# Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches

June 8, 2023

FDA U.S. FOOD & DRUG ADMINISTRATION | Duke MARGOLIS CENTER for Health Policy

# Welcome and Opening Remarks

*Mark McClellan*

Director, Duke-Margolis Center for Health Policy

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# Workshop Agenda

| | |
|---|---|
| **9:00 am** | Welcome and Opening Remarks |
| **9:15 am** | Current Regulatory Frameworks and Tools |
| **10:15 am** | Case Studies and Lessons Learned |
| **12:35 pm** | Regulatory Challenges to Adoption |
| **2:20 pm** | Advanced Manufacturing Technologies Designation Program |
| **2:30 pm** | Regulatory Strategies for Adoption and Next Steps |
| **4:15 pm** | Closing Remarks |

# Current Regulatory Frameworks and Tools

*Larry Lee*, Center for Drug Evaluation and Research

*Manuel Osorio*, Center for Biologics Evaluation and Research

U.S. Food and Drug Administration

# Current Regulatory Frameworks and Tools

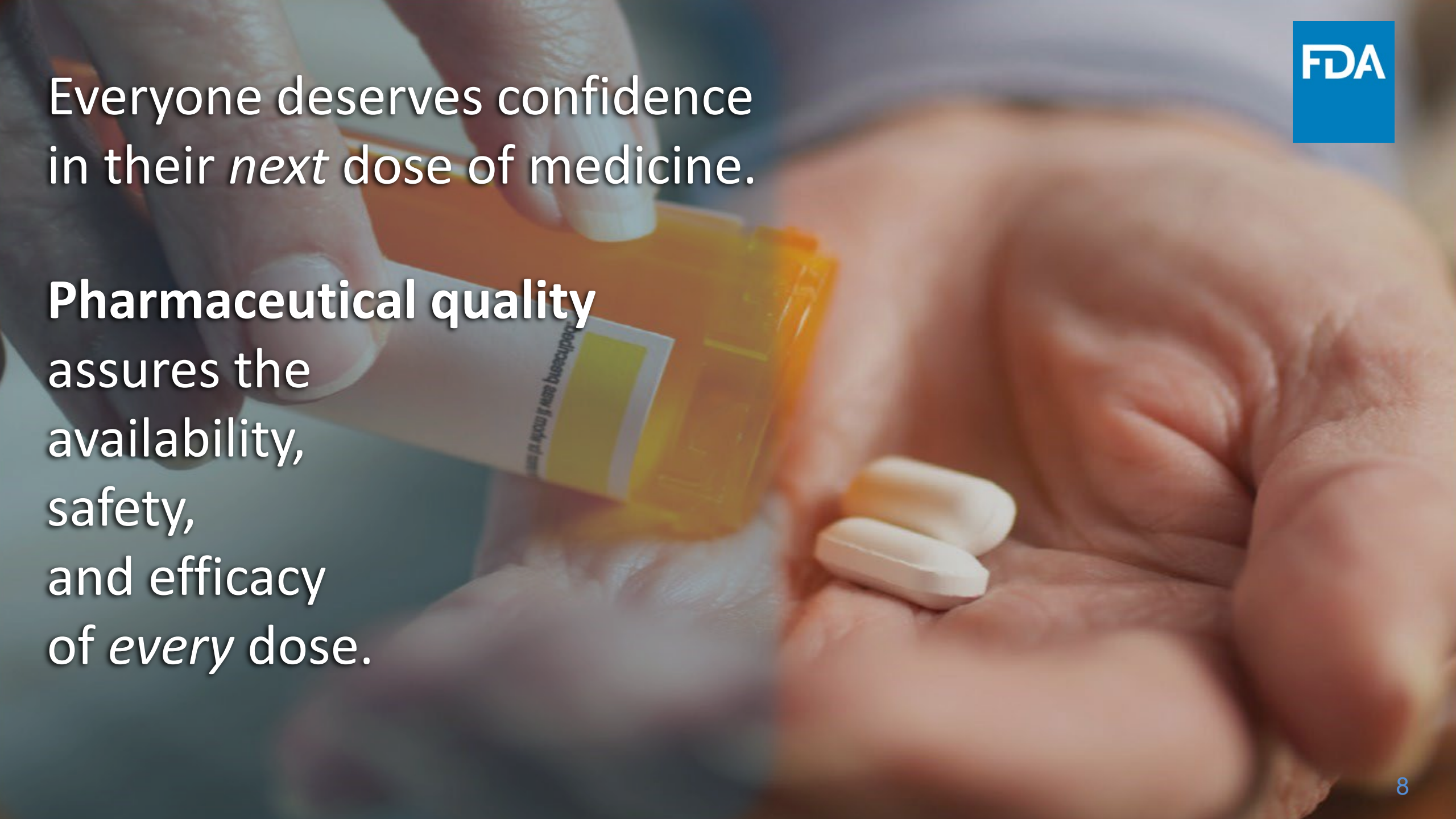

**Emerging Technology Program**

**Sau (Larry) Lee, Deputy Director of Science – Office of Pharmaceutical Quality/CDER**

**US FDA Center for Drug Evaluation and Research**


Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches

June 8, 2023



Everyone deserves confidence in their *next* dose of medicine.

**Pharmaceutical quality** assures the availability, safety, and efficacy of *every* dose.

# Advanced Manufacturing Benefits

- **Produce better quality medicine**. Facilitates six-sigma operation, no more than 3.4 defects per 1M opportunities.
- **Re-shore drug manufacturing facilities.** Helps domestic drug manufacturers compete in a global market.
- **Develop drugs rapidly.** Speeds the development of novel or patient-focused therapeutics.
- **Prevent drug shortages.** Reduces today's quality-related manufacturing issues causing 62% of drug shortages.
- **Improve emergency preparedness.** Provides more agility and flexibility to help pivot in a public health emergency.

# Impact of Continuous Manufacturing

Advanced manufacturing **offers many advantages over traditional pharmaceutical manufacturing**, including that, once implemented, it can be used far more cost-effectively than traditional manufacturing.

