Table 1: Comparability Considerations for ATMPs

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Scope:

In 2019, The Committee for Advanced Therapies (CAT) from EMA, issued a Q&A on Comparability considerations for Advanced Therapies Medicinal Products (ATMPs). Establishing suitable programs for ATMPs is often a challenge due to the specific nature of these products. Looking at the last 15 years of ATMP status existence in EU, we cannot but notice that comparability has been a core challenge in developing these products. While it is generally acknowledged that Gene Therapy Medicinal Products (GTMPs) development can rely also on the quality paradigm established for biologicals (Guidance on comparability for biotechnological products, ICH guidance (Q5E…)…); Cell-Based ATMPs present a different challenge, where multiple sources for potential variability must be considered (living product, scarcity of material, depletion of cell stocks, changes in cell culture materials...). If we also consider not all analytical tools at our disposal are mature enough to fully explore the mechanism of action of these products, then we are forced to recognize that developers face additional difficulty when selecting the appropriates CQAs for comparability.

Questions for Discussion:

Focusing on the most critical questions from the EMA guidance, this Roundtable will aim at discussing:

- Real life example of challenges encountered by the participants
- Preferred approach for comparability and current solutions to appropriately address comparability issues and match regulatory authorities expectations
- Specificities for each ATMP product type
- Insight on EU and US framework evolution regarding change management and comparability assessment, anticipation strategies to ensure development continuity over clinical trials and commercialization (also constraints from accelerated development pathways)
- Strategies for development of analytical tools supporting comparability (additional characterization assay’s, potency assay candidates, CQA and stability indicating parameters to monitor…).

Discussion Notes:

Topic #1: Where do we start from:

The participants came from different background encompassing multiple product types which allowed to both understand continuity with the pre-existing recombinant biological framework and the specificities of each ATMP (Cell and Gene) Product category. It quickly appeared that while providing preliminary guidance, ICH Q2 and Q5 are not designed to match C&G specificities, and that while principles mays be taken into consideration, some requirements are not applicable. In addition, for C&G, local requirements and differences in comparability approaches comparing EU and US create additional challenges. It was noted by the participants that, availabilities of formal procedure to submit comparability protocols at the FDA compared to unharmonized local authorities in EU was probably helping in ensuring comparability studies are well prepared and appropriately conducted. Please keep in mind that while FDA deals with both Clinical Trials and Marketing authorization, EMA is on the competent authority for centralized MA. The 2019 Q&A from EMA (topic for this session) is only part of what is coming on comparability, FDA is working on a guidance for 2022, and EMA might consider a guidance based on feedback received on the Q&A. The participants decided to exclude Tissue from the discussion as they face very specific challenges.

Topic #2: Real Life example:

A key quality parameter for comparability is potency: Reminder that even for "classical" biologicals, it took decades to establish well perfuming potency assay surrogates and eliminate intrinsic variability from functional potency assays. Considering the current struggle in developing suitable potency assays for C&G, the industry has a limited/immature analytical toolbox at its disposal which do not allow for extensive comparability if not by using overlapping orthogonal methods. The participants concluded that the only way to cover for not fully elucidated quality parameters, would be to extend characterization, early on to generate sufficient data and reference points for later comparability. This is in line with both FDA and EMA recommendation as per 2022.

Among the proposed / validated approaches:

- Explore a large panel of CQAs early on, build experience, gather information on informative vs non informative methods
- Move characterization to other aspects (include materials testing, explore process ability to accommodate variability – aim at delivering consistent batches.). Differences in materials between lots even from the same vendor although rather small (i.e. within specs) can cause significant change
- For C&G you cannot rely on the process itself – Contrary to some biologicals, the" Process is not necessarily the Product". This has been experienced in particular in validated mature processes tech transfer.

Topic #3: Product specificities and potential approaches:

The Guidance discusses comparability, when sometimes it is more about Product development continuity. A good example was used when for Individualized medicines, the variability on the product is by design. In this case it is about process knowledge and experienced gathered to date, plus validation to cover for batch to batch consistency rather than strict side by side product comparability. This challenge extends to other approaches such as : C&G incorporating an autologous component (patient variability + Cell collection from patients versus validation using healthy donor cells that may not be fully representative). Similarly even for allogenic products, the 1 donation / 1 batch approach may prevent you from validation that fully removes donation related variability. Sometimes it is not even feasible to define what a healthy Cell is (Eg "healthy T Cell, vs patient T cell". The corner stone for proper comparability will be to make the distinction between what needs to remain the same and what is acceptable variability. The authorities, as they see more development programs than each individual developer may help in defining "acceptable" in that context. Comparability requirements may need to be defined for each type of C&G to ensure products are not facing requirements that are impossible to meet.

Topic #4: Wish list:

- Template for comparability protocols tailored to ATMPS, both in EU and US. High level enough to allow for flexibility, but detailed enough on the "points to consider, General warnings…"
- Whenever flexibility is granted, more details on phase appropriateness / fit for purpose would be beneficial
- Guidance on Acceptance criteria definition and extended characterization, including recommended strategies for assay correlation and statistical approach.
- Overall continued effort towards global harmonization and established standards where applicable.
- Industry knowledge sharing, considering the currently existing data, the industry should be able to define along with the authorities the absolute "must have" for comparability.