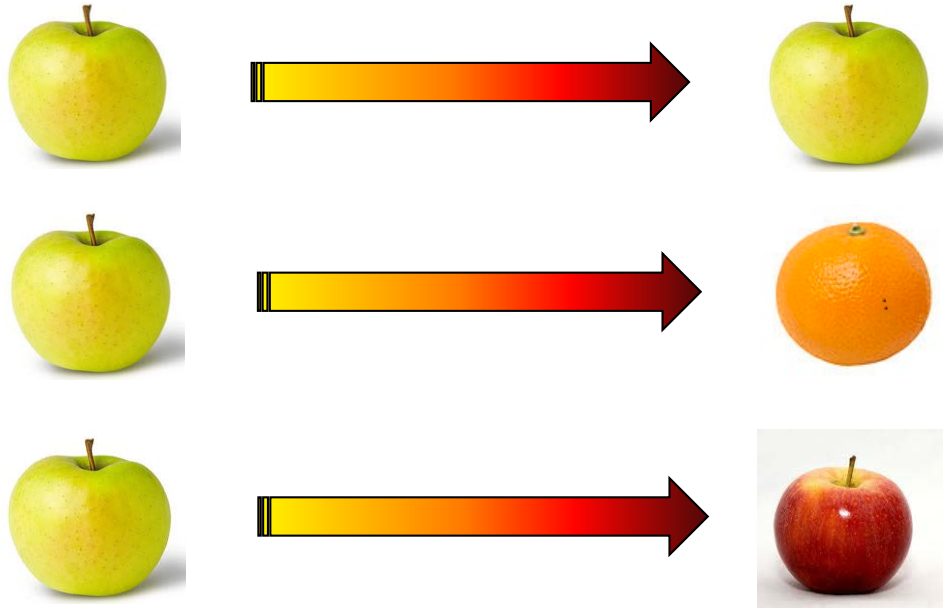
Biologics vs. Autologous CAR-Ts

Stage/ Product Type	Biologics	Autologous CAR-T Therapies
Development	➢ Well characterized Biologic product and process understanding. ➢ Critical Quality Attributes (CQA's), Methods and Process well defined.	➢ Shorter development with limited batches. ➢ Correlation to clinical outcome is in early stages of understanding (process, analytics). ➢ CQAs/Methods/Process evolve throughout the development. ➢ How patient heterogeneity influences T cells biology and process understanding is complex. ➢ Chain of Identity (COI) has to allow for full traceability.
Registration	➢ Registration framework well established contrary to CAR-Ts.	➢ Extensive manufacturing experience correlate to clinical outcome and helps to finalize the strategy. ➢ Leverage data from Clinical studies: Methods validated/Process/CQAs. ➢ Process Performance Qualification (PPQ) helps to refine the specifications: process parameters and CQAs are finally established.
Post-Approval	➢ Post-approval framework well established contrary to CAR-Ts.	➢ Constant improvements (manufacturing process, analytical methods...) ➢ Comparability studies...

II. Special considerations on comparability

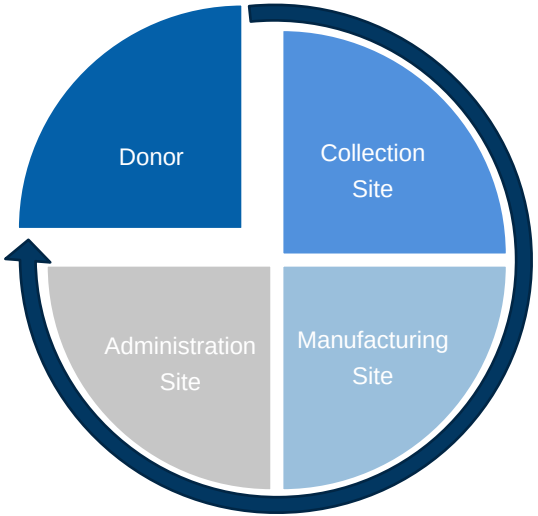
Comparability (of apples and oranges)