**– 100-Day Report by The White House**

THE WHITE HOUSE
WASHINGTON

- **CM applicants had shorter times to approval and marketing compared to batch applicants**
  - 3 months faster to approval
  - 4 months faster to marketing
  - Translates to ~$171-537M in early revenue
- **No substantial regulatory barriers for CM related to:**
  - Manufacturing process changes
  - Pre-approval inspections

International Journal of Pharmaceutics 622 (2022) 121778

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journal homepage: www.elsevier.com/locate/ijpharm

An audit of pharmaceutical continuous manufacturing regulatory submissions and outcomes in the US

Adam C. Fisher, William Liu, Andreas Schick, Mahesh Ramanadham, Sharmista Chatterjee, Raphael Brykman, Sau L. Lee, Steven Kozlowski, Ashley B. Boam, Stelios C. Tsinontides*, Michael Kopcha

Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD 20993, United States

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*Keywords:*
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Pharmaceuticals
Economics
Regulatory
Innovation

ABSTRACT

Continuous manufacturing (CM) sends materials directly and continuously to the next step of a process, eliminating hold times and reducing processing times. The potential benefits of CM include improved product quality, reduced waste, lower costs, and increased manufacturing flexibility and agility. Some pharmaceutical manufacturers have been hesitant to adopt CM owing to perceived regulatory risks such as increased time to regulatory approval and market entry, more difficulty submitting postapproval changes, and higher inspectional scrutiny. An FDA self-audit of regulatory submissions in the U.S. examined the outcomes, at approval and during the product lifecycle, of continuous manufacturing applications as compared to traditional batch applications. There were no substantial regulatory barriers identified for CM applications related to manufacturing process changes or pre-approval inspections. 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 9 months faster) and marketing (12 or 4 months faster) from submission, translating to an estimated $171–537 M in early revenue benefit.

