**Roundtable Session 2 – Table 13 – Method Transfer Challenges at CMOs/CROs**

Facilitator: Babu Kunnel, *Arcus Biosciences*

Scribe: Claudia Gributs, *Eli Lilly and Company*

**Abstract:**

With development of large molecules as therapeutic agents in the pharmaceutical industry, a number of service providers for drug manufacturing and/or testing has also been established across the globe. Small and large biopharmaceutical companies increasingly depend on contract manufacturing organizations (CMOs) and contract research organizations (CROs)/ contract testing labs (CTLs) for their manufacturing and analytical testing needs. By outsourcing the above activities, companies can develop and obtain regulatory approval for medicines much faster than if they had to build their own internal capabilities. The above opportunity also presents challenges for transfer and establishment of GMP compliant analytical methods in a timely fashion, a key component of a successful manufacturing process transfer. The round table discussion on this topic is to understand the common method transfer challenges encountered by the industry and ways in which the issues are resolved.

**Discussion Questions:**

1. What is your role in method transfers to CMO/CRO/CTLs?
    a. Do you outsource analytical testing to CMO/CRO/CTLs?
    b. Are you a CMO/CRO/CTL who receives analytical methods?
2. What was the nature of the transfer (early/late stage, internal to CRO, CRO to CRO)?
3. What are the major challenges that you have encountered during the method transfer?
4. Are there any recommendations that can be followed to proactively avoid pitfalls?
5. What are some best practices for troubleshooting and resolving technical issues during method transfers?

**Notes:**

*The term "CTL" (contract testing lab) is used as an abbreviation for "CRO/CMO/CTL" throughout these notes.*

The round table discussion included scientists from pharma companies and from CTLs. Participants had experience with transfers for established modalities (e.g., mAbs) and new modalities, in early and late stages of development. Scenarios of method transfers from a sponsor company to a CTL and within a CTL (e.g., from the CTL's development lab to their QC lab) were discussed.

Five types of method transfer challenges were identified. Best practices for avoiding or more quickly resolving issues were shared.

**Gaps in contract or quality agreement:**

- Scope of the agreement may have gaps. Recovering from this is difficult. It is important to spend time up front getting it right to save time later. See the two bullets below to reduce risk of gaps.
- There need to be meeting minutes for the initial discussions to document what was said and to ensure that all items are included in the agreement.
- Before finalizing the CTL choice, visit the site to understand what you will be getting/not getting.

**Insufficient clarity and/or completeness of method instructions and supporting documentation:**

If the method or supporting technical document does not contain all the critical information, method transfer issues may ensue. This risk is higher for non-platform methods. To mitigate this risk:

- Ask the CTL to write the local draft method before starting method transfer work. Authoring and reviewing the draft method often reveals information gaps and/or misunderstandings between the sending and receiving lab.
- For methods that may be used for multiple analytical properties, clearly define the scope of the method transfer. For example: transferring just the ID portion of a method that could be used for ID and charge heterogeneity.
- Ensure that the quality agreement includes access to chromatography to allow detailed review of the raw data.
- Hold a meeting where experienced scientists from the sending/receiving lab go through the method together. Discuss even small details like pipetting technique. Investing this time up front will save time later. This is particularly important for complex methods (e.g., bioassay) or if there is a desire to cut method road testing to save time and cost.
- Perform wet lab work before the transfer, if possible. For example, method road testing, on-site demonstration and training, or a video of how the method is executed in the sending lab can be very helpful.
- Talk through the assumptions used to calculate the material quantities for the transfer (e.g., single vs. multiple aliquots from the same vial). This reduces the risk that the receiving lab will run out of sample during the transfer. Include some extra, to cover unexpected situations.

**Communication issues:**

Effective communication, including face-to-face interaction, is crucial for successful method transfers.

- Building a partnership mentality (not an “us versus them” mentality) significantly improves the working relationship. Ensure that team members are empowered to speak up and that their input is heard.
- Consider face-to-face interactions during a method transfer:
  - Method transfer kick-off.
  - Method training.
  - During investigations.
  - If travel isn’t possible, then use video tools where possible.
- Do not assume that different sites of the same CTL operate the same way and that the sites communicate with each other.
- Provide project context by sharing information and milestones. If the timeline changes, communicate it quickly so that the CTL resources can be leveraged for other work.
- Prepare for the future. While the method transfer is in progress, provide a sample forecast so that the receiving lab can appropriately plan and execute local activities to be ready for testing the first routine sample (e.g., train additional analysts, set up LIMS system).
- Periodically touch base with the receiving lab on material inventory status (e.g., reference standard, control sample…) Careful: do not bog the lab down with too many requests for information.

**Timeline delays:**

- Method transfer timeline and other expectations are not always sufficiently clear. Define and agree on the exact scope of work at the beginning of the project. For example: number of runs, which reagents will be supplied by the client vs. sourced by the receiving lab.
- The timeline may not be realistic or complete:
  - The contract is sometimes developed by a sales person at the CTL. More accurate plans are developed when scientists talk to scientists and when QA is included in the discussion. Some CTLs have technical project managers, which helps significantly.
  - Seasoned project managers/scientists are more likely to develop realistic timelines.
  - Investigation timelines are hard to predict.
- Most method transfers start late. Common scenarios are:
  - If takes longer than expected to sign the contract and the sending lab is unable to quickly get the required materials to the receiving lab; as a result, the reserved time slot is missed and capacity issues ensue. Plan ahead. Get materials ready early (e.g., reagents, reference standard…) so that lab work can start as soon as the contract is signed.
  - Lab capabilities may not meet the requirements of the method. An analytical scientist should be included in the choice of the CTL to reduce this risk.
  - Resources at the client company often split their time between interfacing with the CTL and doing other work. This leads to delays in responses and slower progress.
- Strategy changes during the method transfer.
  - Change orders take time. Look for ways to minimize impact. For example: Notify project manager and partner with them to identify options. There is often some flexibility if there is an established relationship between the client and CTL (e.g., it may be possible to start the work at risk).
- Other options for addressing timeline delays:

- Sponsors sometimes resort to emergency implementation of the method internally to allow GMP testing to start as planned.
- For investigations, analysts and SMEs should work through the investigation directly, rather than relaying information through project managers.

**Information sharing barriers:**

- If the receiving lab uses paper notebooks, it can be more difficult to collaborate on investigations.
- For ID methods, it is difficult to demonstrate specificity when the sponsor does not have access to information related to the other molecules at the CTL's site.
  Proposed solution: Specificity can easily be demonstrated against other products from the same sponsor. The CTL can generate specificity data for the other molecules at their site, keeping the sponsor blinded to the detailed information. The data remain at the site and get shared directly with a health authority when needed.