**Roundtable Session 1 – Table 9 – Advanced Manufacturing**

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**Abstract:**

This roundtable discussion aims to cover current trends in advanced manufacturing, including efforts to increase manufacturing agility, reduce susceptibility to drug shortage, improve measurement and control of product quality, and accelerate the delivery of medicines for patients. Participants will share insights and experiences with advanced manufacturing strategies and provide valuable perspectives on the advantages, challenges, and risks of implementation in the dynamic regulatory environment.

**Discussion Questions:**

Question 1:

What advanced manufacturing strategies (process analytical technology, continuous manufacturing, distributive manufacturing, artificial intelligence, etc.) are most applicable for biologics across industry?

Question 2:

How has the implementation of process analytical technology (PAT), to supplement or replace traditional release testing, impacted time to release? What are the challenges internally and externally?

Question 3:

How does industry view the Advanced Manufacturing Technologies Designation draft guidance?

Question 4:

What has been the impact of FDA initiatives like the Emerging Technology Program (ETP), CBER Advanced Technologies Team (CATT), and the Framework for Advanced Manufacturing Evaluation (FRAME)?

Question 5:

What has been the impact of international initiatives like the EU Innovation Network, Quality Innovation Group, or the Innovation Task Force? How can companies manage different global programs internally, and what are the challenges if any?

**Notes:**

Often hear Adv Manuf and consider continuous manufacturing. Clarification was provided – Advanced Manufacturing isn't continuous manufacturing per se. Other examples include distributed manufacturing, applications of artificial intelligence, There is opportunity in biologics

manufacturing for continuous but considerations are beyond this. Moving in that direction for biologics.

Recent events (viz. obesity peptides) highlight considerations as to whether synthetic molecules can be considered biologics…. MOA and process considerations are more aligned with biologics than with synthetic organic molecules. There have been examples with these peptides by one innovator to apply continuous manufacturing.

Certain oligos (under NDA) are also considered more biologic in manufacturing and processes. ICH Q2 and Q14 are focused on advanced analytics and control strategy development and maturation (lifecycle) as the process develops. Another consideration is the selection of technologies that are readily transferable and can be implemented in the process. This is more prominent (PAT) in small molecules than in biologics owing to the technologies that need to be applied to cells and other biologics.

There is trend for process developers to apply guidance and examine the implementation of transferable technologies.

As process development is initiated is there consideration for continuous manufacturing? Can these considerations make implementation and development faster? More effective?

Lifecycle management of method sin the control strategy is also important to process development and application of advance technologies. Is Lifecycle management intimately tied to advance manufacturing and control strategy development. The advancement of the methods through the lifecycle from characterization through final validated methods. Some methods will survive and others will remain characterization or be eliminated. Assays and control strategies are dynamic. Investment in analytical technoiloges to better characterize the product and process is valued by the regulators.

There are significant utilization of platform manuf methods and platform analytical methods. Derisking the product and the process is a significant aspect and provides benefits. Real time analytics has advantages. Doing the same thing will not provide new results.

There is a need to communicate to vendors regarding what is needed in to support new processes and characterize products and processes to derisk development. New technologies leveraging multi-attributes may hold advantage and be needed.

Will new technologies and analytical techniques require special consideration and assistance. We need to apply new technologies. There is a hesitant by established companies to take risks with new unproven technologies. There is an imbalance in risk and inertia.. small companies cant afford risk and estabsihed companies do not necessarily see benefit of changing what works. Does the burden of risk lie with large companies?

Small biotechs have a high risk position and limited assets.

Can large companies tie exploration of new technologies in parallel with exploration or acquisition of new assets (i.e as part of M&A).

Does the new draft Guidance on Enhanced Technologies Program (ETP) the FDA is pushing advanced technologies and MAM techniques have been part of this. These programs CATT and

ETP have multiple pathways for engagement of small biotechs to benefit. CBER CATT representatives have discussed and indicated that you do not need a new product. They will invite companies (e.g. Lumacyte) and be involved in the technology and understand or train. Companies with new technologies can request a meeting to introduce the technology to the agency and potentially have follow-up and assistance.

New technologies are providing alternative solutions to existing critical problems (ie cell viability).

In addition, there are NIST projects and other pathways.

QAG – need to share what is happening and be transparent on new developments

Technologies appear w/o context or application or pre-amble and can take companies (manuf) by surprise.

US needs to be a leader in helping other smaller market countries in understanding how to implement new technologies.