1. Introduction

Continuous manufacturing (CM) is a technology that sends materials produced during each process step directly and continuously to the next step for further processing. In such a process, input materials are continuously fed into production and transformed, and processed output materials are continuously removed. CM has been adopted in many industries (e.g., petroleum, commodity chemicals), while the pharmaceutical industry has been slower to adopt CM (Lee et al., 2015; Rossi, 2022). The U.S. landscape of prescription drug products made using a CM process was roughly $3.09B in 2020 (Fig. 1), representing a small but growing portion of the $172B total market for branded, solid oral prescription drugs. The leading firm in the CM sector captures around 65% of total sales, with 20% of sales captured by the next largest firm. Many have pointed to the slow adoption of advanced manufacturing technologies, including CM, as one of the reasons that the pharmaceutical industry has not achieved the consistent six sigma manufacturing capability (i.e., <3.4 errors per million opportunities) common in other industries (Yuklea and Rakhaz, 2011; Yu and Kopcha, 2017).

The United States Food and Drug Administration (FDA) has long championed the development and implementation of advanced manufacturing technologies like CM for drug substances and finished drug products because of the potential to improve product quality and reliability, lower manufacturing costs, reduce waste, decrease inventory, and increase manufacturing flexibility and agility in response to fluctuations in product demand. The cumulative effects of CM adoption could reduce or mitigate drug shortages (Lee et al., 2015). CM can be applied to all classes of products: new drugs submitted in New Drug Applications (NDAs) (Hernandez, 2015), generic drugs filed in Abbreviated New Drug applications (ANDAs) (Chaudhary et al., 2017), drug substances filed in Drug Master Files (DMFs) (Stauffer et al., 2019), biotechnology products filed in Biologics License Applications (BLAs) (Fisher et al., 2019), and nonprescription drugs (Griffin et al., 2016). There is now a rich source of scientific literature describing the benefits of CM in pharmaceutical manufacturing relating mostly to decreases in production/operating costs and improvements in product quality and reliability (Rossi, 2022; Badman et al., 2019). Perhaps most importantly for patients and consumers, CM has the potential to impact product availability; for example, by avoiding drug shortages due to manufacturing problems or expediting patient access through improved

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# FDA's Advanced Manufacturing Programs


FDA's Advanced Manufacturing Initiatives Helping to Provide Quality Human Drugs for Patients

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Content current as of:
10/13/2021

By: Michael Kopcha, PhD, RPh
Center for Drug Evaluation an
of CDER

This workshop will highlight:

- CDER Emerging Technology Program (ETP)
- CBER Advanced Technologies Team (CATT)
- Advanced Manufacturing Technologies Designation Program

# Emerging Technology Program (ETP)

## Mission

Encourage and support the adoption of innovative technology to modernize pharmaceutical development and manufacturing through close collaboration with industry and other relevant stakeholders

# Team

A small cross-functional Emerging Technology Team (ETT) of 20-30 members, with representation from all relevant FDA quality review and inspection programs

**Team members come from:**

*Office of Pharmaceutical Quality (OPQ)*
*Office of Compliance (OC)*
*Office of Regulatory Affairs (ORA)*

| | |
|---|---|
| **Chair** | Joel Welch |
| **Vice Chair** | Tom O'Connor |
| **Project Manager** | Elisa Nickum |
| **Senior Scientific Advisor** | Sau (Larry) Lee |

# Program Objectives

To serve as a centralized location for external inquiries on novel technologies

To provide a forum for firms to engage in early dialogue with FDA to support innovation

To ensure consistency, continuity, and predictability in review and inspection

To engage international regulatory agencies to share learnings and approaches

To identify and evaluate potential roadblocks relating to existing guidance, policy, or practice

To facilitate knowledge transfer to relevant CDER and ORA review and inspection programs

To help establish scientific standards and policy, as needed


# ETP Progression

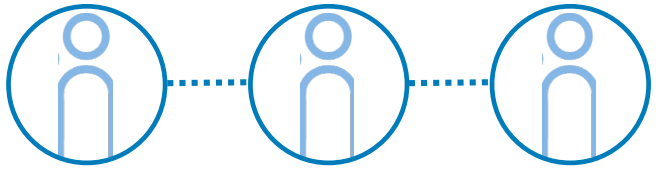
To better meet the changing needs of industry, after six years, ETP conducted a **current state analysis** to review and enhance its existing processes and structures.

