Roundtable Session 2 - Table 15: Small Company CMC Challenges

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Abstract:

Novel technologies, limited resources, and fast changing priorities are ubiquitous within biotech. Small companies, however, experience these challenges to an extreme not seen in large organizations. A lack of platform experience or QA resources is different than having never conducted an internal manufacturability assessment or having no QA group. A late-stage clinical success can mean that the CMC workload multiplies overnight. The team that was designed to support a single early-stage asset will struggle to execute BLA/commercial readiness and advance the pipeline programs that were waiting in the wings for clinical proof of concept. Small companies must do more with less, but also recognize when more resources are required, to solve these problems and grow sustainably.

Questions for Discussion:

1) How can the developability or manufacturability of new lead candidates be assessed without prior platform knowledge and limited in house characterization resources? Could a meaningful developability assessment be performed with only gel electrophoresis and functional binding assays as analytical readouts?

2) Small companies typically outsource GMP manufacturing activities. Engaging in multiyear, capital-intensive, relationships with a single vendor. How should a new CDMO be assessed before committing to a Phase I development and manufacturing campaign (DNA to IND)?

3) Small companies sometimes operate through early-stage clinical trials with no dedicated QA function. As programs enter late-stage trials and approach commercial applications the QA workload expands rapidly, and specialized CMC QA expertise is often needed. How should the QA function at a company entering phase III clinical trials for the first time be structured?

4) Success creates new problems. When small companies see positive late-stage clinical data, demands on the CMC organization expand rapidly. How does the structure of a CMC team designed to support a single clinical stage asset differ from one preparing for commercial launch and managing a growing pipeline?

5) As small companies grow, the place of CMC within the organization can shift dramatically. Budgets become more development heavy, and responsibilities previously assigned to research shift to the technical development organization. How should CMC leaders communicate about these changes up and down the organization chart?

Notes:

- First discussion topic was testing logistics/challenges for small company to manage a CRO

- Generally, collective knowledge within the company is used to manage the CRO with technical challenges.
- Having a PM, a good one, is very helpful to manage the CMC activities. However, a contract PM is not sustainable
- May companies use CMC-reg consultants instead of their own employees
- What are the experiences with CMO- QA?. Some of them are good and some are not
- Having a good relationship with CMO is very important.
- From the regulators standpoint, quality system, deviation managements, audits, change control etc are main concerns wrt CMO and the sponsor needs to be aware of criticality of the above aspects
- Agency wants to make sure that the CMO's quality system is well understood.
- Quality audits are done yearly.
- Some companies get involved in the program early on, understand the third party outsourcing, if any
- Involve in developability and manufacturability aspects if possible early on.
- Some cases, many of the early information was given by the in-licensed entity.
- How do you select any CMO?
    - Many times, the contract was done prior to many of the participants got involved in the project!
    - There for understanding the gaps, mitigating the risks and management was the only option available
- Generally, try to keep all manufacturing and testing including E&L at the same place
- Some cases selection of DP CMO was constrained due to specific formulation requirement (solid dosage form)
- Internal tracking and linking the data through the doc system is important.
- Method transfer is another critical aspect: Gaps in the transfer could potentially hold up a BLA.
- Get involved in the method transfer plan early on
- Regulators suggest even meeting to discuss reference standard strategy but in reality, getting a meeting is challenging
- Regarding agency interaction, the sponsor needs to be very specific about the question for agency to respond. Generic question will not be answered by the agency. It will be difficult to provide a feedback based on incomplete/limited information provided by the sponsor.