Table 5: Translating cGMPs Between Traditional Large-scale Modalities and Small-scale Personalized Medicines

Session 1:
**Facilitator:** Matt Kalo, *Genentech, a Member of the Roche Group*
**Scribe:** Rich Cornell, *Pfizer, Inc.*

Session 2:
**Facilitator:** Beth Anne Bort, *Pfizer, Inc.*
**Scribe:** Elizabeth Schmidt, *GlaxoSmithKline*

**SCOPE:**
cGMP system expectations for traditional large-scale modalities are typically well defined but subject to ever changing industry pressures and regulatory expectations. Implementing phase-appropriate cGMP criteria is critical to project success and can significantly impact the ability to take a product to market, especially for low-volume products, personalized medicine modalities, or other products that differ from the traditional modality workflows. The ability to meet standardized cGMPs for non-traditional modalities can be challenging!

This roundtable will discuss compliance expectations for small-scale products, method validation lifecycle expectations, the use of CMOs for traditional and novel processes, as well as minimal compliance standards for smaller and start-up companies.

**QUESTIONS FOR DISCUSSION:**
1. How are we satisfying the testing requirements for personalized medicines with special consideration to low-volume batch yields and low-volume sample size restrictions (i.e., safety testing, qualification, and validation)?

2. At what step in the product development lifecycle should method validation be required? Does this differ between modalities?

3. Are there emerging considerations for the onboarding and use of CMOs to support personalized medicines? Are their critical lessons learned from traditional modality CMO partnerships at large-scale that can be leveraged to support accelerated or low-volume projects such as personalized medicines?

4. What are the minimal compliance requirements that should be implemented for companies requiring leaner strategies, such as start-ups?

**DISCUSSION NOTES:**
**Day 1:**
1. How are we satisfying the testing requirements for personalized medicines with special consideration to low-volume batch yields and low-volume sample size restrictions (i.e., safety testing, qualification, and validation)?
   - It was acknowledged that the testing requirements of personalized medicines are very different from that of traditional modalities like mAb due to the nature of the dosing regimen (often single use) and the fact that many of these products are designated breakthrough therapies (higher risk tolerance).
Regarding stability testing, the following points were made:
- What does one want to claim? Stability for an extended period or in use testing.
- You test at end of shelf life and how long it takes to get back to the patient.
- Identify CQA's and study extremes in a bracketing approach?
- Given the unmet medical needs that these medicines treat, one can take a more risk-based approach and focus just on in-use testing?

Regarding testing in general and how to deal with low volume the following were discussed:
- The use of a reference standard was brought up. Can a reference standard be used to compare from sample to sample?
- In the absence of a traditional reference standard being available in a large enough quantity to satisfy all testing needs, can some sort of a surrogate material be used as a comparator?
- The regulatory colleagues at the table provided the following perspective:
  - Personalized medicines are very early, and everyone is learning.
  - Expertise in FDA expanding and open to outside the box thinking. Very open to discussion. Accepting new ideas and flexibility if industry gives scientifically sound rationale.
  - Health authorities are looking for the industry to lead the way and regulators will observe and regulate as necessary.
  - Clinical outcomes and benefits allow risk. Breakthrough therapies get regulator priority attention. If you're not breakthrough then it’s hard to get regulator attention.
  - Regulators learn from industry.

Though sample volumes are low, there are other ways to help ensure solid cGMPs are maintained and these were discussed:
- Does dosing happen at a hospital. Need trained cGMP operators?
- Closed processing and single use eliminate individual involvement / people interaction. Validate process for sterility.
- Qualify equipment and devices
- Drive the innovation for more sensitive analytics. Use robotics that R&D uses because they use small volumes. Liquid handlers that can be GMP validated.

In general, there are many unknowns with personalized medicines and some thoughts around the unknowns resulted in the following comments:
- How much product knowledge do you have?
- Start with wider specs and narrow-in as we go to clinics.
- We often don't know the mechanism of action and the CQA's impacting potency or clearance, but we can focus on patient safety (focus on micro pieces).
- The potential for lifesaving therapies allows for the assumption of more risk based approach and then the patient tolerance adjusts the specs.

2. At what step in the product development lifecycle should method validation be required? Does this differ between modalities?
- Back to the early days of mAb technologies. Control reagents and use GMPs. What can be controlled and focus on that.
- Validation means repeatability.
- Focus on micro methods. Safety should be primary consideration.
• Focus on robustness rather than the traditional validation elements
• Can we consider this a continuous verification rather than strict method validation?
• cGMPs are the full package.
• The clinical method is the commercial method so validate/qualify phase appropriately.
• Having no reference standard makes it hard to have something to compare to, making it harder to validate. Having a pseudo standard needs to be justified and it takes time to justify the pseudo standard. The reason is because there is batch to batch variability.
• Allogeneic strategy could solve a lot of problems. Give more volume?

3. Are there emerging considerations for the onboarding and use of CMOs to support personalized medicines? Are there critical lessons learned from traditional scale modality CMO partnerships that can be leveraged to support accelerated or low volume projects such as personalized medicines?
• You want to own your own process.
• Need to hire the right people to manage the CMO
• Critical to merge quality systems. Not a lot of companies out there. How to manage cross-product contamination?
• Recommendation to test where you manufacture.
• If you go with a CMO there is wisdom to go early and stick with the same one. Avoid comparability. Too risky to fail comparability.