This review resulted in the development of the next phase of the Emerging Technology Program, known as **ETP 2.0**, which was created to:

- ✓ Standardize and streamline ETP's technology lifecycle
- ✓ Align organizational and existing quality assessment components
- ✓ Identify opportunities to strengthen the program's performance

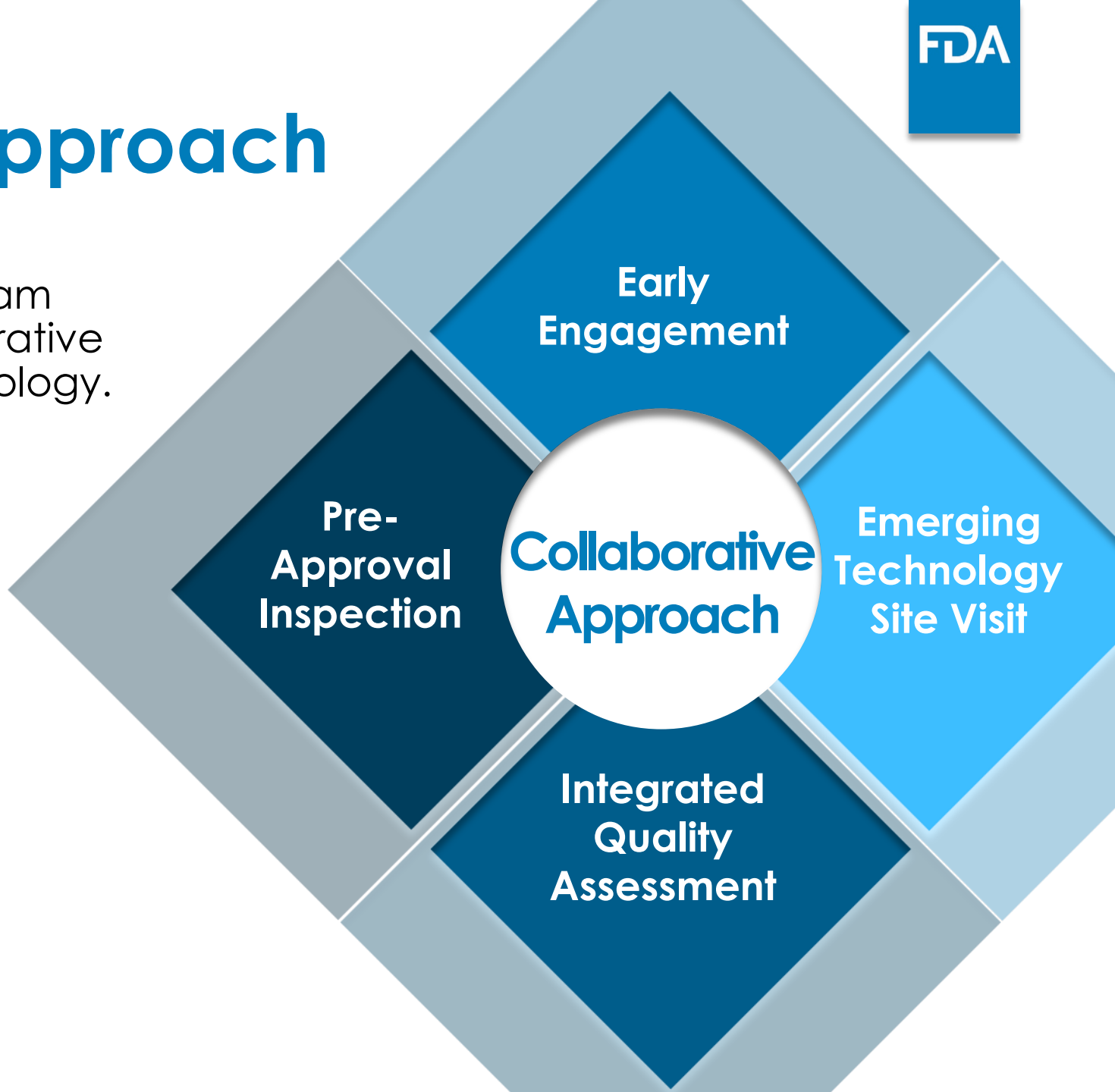
# ETP Collaborative Approach

Over the course of the ETP Technology Lifecycle, the Emerging Technology Team may employ a combination of collaborative approaches to engage with the technology.