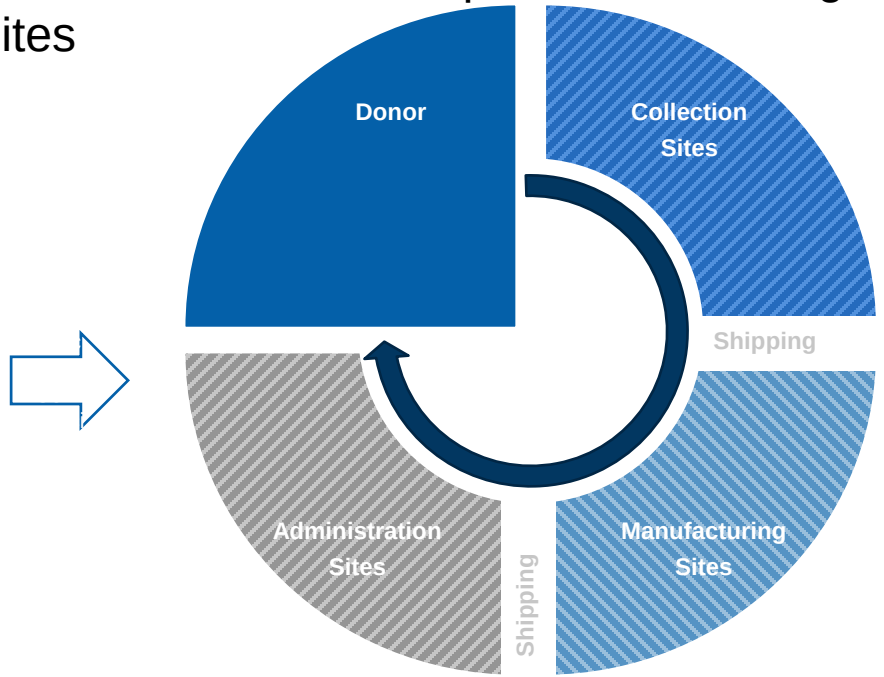


The same?

Challenges with adding a new manufacturing site

- From one academic facility to many collection sites, multiple manufacturing sites, and many patient treatment sites

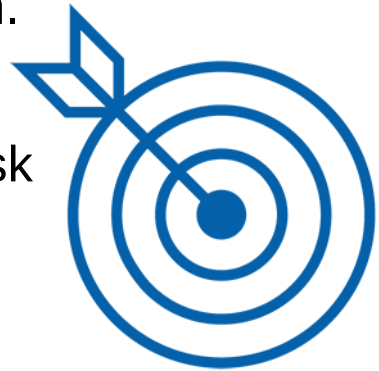




Technology transfer and comparability

→Technology transfer and establishing is necessary and challenging.

- ✓ Use ICH Q5E guideline and Guidelines of 22.11.2017 GMP for ATMPs to define the strategy.
- ✓ Experience and dialogue with agencies helps to limit burden.
- ✓ Transfer the most up-to-date process at the sending site.
- ✓ Perform a detailed site-to-site comparability exercise with risk assessments.
- ✓ Demonstrate “Equivalence” with a comparability study.



How to deal with variability and show equivalence?

Comparability study: comparability protocol includes a study design, an analytical method, a representative data set, and associated acceptance criteria.

- Importance to mitigate the variability resulting from different items :
  - **Starting Material,**
  - **Critical raw material,**
  - **Testing site,**
  - **Analytical methods...**
- Side-by-side Final product sample testing.
- Use “Equivalence testing”.

Process validation: what works?

How to design a process validation approach for a process with such variable starting materials and wide-ranged in-process controls?

Process validation: approaches

EudraLex Section 10.3 and 10.4 of Guidelines of 22.11.2017 GMP for ATMPs

- It is generally accepted that, as a minimum, three consecutive batches manufactured under routine conditions constitute a validation of the process.

- Flexibility in starting materials, possible to use surrogate starting material (healthy donors).

Or

- Concurrent validation can be acceptable considering the urgent medical need and where there is a strong benefit-risk ratio for the patient (needs prior alignment with health authorities).

