Table 27: Best Practices for Working with CMOs for De-centralized Manufacturing

Facilitators –

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Scope:

Centralized manufacturing has been the dominant model for large-scale production since the Industrial Revolution. In contrast de-centralized manufacturing (DCM) also referred to as 'redistributed' manufacturing relies on leveraging manufacturing capacity across several geographic regions, providing local and responsive manufacturing, typically customized to the end user. The DCM concept is especially attractive for certain modalities/products such as cell and gene therapy (CGTs), primarily to overcome challenges associated with long-term storage and long-distance shipping.

CMOs (Contract Manufacturing Organizations) with established platform processes along with comprehensive knowledge of the scientific, technical, and local regulatory requirements and presence in various geographical locations can bring unique capability and capacity. DCM approach also allows utilization of multiple CMOs having unique expertise in distinct unit operations such as initial processing, fill-finish etc.

In addition to several advantages, DCM, also poses challenges such as overall quality control, batch-batch reproducibility and integration/handover of information from one site to other, local regulations, batch sizes and cost as a result of running and managing multiple sites.

In this round table, we plan to discuss key advantages, disadvantages, challenges and individual experience when working with CMOs for DCM

Questions for Discussion:

1. Are there some technologies more suitable for DCM than others?
2. Experience working with/ implantation of new technologies/equipment's
3. Dos and Don'ts when working with CMOs for DCM (keeping CMOs name anonymous)
4. Additional complexity encountered when using multiple CMOs for the same product and best practices for meeting these challenges.

Discussion Notes:

January 26 and 28, February 1 and 3, *combined* –

Highlights:

- Need to set clear expectations up front and make sure they are clearly documented in contracts (supply agreement, quality agreement, etc) - COMMUNICATION IS KEY
- Challenges on both sides (CMO and sponsor) for alignment across sites , Need alignment between sponsor and CMO. Even internally aligning can be difficult, with-in multiple sites.
- Understand capabilities of CDMOs, different modalities, assays, phase appropriate

Challenges:

- Multiple sites for DS and DP
  - Differences in mfg capacities and capabilities and design
- Acceptable to FDA assuming comparability and same specs
- Different agencies may have different considerations
  - EU (Czech) and China only accept one mfg site
  - Puts pressure on supplies
- Ends up having to allocate materials to very specific regions
- Comparability -
  - Not necessarily an additional challenge w/ multiple CMOs
  - Have more frequently been asked for comparability in IP data
  - Some CMOs may push for their own IP control strategies
  - Need to try to reconcile sponsor vs CMO strategies
- Negotiation
  - Need to be agile and have relationships w/ satellite test sites
- Start by looking at CMO platform
- If not wanted can pull out of the contract
  - Having discussions early on
- Need understanding of CMO rationales

- Testing
- Ideal to have it at a single site
- Ideal to have on site
- Best practice to have at
- Key takeaway
- Have conversations early and in depth and translate to contract
- High level of data review of the contracts
- Quality agreements need cross functional review
- New key responsibilities
- Need to include contracts together (MSA, QA, MFG contract)
- Need to update contracts and re-review for changes from clinical to commercial
- Need to make sure non-GMP info is also included in contracts
- Accountability of subject matter experts
- TT docs - same for each site?
- High level, yes, but can be tweaked
- Multiple CMOs leads to more complexity - hard to keep things aligned across sites
- Need continuous alignment
- Oversight that is split adds another level of complexity
- In partnership - need same early definition, continuous dialogue
- Need very defined roles and responsibilities
- Especially when things are moving very quickly
- Having established partners -
- Can have impact when people leave
- Always in flux
- Can be a large turnover of personnel at CMOs
- Can be a big issue, especially if only one point of contact
- Interesting lesson learned:

- Early phase contract and testing contract - didn't opt in on PM
- No flow
- PM is very important
- Need clearly defined roles
- Emerging organizations may understatement need for PM
- From CMOs:
- Large client: many FTEs involved w/ specific roles
- Large clients want a few sites
- Sometimes start competing w/ yourself
- Best practice: have a few sites, not just eggs in one basket
- Having a single person as a contact is a risk
- Small company: might have 1 client who understood the process
- Good for a company to understand their strengths and weaknesses and what they might need from a CMO
- Each has a unique set of problems
- Again: communication is key
- Roles clearly defined
- How to entice CMOs to give you a slot?
- Tight right now
- Guidance came from mgmt
- Harder for small companies to compete
- Option to ask CMO to be ready to jump in if a slot opens
- Choice of CMO is very important - level of flexibility
- Safety slots / sharing materials between sites
- Quality was the biggest hurdle
- Key during the pandemic
- Difficulty in transferring of potency assays that could be key assays for the Drug substance and Drug product that could be needed for release

- Raw materials and supply to different countries and ensuring quality
- Gene therapy -
  - CDMO location is crucial to ensure samples are obtained in a timely manner
  - Capability for complex analyses
- CDMO selection process
  - Geographic location
  - Based on expertise in areas of manufacturing
  - Experience with early development or late stage or commercialization
  - Drug substance or Drug Product or end to end-
  - Advantages and disadvantages of end to end approach
  - Quality Systems to meet stage of the product
  - Compromise between the organization's systems versus the CDMO
  - Quality agreements in place
  - Service agreements in place that are clear and well understood to avoid delays/ payments etc
  - Relationship and open communications – Client and CDMO
  - Project Management
  - Opportunities for flexibility especially with early stage to accommodate changes associated with the development of the product
  - GMP
  - Facility
  - CMO's regulatory experience
  - Understanding of Critical process parameters / Knowledge space
  - Process and Analytical tech transfer depending on the stage of the program and demonstration of a successful transfer
  - No list of CMO's exist that provides the capabilities
  - A network of CMOs – early phase to late phase

- Suggest having a list available on CMO's capabilities on vaccines – bacterial or viral , Mabs , etc.

- Challenges with CDMOs
  - While there is a platform approach that is well established for producing Mabs, vaccines, gene therapy are more complex and unique
  - There are different issues at an early stage versus late phase
  - Devices – use of an off the shelf device ?
  - Regulatory readiness
  - Container closures/ Devices/ Extractables and leachables
- Do's and Don'ts when working with CMO's
  - Agreements and Quality agreements
  - Clarity and expectation on the Quality systems as it may not match your expectations
  - Remember you are not the only client
  - Relationships while working with the CDMO
  - Flexibility