The same Emerging Technology Team representative(s) will be involved in the entire process.

The composition of a review team will likely remain the same throughout the entire process.



# ETP Collaborative Approach

## Early Engagement (Pre-submission)

- Meeting(s) with the Emerging Technology Team (ETT) provide upfront scientific input under the Emerging Technology Program

## Emerging Technology Site Visit

- Participation by OPQ (including the ETT member(s)) and/or ORA members

## Integrated Quality Assessment (IQA)

- Interdisciplinary team with experts in Drug Substance, Drug Product, Process/Facility, Biopharm, and/or Inspection
- ETT member as an Application Technical Lead (ATL) or co-ATL to lead the IQA team when the ET impacts most parts of a CMC section

## Pre-Approval Inspection (PAI/PLI)

- Conducted by team members from OPQ (including the ETT Member(s)) and ORA

# Lifecycle of an ETP Technology


Industry requests input and feedback on an emerging technology while preparing a regulatory submission

ETP works with industry to discuss, identify, and resolve technical and regulatory issues related to the development and implementation of the novel technology

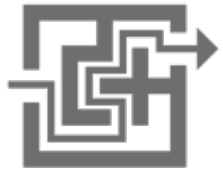
Technology is no longer considered "emerging" and passes through the standard quality assessment pathways

**A technology is eligible to graduate from ETP when at least three applications have been received from three unique companies. Meeting this threshold does not automatically initiate graduation.*

# Graduation Definition

***An emerging technology qualifies for graduation and is no longer considered emerging within ETP when:***

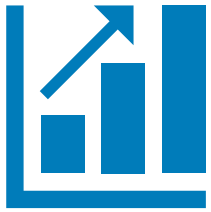
***FDA has gained sufficient experience with the technology***



***The technology can proceed fully through the standard assessment process with no or minimal support from ETT members***

# Graduation Benefits

Graduation indicates that FDA has gained sufficient experience with the graduating technology and is **confident in the ability of industry to submit successful future applications**



