Table 27: New Advances and Applications in Real Time Release Testing

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Scope:

Real time release testing (RTRT) is the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls (ICH Q8 (R)). While the concept of RTRT has been in place for some time, the number of industry examples of RTRT in the manufacture of biological products has been somewhat limited. Advances in technology (methods and controls) and increased process understanding could accelerate the utilization of RTRT in the control strategies of biologics production. The purpose of this round table will be to discuss ideas and share experiences (both challenges and benefits) with RTRT.

Questions for Discussion:

1. Although there is a formal definition for RTRT in the ICH guidance, what has your experience been when discussing RTRT? What does it look like to you?
2. What are your experiences with using RTRT in a control strategy?
3. Are there any technologies that are or should be considered in RTRT? What are the factors in selection (speed, efficiency, better information) and tradeoffs?
4. If you have tried RTRT in your strategies, what are some of the challenges experienced? What are some of the benefits?
5. For industry: have any strategies been accepted by multiple Health Authorities? For HAs: are there examples of accepted RTRT applications?

Discussion Notes:

1. What is your vision for real time release?

- Discussion about practicality of RTRT (i.e. what methods/technology is currently amenable for RTRT.)
- N.D. shared some examples: Separations methods are amenable. Bioassay are not. Cell based assays are not. Nothing in-place for RTRT. Could some of the lengthy release assays be done upstream? Can it be demonstrated that upstream material would be representative of final release material? Is there any regulatory precedence for this?
- Company X is in discussions with regulatory agencies. Suggests that sponsors need to take small steps. If we don't try, we will never know.
    - Additional discussion on lengthy tests:

    - Need to adopt new tech or use models for Bioassay. Need open dialog with regulators.
    - Questioned if anyone has implemented rapid methods for sterility or endotoxin? Some companies are evaluating alternative techniques but it is still an offline test.
- Discussion then shifted on maintenance of PAT.
    - M.H. from Process side. How does PAT pair with adaptive processes? Can testing be more reactive to the process?
    - Discussed Minh Luu's presentation from the morning. Suggest to review this publication: Multi-attribute Raman spectroscopy (MARS) for monitoring product quality attributes in formulated monoclonal antibody therapeutics https://www.tandfonline.com/doi/full/10.1080/19420862.2021.2007564
    - L.L. shared the experience of bringing in the vendor. The use of Raman (NIR). Multivariate data analysis is still necessary, and many samples are necessary to build that model. Have to build new model for every mAb?
    - Model maintenance in critical with this technology.
    - What are pros and cons of Raman vs FTIR. Raman is star in biopharm processes because it is blind to water. Is certain examples IR is promising and new systems have very low LOD.
    - MAM are also being considered as a step towards RTRT.
    - In addition to real time laboratory testing, QA procedures could be improved to be real time.
    - How much advantage in non-technology advances for release testing.
    - L gave example of removing HCP step testing steps post process validation. And questioned if the the regulatory framework be updated? K seconds this idea. And shared experience of not being successful in removing HCP test. While, Company X has been successful. Some impurity tests are part of release step validation data exists to show clearance. N shared different experience with different agencies.

2. To companies that haven't taken an RTRT approach, what are some challenges?

- Difficulty changing minds on traditional ways of thinking.
- Difficulty to gain global consistency of acceptance by regulatory agencies. No one wants to do duel testing is one region doesn't accept supply from RTRT batch.
- Not all tests are amenable to RTRT.

3. To companies that have taken steps towards RTRT, what are some examples of success?

- DP solutions: Move some tests to formulated bulk. Show that nothing is changing during bottling process.
- ADC: Not all tests are completed on ADC. Some methods are easier to test on small molecule itself or large molecule itself. So don't test on the final product. Not framed in the literature as RTRT but follows the same principle.

4. Final Thoughts:

- Reflect on what we are already doing. Could this be considered to push RTRT to the next level.
- What information is critical in WCBP and what information is redundant. A lot of import testing is redundant. Difficult to manage supply chain without delays to patients if not release testing is not globally accepted. Can mutual agreements be set up? Can we push for a waiver and no longer waiver case by case? Sometimes more political than scientific because creates jobs for the region. Suggest to start discussions with FDA, EMA or ICH countries. Better to start discussions earlier and make scientific arguments. Other agencies may have more rigid regulations.
- RTRT could be achieved by different approaches for different tests. Some steps towards RTRT include:

    i. PAT of final product.

    ii. Testing an in-process test.

    iii. Validating process control and remove confirmation testing.

    iv. MAMs

    v. Modeling

    vi. Streamlining/automating QA