Roundtables Session 1 – Table 2 - Industry Feedback on FDA Comparability Guidance

Facilitator: Virginia Andreotti-Jones, *ValSource, Inc*

Scribe: Barbara Bonamassa, *Italian Medicines Agency*

Abstract:

The FDA published draft guidance Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products on 13Jul2023 for public review and comment. In addition to existing guidance for biological products, this guidance seeks to provide information specific to CGT products for managing manufacturing changes and the need for and design of comparability studies.

We will discuss feedback on how the information in this guidance can support manufacturing change management for CGT products, what information could be clarified or included, and if your firm plans to make changes based on this information.

Specifically:

Does the guidance provide sufficient information to address challenges of manufacturing changes and the use and design of comparability studies for CGT? Where has helpful clarity been provided? Are there areas where a particular topic or issue was not fully addressed? Does the guidance impact your firm's approach to comparability study design?

The guidance unambiguously states that risk should inform the need for and design of comparability studies. Does the guidance provide sufficient information to implement a risk-based strategy for manufacturing change assessment and comparability study design? What approaches does your organization use or plan to use to achieve this requirement?

The guidance discusses material selection for CGT comparability studies and recommendations for overcoming challenges. Split-source study design is recommended whenever possible for products derived from variable cellular materials to reduce the number of batches needed. Is this a suitable solution for most situations? Are there other options that might also be acceptable? The number of vectors available for comparability studies for GT vectors may be small. Therefore, including vector lots manufactured during process development or engineering runs may be appropriate. Is this a suitable solution for most situations? Are there other options that might also be acceptable?

The guidance aims at managing manufacturing changes and the need for and design of comparability studies for Cell and Gene Therapies (CGT).

The round table discussed how the guidance supports manufacturing change management for CGT products, what information could be clarified or included, and if the guidance is useful to plan changes based on this information.

Notes:

- among the attendees' reasons to join the meeting, clarity concerning the guidance's ambiguities, absence of information in terms of phase appropriate approaches to comparability, benchmarking, better understanding of the document, heavy statistical requirements, were mentioned.

- the guidance resulted as a useful document as provided by a written document. Nonetheless, the risk-based approach is frequently mentioned in the guidance, which however does not provide specific examples. In this perspective, the FDA guidance "Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products" was referred as a more useful document.

- according to the guidance, a manufacturing process change ending up in a safer product would results in non-comparable pre- vs post-change products, and this has been regarded a major ambiguity/criticality of the guideline and would be in contrast vs the EU approach.

- the statistical requirements were regarded as heavy and not phase appropriate. It was mentioned that the EU requirements are softer since it is acknowledged that the ATMP development frequently suffers from a limited availability of batches. Also, it was commented that, in the EU, in terms of batch number, there is no threshold to ask for heavy statistical requirements or switch from one statistical approach to another one and graphical representations are always regarded as a useful tool to report comparability data.

- FDA also requires stability data in the context of the comparability exercise, which may not be a stringent requirement in the EU.