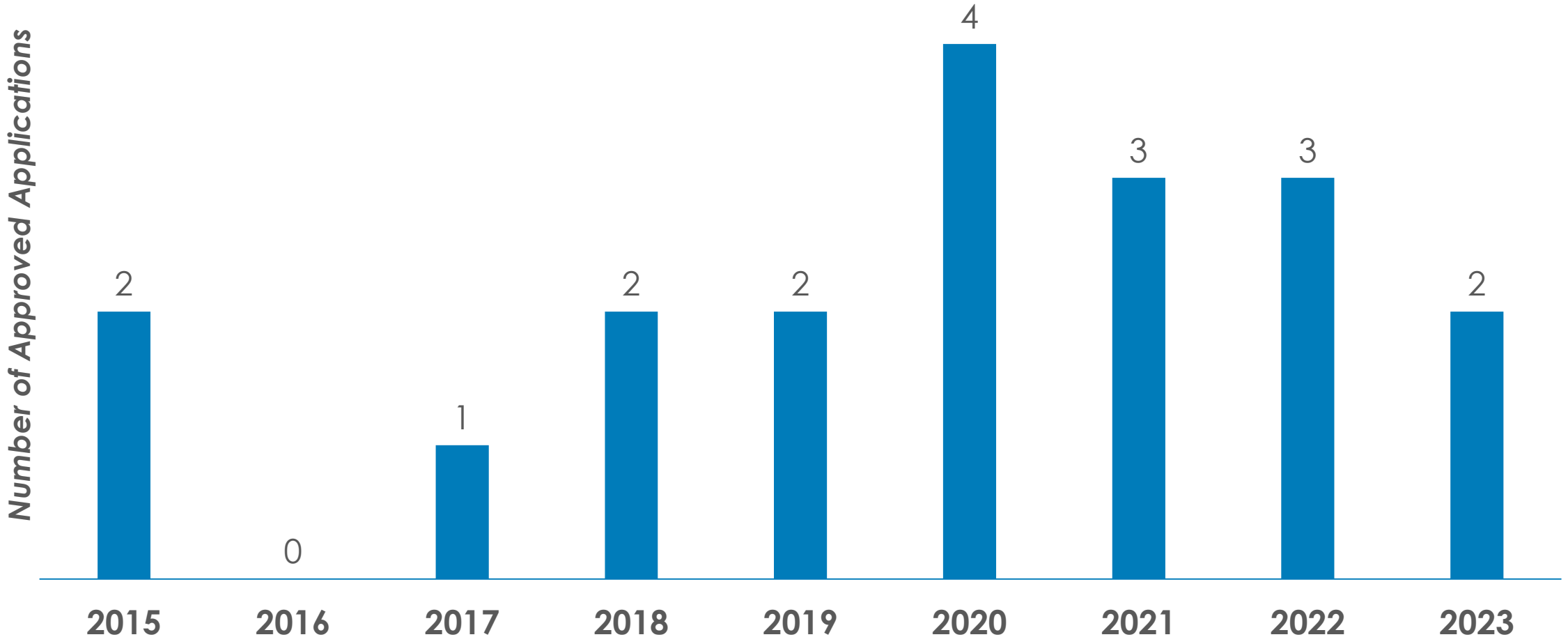
By transferring responsibility for the graduated technology to other FDA offices, ETP has the capacity to **accept future emerging technologies to keep pace with industry innovation**

With more assessors trained to review the graduated technology, **FDA can review more applications while continuing to meet the user fee goal dates.**