Communication by programs needs to improve communication and make the decisions and recommendations more readily available.

Many of the technology discussions occur pre-, pre-, pre-IND which causes challenges. It then becomes unclear on how to communicate with the agencies when there is a detachment between the technology, a product and a filing.

By leveraging advanced testing we can potentially advance manufacturing as well.

CATT and OPQ tend to make recommendations in a product-agonistic manner. This results in confusion as to how to communicate with the agency.

The exact relationship between various programs and guidance is unclear. It is also not clear how regulatory or guidance meetings in these programs fit together. How do products progress between programs? This is unclear.

EMA referenced the quality innovation group in EU which can also be leveraged for implementation of new technologies to fully characterize new modalities.

Key Question- Can data from new technologies be shared with regulators as part of post-approval? i.e. How are new technologies bridged vs initial or approved technologies?

There are often concerns around who to contact on these issues and whether there will be a response. In many cases there are email addresses. It seems that those with inside contacts have an advantage (ie ETP program). Sometimes it seems to be email and wait/hope. It is challenging to get contact names to facilitate. It was not clear whether there are business program managers who can provide support and be contacts. The general impression is that they have been responsive. Timelines for responses are unclear and not specified but are Type C-like (75-days) for responses. There is high level of acceptance and a broad range of topics. They (regulators) also want to learn.

There are examples of instances in which the advanced method/testing has been leveraged to derive an advanced manufacturing process.

How do programs graduate through the various programs?

How can multi-attribute methods be used to enhance adv manufacturing and permit implementation of new manufacturing technologies?

What near-real time technologies can be applied to streamline release testing?

Can these be applied to permit adaptive (change on the fly) manufacturing? This has been a topic of discussion. In small molecule CMC there have been examples for adaptive manufacturing, but what technologies are being applied in biologics? It is not clear if anything has been applied or filed for adaptive technology in biologic. None known in biologics. Sterility was provided as an example of accelerated testing.

Can these technologies enable utilization of PAT for real-time adjustment in biologics processes? There is real time release in biologics (limited cases) with the majority around cells, but there is opportunity for expansion. Raman and other technologies have been applied and are continuing exploration . Real time release exists in biologics (cells) and there is a push to grow this.

There is also opportunity for the real-time/near real time technologies to help address process deviations by providing the data to support impact evaluations and risk assessments.

There us opportunity for real time spectroscopic multi-attribute technologies to be more broadly applied. Specifically IR and Raman technology has been applied for real-time.

Can AI and real-time release be used together to minimize or eliminate the need for release testing? There are challenges on AI implementation. What justifications are needed to support implementation and to validate the outcomes?

There is a draft guidance for in process control for AI. How far can this go?

Is there value in AI modelling and predictive modelling to be leveraged better in process monitoring or process development and material release. Does this eventually result in the elimination of testing?

There will need to be significant scientific support and justification for any new approach.

There needs to be a differentiation between predictive modelling and release testing/monitoring with models.

What problems might drive evaluation of a new technology?

Come from the top

Business driven decision

AI and other technology

There global implications and there must be a will to change…. Culture and commitment make a difference

Variances across global agencies and their tolerances to risk and innovations creates issues

- Huge commitment by drug companies with multiple interactions/filings
- In country testing also represents a challenge in the cost and implementation burden/risk for new technologies.

Consensus is that Biopharma is very conservative and slow to adopt new approaches. There is a tendency to watch from the sidelines.IS good enough, good enough and what is the motivation for change? Does there need to be a problem to fix? Improve what is being done versus invest in new (new analysts tech; versus new methods; versus new manuf processes).

The example of flow cytometry as a traditional technology that could be supplanted by new technologies. This would require significant investment in equipment, in all affected labs and also address infrastructure (quality and training). These challenges create inertia to maintain a status quo.

Animal testing and cell based is a proven example of transition of technology. These efforts require support and initiatives. It comes down to risk and money, as well as assurance of patient safety and efficacy.

Being the first to implement a technology is not always productive. Innovation and being first does not have the requisite rewards so the default is to maintain status quo.

If a technology provides the opportunity to reduce the cost of operation by reducing the complexity of OOS and deviations (investigations)? Can multiple methods be replaced with a single method? Is tere an effect on speed to market or speed to patient (think cell therapy). Is the cost-benefit of introducing a new technology adequate?

Not process related but, with 900 candidates in biologics globally is there opportunity to use AI to somehow facilitate clinical trials?