Bracketing approach

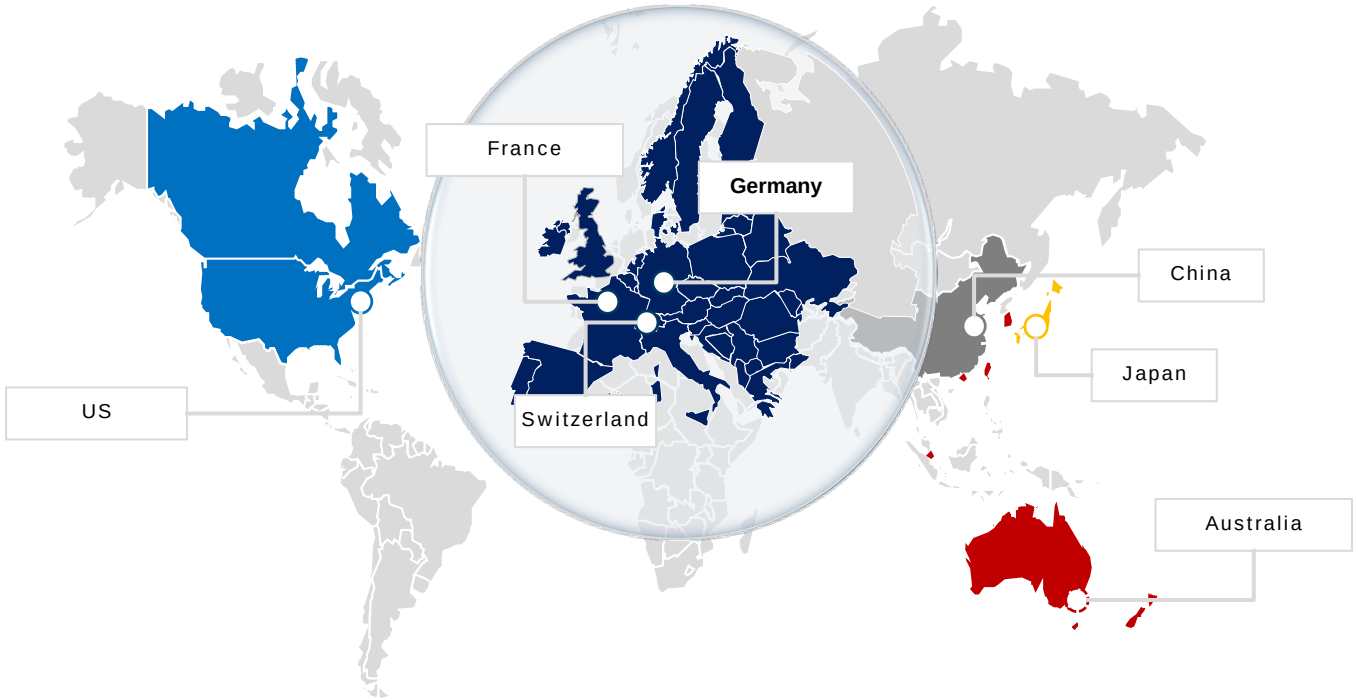
EudraLex Section 9.58 of Guidelines of 22.11.2017 GMP for ATMPs

- *9.58. In case of manufacturing of various types of ATMPs, consideration can be given to the matrix and/or bracketing approach. Under a bracketing approach, only samples on the extremes of certain design factors would undergo a full process simulation. This approach can be accepted if the handling of different products is similar (same equipment and processing steps). Under a matrix approach, it may be possible to combine media fills for different ATMPs sharing similar processing steps, provided that the worst case is covered by the matrix approach. The use of bracketing and matrixing together should be duly justified.*

→ **Perform validation runs on Higher and Lower doses for different indications of same CAR-T product to cover all dose ranges.**

- Demonstrate the capability of the site to formulate and cryopreserve the higher and lower doses. Cover intermediate dose by bracketing as it does not represent an extreme dose strength; the process is the same for all indications across the dose ranges.

Novartis CAR-T Manufacturing Network Today



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Conclusion

- **Novartis acquired unique RA CMC Global experience** for the development and commercial registration of CAR-T Therapy.
- The **manufacturing experience** gained throughout the Clinical phase allows to assess the **best commercial strategy**.
- After the approval, the product experience is increasing and a significant number of changes are needed with **demonstration of comparability** pre- and post-change.
- The **manufacturing expansion** is necessary for this type of product in order to reach out the maximum of patients and decrease the shipping time.
- **Manufacturing site addition** involves multiple comparability exercises to show the equivalence between the products manufactured at the different sites.

Thank you

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