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Engaging with the FDA ETP: Case Studies

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Engage with FDA Emerging Technology Program

The program provides an opportunity for industry to engage and collaborate early with the FDA to discuss, identify, and resolve technical and regulatory issues during a novel technology's development

- Case 1: Portable Continuous Modular Manufacture
- Case 2: Portfolio level primary container change for sterile injectables
- Case 3: iSKID™
- Future Engagement: Co-processed API

Case 1: New Technology: Portable Continuous Modular Manufacture of Drug Products

Continuous Manufacturing enhances manufacturing supply chains and drives access to medicines for patients. With this promise to help transform industry practices came new regulatory hurdles.

- Potential benefits include:
  - Ability to accrue knowledge on the same platform used for development and manufacturing
  - Material conservation- dial in the exact amount of API needed to produce product
  - Opportunity to go fast- launch out of R&D facility
  - Enhanced quality- establish multi-variate relationships using commercial scale equipment, advanced sensors and high data density allow for feedback and feed forward control opportunities

(Continuous Mixing Technology – CMT)

GEA Courtoy Modul™ P

Rotary Tablet Press

In-Line Near Infrared (NIR) Monitoring Probe Mounted in Feed-Frame

Tablet Metal Detector and Deduster

Overview of PCMM Continuous Manufacturing System

PCMM platform allows for seamless tech transfer with no scale up, reduced process validation and inspections, and cost savings

Multiple ETT engagements.

- *Initial discussions on novel PCMM system, control strategy and filing strategy*
- *Subsequent discussions as technology continued to emerge on flexible batch size, use of multiple API batches, and use of NIR-SS.*

Case Study 1 Discussion Points

Flexible batch size

- Flexible batch size and production rate as demonstrated during design of experiment trials, registration stability and clinical runs
- Variable production speed for commercial manufacture

Sequential addition of different API lots

- Manufacture in a continued state of operation by demonstrating that targeted batch quantity drug product is uniform in quality
- Allow sequential addition of different API and excipient lots in the feeders to run for longer manufacturing times

Hybrid Near Infrared (NIR) and soft sensor

- Real time NIR in process testing is part of PCMM integrated control strategy
- Soft sensor provides enhanced method robustness for real time quality assurance

Process Validation/Technology Transfer

- Reduced technology transfer requirements because identical manufacturing equipment and processes used at development and commercial manufacturing sites
- FDA agreed to staged validation approach (concurrent)

Case Study 1 Outcome

- Flexible batch size
- Multiple API lots
- Use of NIR-SS
- Tech transfer/validation approach

PCMM ensures streamlined transfer to the commercial site, eliminating the need for scale up, thereby providing increased agility (since the equipment are like-for-like by design).

In a recent paper, authors from the FDA reported that "CM applicants had relatively shorter times to approval and market as compared to similar batch applications, based on the mean or median times to approval (8 or 3 months faster) and marketing (12 or 4 months faster) from submission)."[1]

[1] DOI: https://doi.org/10.1016/j.ijpharm.2022.121778

Case Study 2: Multiproduct Change from Borosilicate to Valor Glass

Corporate driver to transition from borosilicate glass to valor glass for solution/suspension and lyophilized products (~20MM vials in scope)

Reduction in rejected product, investigations, & remediation

Estimated to take 2-3 years from start to regulatory submission for each product representing a huge time and resource cost

Case Study 2 Discussion Points

Risk-based approach to assessment of the impacted portfolio.

First phase products

- Highest potential impact on glass corrosion/ leaching and greatest product degradation
- Three batches on stability. Bracketing strategy, 3 months accelerated stability data
- PAS submission

Second phase products

- Low potential impact on glass corrosion/ leaching and greatest product degradation
- One batch on stability with 3 months of accelerated stability data
- CBE-30 Submission

Case Study 2 Outcome

- FDA Agreement to bundle worst case products with lesser experiments & documentation as PAS and low risk cases with lesser experiments/documentation and lower reporting category to CBE-30.

- This enabled quicker and more efficient regulatory variations to achieve quality cost savings on the portfolio of products that use glass vials.

