Session 1 – Table 3: Comparability Approaches - Focus on Cell and Gene Therapies (see FDA draft guidance)

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Abstract:

Process changes (i.e. manufacturing site/scale, formulation, processing step…) are an integral part of a cell & gene therapy product's manufacturing life cycle both during development and after approval. These changes often affect product quality attributes. The goal of a comparability exercise is to ensure that the changes made have no adverse impact on quality, safety and efficacy of the drug. Typically, a risk assessment is performed to assess the potential impact of changes on product quality as it relates to safety and efficacy, and to inform on the appropriate comparability strategy. The new FDA draft guidance "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products" provides the principles for assessing the comparability of cell & gene therapy products before and after changes are made in the manufacturing process. This roundtable aims to discuss approaches, best practices, and regulatory expectations of comparability exercises for cell & gene therapies.

Questions for Discussion:

1. How are risk assessments used to assess the potential impact of changes on product quality as it relates to safety and efficacy?

2. What are some best practices for demonstration of analytical comparability for C & GT programs?

3. What statistical assessments are performed to justify pre- and post-change differences in product purity and potency and for method equivalency?

4. What strategies are used to overcome limited amounts of material available for analytical comparability testing of C & GT products?

5. What strategies are used for stability studies supporting comparability of C & GT products and other complex products?

6. For cell therapy, what are best practices to address patient-specific variability? What items are considered utilizing as risk based approach?

Notes:

- Most attendees were representing industry analytics and development, business development, and ex-regulatory
- Lots of large molecule/protein experience
- Mix of internal and external partnership experience (in-house vs contract)

Any specific questions?

- How do teams think about comparability as you get to later stages? Cell therapies in particular.
    - Comment: Do Cell and Gene therapies go together? They seem very different.
    - RNA based therapeutics may be more similar to protein in comparability design
    - Regarding recent guidance combining Cell and Gene Therapies: Cell and gene therapy is so broad, how can they have similar guidance?
    - AAV may be more similar to protein workflows also
    - Ongoing debates on delineation between cell vs gene therapies. Ex-vivo gene editing lumped into gene therapies, do we need specific sub-categories in guidance?
    - Even within Cell therapies, autologous cell therapies vs others should be considered
    - Quality, efficacy, safety needs to be addressed regardless of therapy type
    - In the guidance they're listing specific changes as major changes, does the table agree? Site manufacturing changes, maybe?
    - Don't read too much into the fact that there's a list, maybe it's just examples - when things become clear cut, it will be definite as final guidance is issued.
    - General Comment: If the agency puts anything in writing, industry will interpret it as a rule.
    - Is the guidance useful? Some say it's moving in the right direction - looking like ICH q5E, could be useful/favorable - some say it's a little repetitive - new guidance repeats same concepts over and over again –
    - Why new guidance vs adding new modalities to existing guidance - driven by the need as is perceived by agency leadership - based on feedback from leadership, congress, to address concerns of industry and public
    - Guidance is intended to help accelerate the industry
    - If there is repetition, it could be new to the authors, or they think it could be useful and may not be known by the intended audience. Drafting is very intentional
    - Companies that come from biologics space may already be familiar and so see the guidance as redundant, but new companies may not be familiar with ICH guidance that exist for biologics/devices
    - Smaller companies see value in having the guidance to help drive conversations with corporate leadership, justify phase appropriate development plan
- What to do with limited materials? Guidance does provide for limitations
- Focus on statistical analysis for gene therapies in the guidance?
    - Autologous products, with N of 5, is it powerful enough?
    - Can run these tests, but it won't mean much due to low N?
    - Statisticians say there's not enough data to do anything. 5 patients, 200k dollars per run for autologous cell therapy development - cell therapies have lots of hurdles
    - Not running stat analysis just because you don't think it will be informative? We should still do it.
- Casss CGPT symposium - limited materials with respect stability studies - If you have stability panel but don't see any changes when do you stop given how limited the materials are, does storage condition matter? Eg. At -70C we don't anticipate any stability issues, risk based assessment?

- Early stage, is it okay to run comparability while learning about the product - later for approval you should have done the work and select methods that are appropriate for the product
- At comparability session earlier at WCBP - comparability at the point of change as advocated - how does this apply to gene therapy? For RNA, we could definitely apply such concepts, but for cell therapies? Point of change is the patient.
- Organ on chip function - would be useful, maybe not developed enough
- Healthy donor vs real patients - been an issue - pulling samples from past patients to develop assays is impractical for cell based assays
- Cell therapies are so different, needs to separated from other therapies
- For RNA therapies - Focus on statistical analysis seems to be arbitrary relative to existing expectations for other macromolecules, e.g. mAbs
- Cell therapy space comparability is difficult –
    - In process testing seems important to help build comparability argument
    - Development of functional assays critical, potency assay interpretation
    - What battery of testing is needed for establishing MOA
    - T-cell - interferon gamma, cell culture/viability
    - What additional methods would be needed may be specific to the therapy
- Prospective Type C interactions with agency has been helpful
- Type D meeting may also be an option
- Platforming of gene therapies - is there enough prior data?
    - LNP or AAV vector could be platformed.
    - Platform methods for platform products
- What about starting material - how do you handle a change in starting material?
    - DS gated comparability
    - Cell line changes could result in finding that the material is a new product, if the cell change is large enough
    - Same transgene same product, different cell line for expression, strong comparability package assembled including non-human primate but lots of pushback from an undisclosed EU country - wouldn't accept analytical justification?
- How do you handle method changes? Bridging studies? Cell products may have limitations –
    - Bridging can be done by comparing a historical lot?
    - For Cell therapies you may not have material to run on two different systems
- Comparability stability study using same testing panel as normal - probably not necessary
- Any success for making case for using same expiry as pre-change material? Or do you need to start all over again
    - Somewhat dependent on change - formulation, container closure, maybe need new stability
    - If upstream, but have same formulation and closure, maybe
    - Should be able to use same logic as with mAbs
- Do you need to do stability on cell therapies?