Table 34: RNA- Vaccines and Therapeutics

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Key Words:

RNA, vaccine, control strategy

Scope:

The mRNA platform has revolutionized the way we prevent and treat infectious diseases with the swiftest response to addressing the Covid-19 pandemic vaccine need. The therapeutic use of messenger RNA (mRNA) has led to interesting targets for many companies. Unique challenges such as control strategy for novel raw-materials, in-vitro transcription reaction variability and RNA shortmer impurities and various others are encountered from a manufacturing perspective when advancing this novel platform. This session will discuss analytical control strategy issues from end-to-end perspective when advancing this platform.

Questions for Discussion:

1. Approach to Potency Assays for mRNA: Do you use antigen/target expression or is sequence enough to confirm potency of the mRNA vaccine or therapeutic?
2. Control of the Untranslated Region- How do you control for 5' capping and Poly-A length- are you using mass spec methods vs molecular-biology based techniques?
3. mRNA analytical control strategy has opened a new era in molecular analytics what are the new technologies your company has adopted in QC and on characterization to understand mRNA lot to lot variability?
4. Approach to validation of new analytical technologies in QC?

Discussion Notes:

- Most important quality attribute- integrity of mRNA
    - Do we need a potency assay as well?
    - If we can show dose response curve with integrity/immunogenicity, do we need an antigen expression assay? (on characterization but not release potentially)
    - Always felt we should have a potency test and WHO documents indicate we should demonstrate gene expression (potency, states Western or ELISA)- during project Warp Speed, did we let this go possibly?
    - Encapsulation and performance are critical
    - FDA and Health Canada- would like expression confirmed (confirmed translation, through a potency assay)
    - Still seeing some potency assay (at least on characterization) should be done to confirm expression
    - Dean (Health Canada)- if you know attributes that impact potency and can measure these with better precision, do these
    - Consider using a model to confirm that integrity is reflective of potency
    - Many sponsors doing integrity only to confirm potency

        - Integrity is biophysical, potency is usually either cell-based on ELISA
        - Need information that this relates to mechanism of action and then the assay can be considered a measure of potency
        - Doesn't need to be an immuno assay or a cell-based assay for potency
- 5' capping - mass spec to confirm 5' cap
- Poly A- more complex, can be heterogeneous - distribution of Poly A- How critical is the exact number of Poly A? No one truly knows, but there is usually a product specific target
- Poly A tail stops transcription/translation (ribosome falls off) - protein has been made - poly A just needs a minimum length for this to happen
    - Minimum length of Poly A varies - at least in 50 bp range (CQA is minimum length of poly A tail for consistency)
    - Poly A should not change on Stability - should not fall off on stability
    - Suggestion of HPLC method for Poly A tail
- Sequencing - technologies used to understand mRNA (NGS, etc)
    - NGS and sequencing - limited to pre-clinical development to determine sequences
    - How do you look at misincorporation in IVT? Illumina sequencing, etc - may not need sequencing if you have other assays to confirm that you have what you expect to have
    - Need to demonstrate that you have fidelity of the mRNA
- Validation of new Analytical Technologies
    - Looking for multi-attribute mass spec method on release
    - Q14- build validity into the assay/technology and traditional "validation" becomes less relevant
    - If you change something that doesn’t impact performance, less burden for implementation of the change

- Lessons learned from mAbs: translatable to mRNA
    - Once Mass spec is validated and ready, its not hard to incorporate mRNA
    - Time and training factors- mass spec harder to use
    - More about getting the technology into QC
- RSV Older adult race- GSK protein subunit vaccine with adjuvant - Moderna data: mRNA vaccine for RSV is 80-90% efficacy
    - RNA vaccines- not sustainability like protein subunit vaccines have (preference for protein subunit vaccine)
    - Other protein subunit vaccines have significant advantage in durability
    - QS21 adjuvant in RSV vaccine (same as adjuvant in Shingrix)
- PATH- does not deal with US market (only international). Project in Africa to build a hub to train for vaccine manufacturing.
    - Reg agencies in these parts of the world not as sophisticated
    - Supporting process and analytical development worldwide
    - China- still need to do in vivo potency separately for China - have not seen change in this area (Gardasil license with an in-vitro potency test vs an in-vivo test)
    - Chin has the goal of being an exporter of vaccines
- Everyone wants to get on the mRNA bandwagon- we have made it look easy. Devil is in the details..
- Gaps in ICH? Unless its safety or efficacy, takes a while for ICH to catch up.
    - mRNA mfg is not a complex process
    - More open access to information
- RNA good for speed- not sure how good it is currently for long term protection