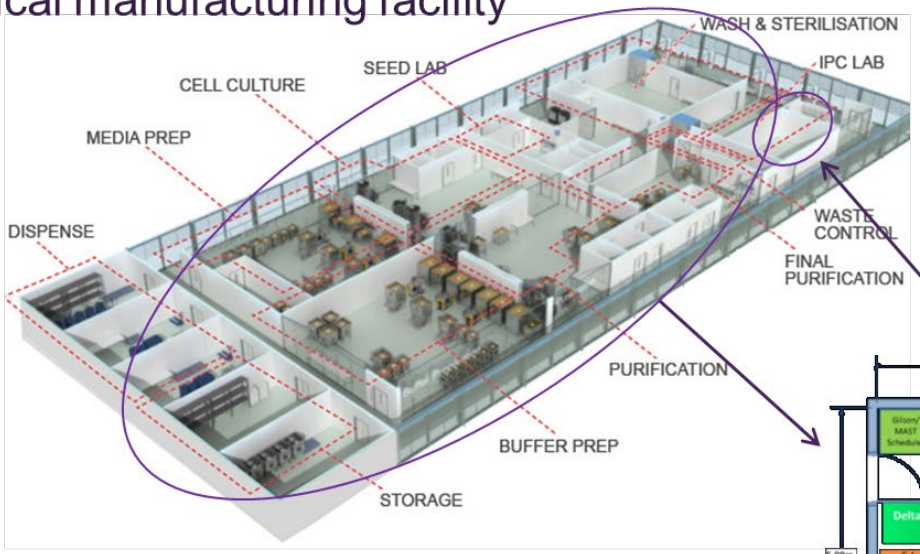
Case 3: iSKID™

- Innovative Next Generation Biomanufacturing continuous and integrated processing platform for biological drug substances
- The technology incorporates a non-steady state perfusion cell culture process integrated to a periodic downstream process that includes continuous viral inactivation
- Scalable to accommodate increase in demand - Current hardware design supports multiple scales
- Integration and automation facilitates improved operational excellence

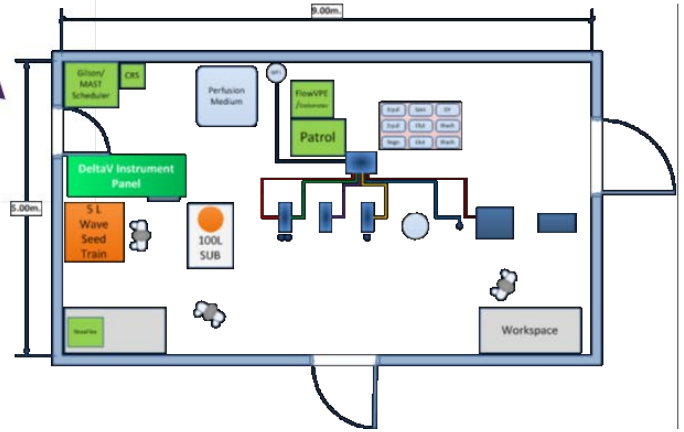
Reimagining Bio-Manufacturing

Current state of the art

Clinical manufacturing facility



Future State: iSKID



Case 3 Discussion Points

- Manufacturing approach, operation and process control for the iSKID™ technology for GMP mAb drug substance
- Microbial control strategy to control and confirm low bioburden for the manufacture of drug substance
- Use of iSKID™ technology for the manufacture of clinical and commercial materials
- Comparability of iSKID™ to conventional batch manufacturing
- Alignment with regulatory expectations on topics such as process validation, technical transfer plan, in-process testing, batch definition, yield calculations, viral clearance strategy.

Case 3 Outcome

The iSKID™ platform is designed to compress process development time, minimize the need for process development, enable process scale-up, reduce the need for product comparability, and improve quality assurance during late-stage clinical development and product commercialization.

Engaged and productive conversation

No major objections or concerns with the proposed approaches

Next Steps identified

- Viral inactivation/viral clearance
- Inputs to consider for late-stage implementation – considerations for process validation, hold time qualification

Future Engagement

- Industry IQ Consortium group plans to approach the FDA ETP to discuss co-processed API.
- Propose to define co-processed API as one that is manufactured in a drug substance facility containing the API and one or more non-covalently bonded nonactive components.
- This distinction from in-process materials or DP intermediates overcomes significant hurdles to commercializing co-processed APIs including GMP manufacturing, primary stability and expiry dating, and characterization and release test expectations.

Global Harmonization

Opportunities and Challenges

- Global Harmonization remains a risk for expedited access of important medicines (US and ROW)
- Industry manufacture products for the world, not one market; thus is “limited” by the “lowest common denominator”.
- Innovation, new technology, lifecycle improvements are hampered by the global “bottleneck” (industry can not afford a few markets that need special manufacturing)
- The lack of global harmonization creates disincentives for new technology and manufacturing innovation

How can the FDA relationship with Industry help

- FDA is a global leader among regulatory agencies; very well respected
- FDA can use its leadership platform to align global agencies; industry has struggled alone
- FDA can help establish a global strategy to achieve faster adoption of new technology; industry can not do this alone
- Build upon the success of the response to the COVID pandemic for rapid access, innovation and improved harmonization

Summary

FDA ETP engagement may be used for a new technology for a specific product or as a platform.

Advice may be sought for a post approval change that impacts a whole portfolio of products.

Multiple companies may approach the FDA ETP with positions that impact how products are registered in the future.

FDA is a leader in regulatory strategy that enables new technologies; we need an aligned global regulatory position to help accelerate the use of new technologies.

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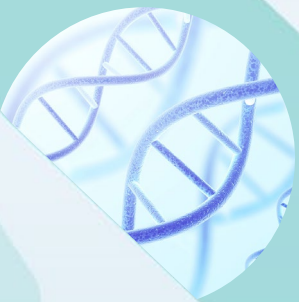

Coming together is a beginning;
keeping together is progress;
working together is success

- Henry Ford

Thank you for your attention