**ETP core members remain available to FDA assessors as needed on regulatory submissions of graduated technologies.**

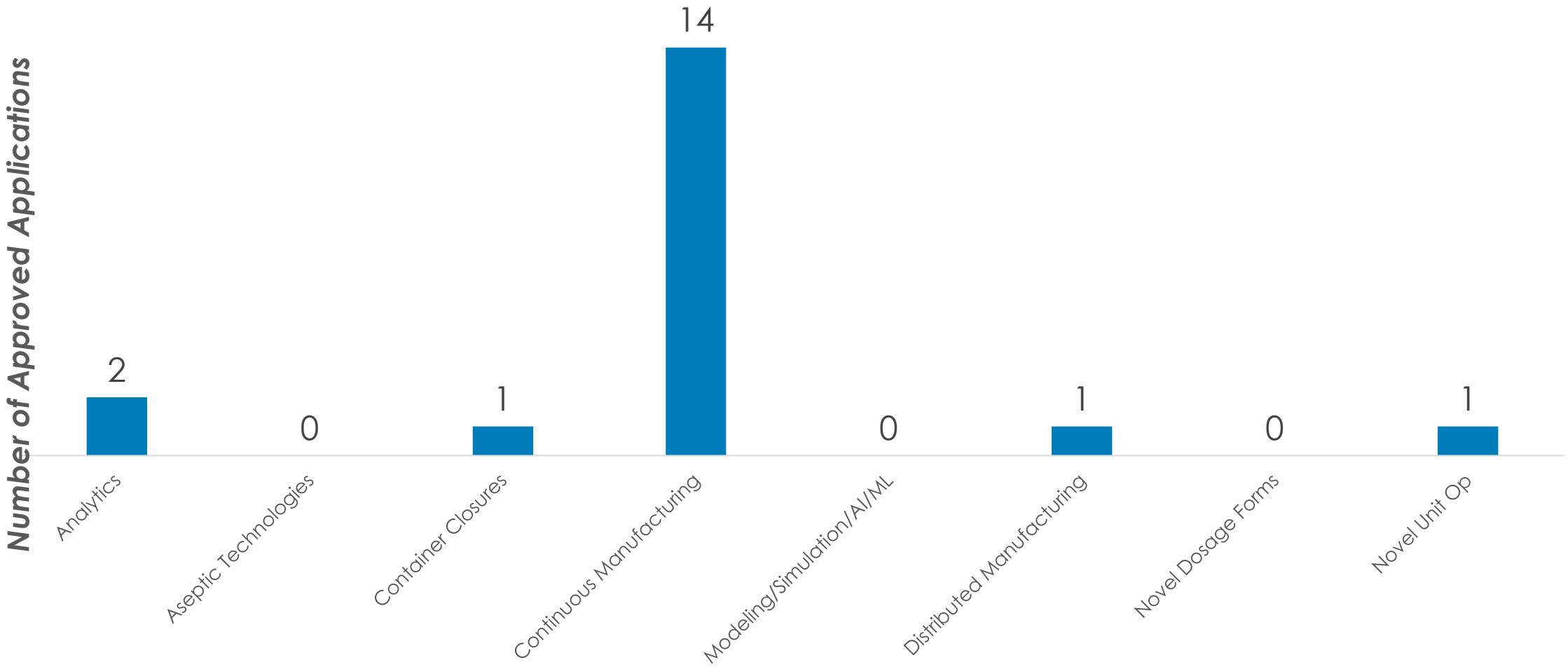
# Total Approved Applications

**There have been 19 approved applications since July 2015***




*As of April 2023

