Roundtable Session 2 - Table 3 - FDA Draft Guidance on Potency Assurance

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Abstract:

In a significant update, the FDA released a draft guidance document titled "Potency Assurance for Cellular and Gene Therapy Products" in late 2023. When finalized, this long-awaited document will replace the 13-year-old guidance on potency testing.

The new draft emphasizes a holistic, risk-based approach. It goes beyond final lot release testing and incorporates elements such as manufacturing process design, material control, process understanding, in-process testing

The FDA also highlights the importance of a life-cycle approach for ensuring potency throughout the development and commercialization of these therapies. This guidance aims to be a roadmap for sponsors to develop and implement strategies that guarantee every batch of a CGT product has the potency needed to deliver the intended therapeutic benefit.

Roundtable Notes:

Our roundtable delved into these key aspects of the new guidance:

Key Takeaways: What are the most important points you glean from this new guidance?

- Guidance doesn't seem ready yet – people want more specific examples; mixes difference GT products and differences need to be outlined better
    - Comments were provided
- Principles make sense in theory, but the practice isn't very well defined
    - Vaccines include QbD, risk assessment, but even with this type of package, agencies will still expect a certain level of potency development to look at biological activity
        - Is the agency ready for a risk based approach that doesn't include a bioassay?
        - Most cases, bioassay is required, but in some cases (ex vivo) surrogate makes sense.
- Organization design and regulatory strategy – how do we set this up and document in our eCTD.
    - Much of it should be available
    - After you file the IND, you can update your strategy over time
    - 3.2R in the eCTD is a good place to put the potency assurance strategy
        - Implementation of the strategy elsewhere within the filing

- Don't need to be completely analogous to DP process
    - 3 parameters with cell culture – can you design potency to all use same cell culture
- Would appreciate the separation of cell and gene therapy
    - Flexible and relies on information supplied in filing
    - Ex. programs often look just at protein expression – not a defined activity assay
    - 2011 guidance says assay needs to be reflective of MOA, but expression isn't activity
        - Flexibility for sponsors to show expression instead of MOA as long as you can also link this to potency CQAs (good change)
- Previously people consider in vivo methods to really show the MOA, but separating out the release potency vs real MOA takes some pressure off
- Recommend gRNA and mRNA – maybe not potency, but activity assay to show active
- Link of potency to quality (CQAs) is an emphasis on how the CQAs can impact your potency
- Terminology changes noticed: the new guidance does not include terms such as matrix approach, surrogate assays

Impact on Potency Strategies: How will the guidance affect your current approach to ensuring potency?

- ddPCR based potency vs TCID50, mRNA expression assays, looking at correlation between all of these is important
- With this guidance, we see emphasis on a holistic view of what may impact the potency within the manufacturing of the product
- Post-approval changes – need strategy for how you'll assess potency/activity of the product moving forward
    - Assess impact of any changes to the potency of the product
- Guidance makes sense, but the struggles to pull together potency assay for IND/briefing book – a lot of additional details are required now and need to be discussed early on
    - This is a draft guidance, no need to implement right away
    - Yes, but they'll be referring to this guidance
    - For early phase all risks may not be well understood, but the guidance seems to be towards later phase
- For early phase, there used to not be a need to document all of the potency CQAs, now we need to spend time and resources to appropriately document within the IND
    - Not intended to be additional work for sponsors, but it really is
- People start thinking about potency assay for ph3, even early in development
- IND is already pretty inclusive of all of these pieces, but now pulling together a master plan that connects all the dots to provide to the FDA
- Hopeful that the guidance will support any post-approval changes
- QbD lens – first align on MOA, complex disease may not be well understood
    - Can look at cascade of events - transduction, mRNA expression, protein expression
    - Align with agency on what the MOA is will be important for potency assay development
        - Could use protein expression where fully understood MOA isn't available
        - Retains are helpful for later testing samples for MOA potency method
        - MOA evolves as we better understand the product
    - Very difficult to put together an IND when you don't understand the MOA
    - Definition of MOA for GT is on the gene editing event

        - Multiple MOAs (DP vs disease)
            - Easy for DP – use NGS
            - How the protein works to treat the disease
    - If you understand that the protein does something… you need to understand what downstream effect it takes (MOA) – you need some level of understanding of your MOA

Implementation Challenges: What concerns do you have when putting these recommendations into practice?

