Advanced/Innovative Manufacturing 101

What are advanced/innovative manufacturing technologies?

- FDA defines advanced manufacturing as "a collective term for new medical product manufacturing technologies that can improve drug quality, address shortages of medicines, and speed time-to-market." These technologies often "integrate novel technological approaches; use established techniques in a new or innovative way, or; apply production methods in a new domain where there are no defined best practices or experience."[1]
- Examples of advanced/innovative manufacturing technologies (categories and specific examples) used in biologics, cell, and/or gene therapies include:
    - Process Digital Twins
    - Advanced analytics, "big data", and machine learning
    - Adaptive processing and prescriptive process controls
    - Multi-attribute methods (MAM)
    - Real-time release (RTR) testing
    - Performance qualification (PQ) tuning through additives and/or real time process adjustments
    - Portable biomanufacturing
    - Continuous manufacturing
    - 3D printing

What are **NOT** advanced/innovative manufacturing technologies?

- New biopharmaceutical modality types (e.g., cell and gene therapies, complex biologics)
- Well-established, commonly used manufacturing processes. Examples include:
    - Fed-batch and/or perfusion bioreactors
    - Alternative cell line types (e.g., non-CHO)
    - Custom media formulations

What are the **potential benefits** of advanced/innovative manufacturing technologies?

- Optimize efficiency and promote scalability for medical product developers and manufacturers by:
    - Establishing novel pathways for active pharmaceutical ingredient (API) and drug substance synthesis.
    - Shortening supply chains, increasing manufacturing resilience, and reducing costs long term through process intensification[2].
    - Improving process control and automation to reduce variability and increase product quality assurance.
- Improve public health and global impact by:
    - Providing new tools to address drug shortages and expediting emerging therapy availability.
    - Enabling potential treatment personalization through adaptive production of smaller manufacturing lots.
    - Increasing environmental sustainability through improved controls, parameter optimization, integration of supply chain innovations, and potentially mitigating supply chain challenges, e.g., potential to improve capacity.[3]

What are the **current challenges** to implementing these technologies?

- Requirement for large capital, resource investments, and workforce up-skilling that companies may not be willing to embrace without understanding long term benefits.

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[1] U.S. Food & Drug Administration, 'Advanced Manufacturing', https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/advanced-manufacturing, (accessed 19 January 2022).

[2] National Academies of Sciences, Engineering, and Medicine. 2021. *Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations*. Washington, DC: The National Academies Press. https://doi.org/10.17226/26009.

[3] Jin et al., *Impact of advanced manufacturing on sustainability: An overview of the special volume on advanced manufacturing for sustainability and low fossil carbon emissions*, Journal of Cleaner Production, Volume 161, 2017, Pages 69-74, ISSN 0959-6526, https://doi.org/10.1016/j.jclepro.2017.05.101.

- Requirement for more robust CMC submissions than required for current technologies (tighter controls, more established conditions) with unclear understanding of regulatory expectations.
- Uncertainty in regulatory expectations and lack of clear regulatory pathways for advanced/innovative technologies.
- Limited opportunities for discussion with regulatory agencies and other stakeholders (e.g., technology/product developer) on these technologies and what might be needed for implementation.
- Utilization of CMOs which may not have an incentive to implement and support advanced/innovative technologies in the absence of clear regulatory guidance/acceptance
- Limited sourcing (e.g., new technology likely limited to one or few vendors)

What are key ***regulatory* aspects** that are missing for the adoption of these technologies?

- Clear FDA framework for the use of these technologies; currently there is limited guidance, particularly in the biologics space. This can provide sponsors a better understanding of the risk-benefits of adopting these new technologies.
- Transparency into regulators' current thinking by publication of "leapfrog" guidances (e.g., initial thoughts on emerging areas and technologies such as the 2017 Guidance *Technical Considerations for Additive Manufactured Medical Devices*) in order to bridge current guidance with tomorrow's innovations.
- Consistency among review and inspection staff.
- Global discussions to move toward more global acceptance, convergence, and standardization of advanced technologies. If Sponsors are only able to utilize a new approach in one region, creating a business case for adopting advanced technologies will be more difficult (for example different regions will require different development and post-approval maintenance).
    - Broader knowledge sharing across regulatory agencies, mutual recognition/reliance pathways.
    - Opportunity for joint-HA meetings or observer role; allowing sponsors to use *Model Owner's Authorization* mechanism to allow FDA to share confidential information with foreign agencies or international organizations.
    - Harmonization of guidances, expectations, and requirements among global Health Authorities.

What ***non-regulatory document*** related steps can industry and FDA take to promote the use of advanced manufacturing technologies?

- Utilization of small business webinars.
- FDA and industry knowledge sharing including use cases of various technologies.
- FDA/regulator tours of facilities utilizing advanced manufacturing technologies to see firsthand their implementation (manufacturing site visits).
- Industry publication of case studies to help socialize current regulatory practice and acceptance.
- Continued joint participation in technical conferences (e.g., IFPAC) to share knowledge in a pre-competitive space
- Multi-stakeholder consortia on a domestic and international platform to discuss needs, demonstrate new technologies, and discuss implementation to ensure harmonization.