- Strategy for potency and implementation of potency methods
- Every time a risk assessment is performed, cell bank testing, certain points need to be addressed specifically (even facility, controls, etc) in the IND
    - Everything involved will be subject to inspection and needs to be documented properly
- Multiple gene edits – each needs a potency method
    - Where does the inclusiveness of the cascade stop for all edits? Can some be editing and genome level, or do all need to be downstream (flow for example)
        - Looking for correlation for later phases
        - Seems like all could be addressed with expression
    - Comments on draft guidance closed on March 27
        - Some industry personnel didn't get a chance to comment
        - Different standards for different attributes of a product – need more consistent feedback for sponsors
- Ensuring that commercial strategy can be maintained is a layer of concern
- Challenges are internal – timeline driven
    - Business decisions were made, but may need to bridge to new method, appease all markets
- Dealing with multiple programs, all have own strategy which becomes more defined as you move on
    - Better to have a guidance, but as far as implementing it, most programs will require their own strategy
        - Good understanding of instructions will help to define strategy later on
- Challenge to resources
    - Clear recommendations from pre-IND, but smaller companies may not have the resources to take on technical challenges; communication is important

Future Guidance Needs: Are there any additional potency-related guidance documents you'd like the FDA to issue in the coming years?

- Separate guidance for GT and CT
- Clarifying potency requirements for certain stages/modalities
    - Need for cell-based assays vs cell free
- More clear examples of what has been successful and what's possible
    - Phase appropriate strategy for early phase
    - Removal of TCID50, for example, when functional potency is available

- Related guidance on RS and development over time (Lily has a great paper on this: Journal of Pharmaceutical and Biomedical Analysis 191 (2020) 113577)
    - Would be great to see bridging of RS and examples for later phase programs
    - Lot to lot variability can be a big issue
- Phase appropriateness of potency assays

Andrew Byrnes (FDA)'s presentation at this meeting discussed a comprehensive approach - discuss

- Transduction, expression, activity
    - If you have an activity assay, do you need the others on release?
        - No, and it's nice to have this in writing
        - It is nice to have these orthogonal measures – can deprioritize these on release and include for comparability and characterization
- Based on your experience, how often do we expect this guidance to change over the years
    - Unlikely to be every few years
    - It's been more than 10 years, but there are a lot more submissions lately
    - It's unlikely that anything entirely new will pop up every few years and may not be helpful to revise every few years
    - Maybe 5-7 years for revisions
- This guidance isn't as clear as some ICH guidances, so this may need to evolve over the years to give better guidance
    - Industry wants guidance on that actual potency assays, but this is more about the potency assurance and doesn't focus on the potency assays
        - 2011 guidance doesn't seem to be replaced, this is more of an add-on, but it will be obsoleted
            - 2011 guidance says that more than one potency assay may be necessary for multiple MOAs, but the new guidance seems to suggest only one is sufficient
            - May result in meaningless feedback or confusion
            - More restrictions or flexibility?
    - Motivation from FDA is to provide more flexibility for potency strategy
        - Less MOA and more on a holistic approach to potency
        - Based on product, and less on MOA – what is needed to generate the biological effect of the product
- When do we get the final guidance?
    - Usually takes a year or more, depending on how many comments were received
    - Public comment period is over now – too late to comment if you don't like it
    - May be additional town halls where people can comment
    - ASGCT feedback may come into play for final document (potentially other societies/channels as well)
- How does this link to EMA guidance
    - No specific EMA guidance on potency
    - EMA is stricter because they require potency assays for Ph1