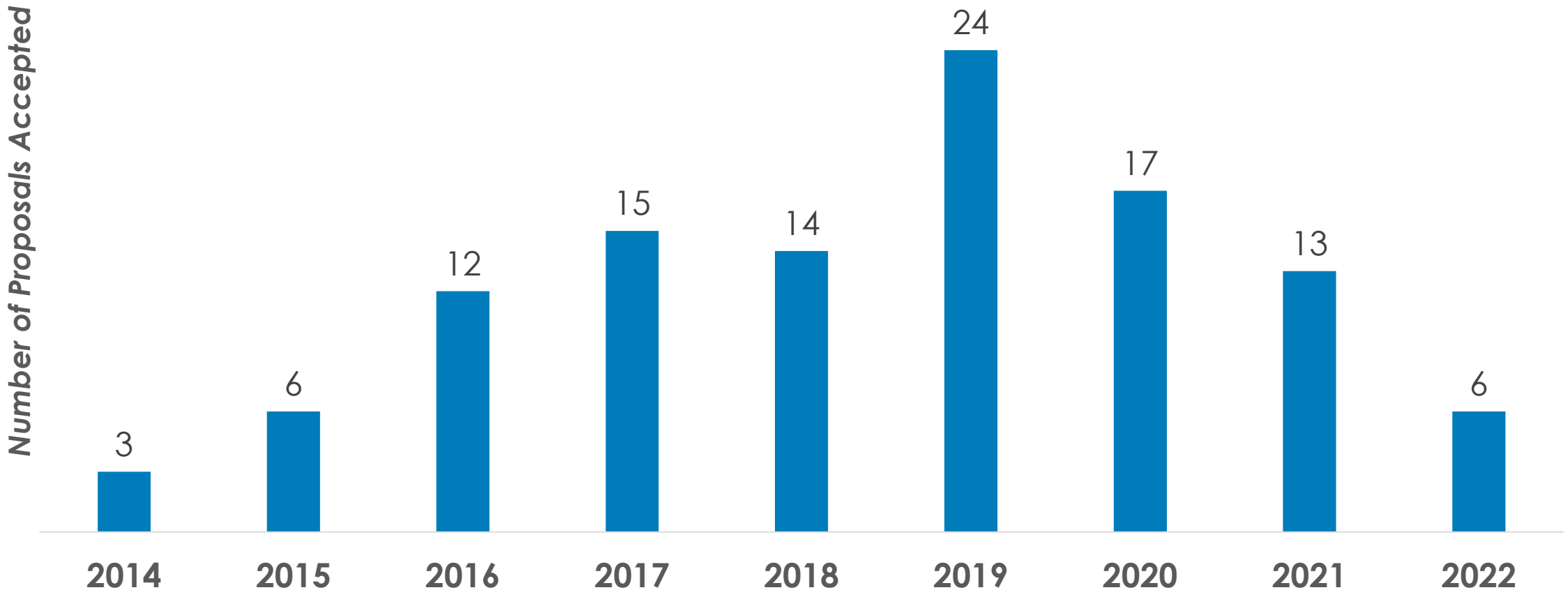
# Approved Application Technologies




*As of April 2023

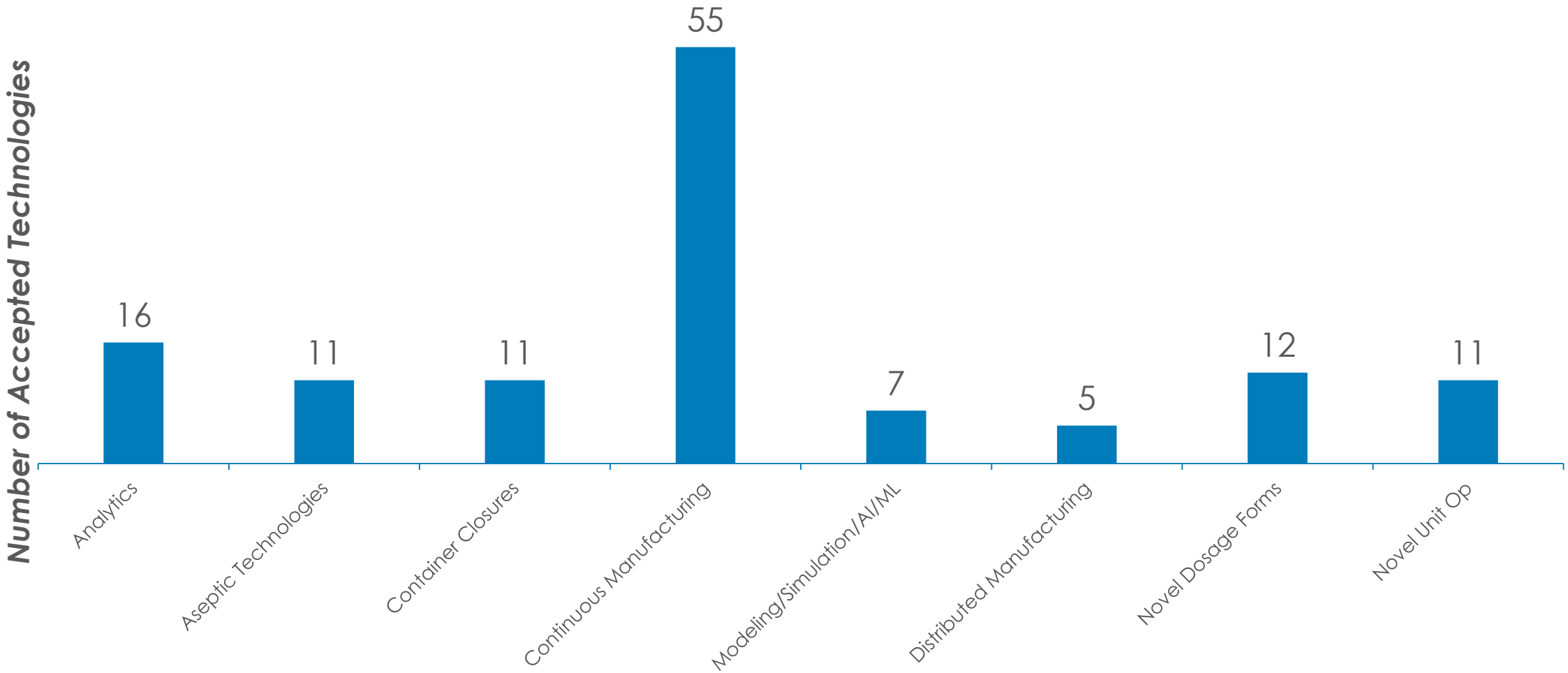
# ETP Accepted Proposals

**The Emerging Technology Program has accepted over 120 proposals since 2014**




*As of April 2023

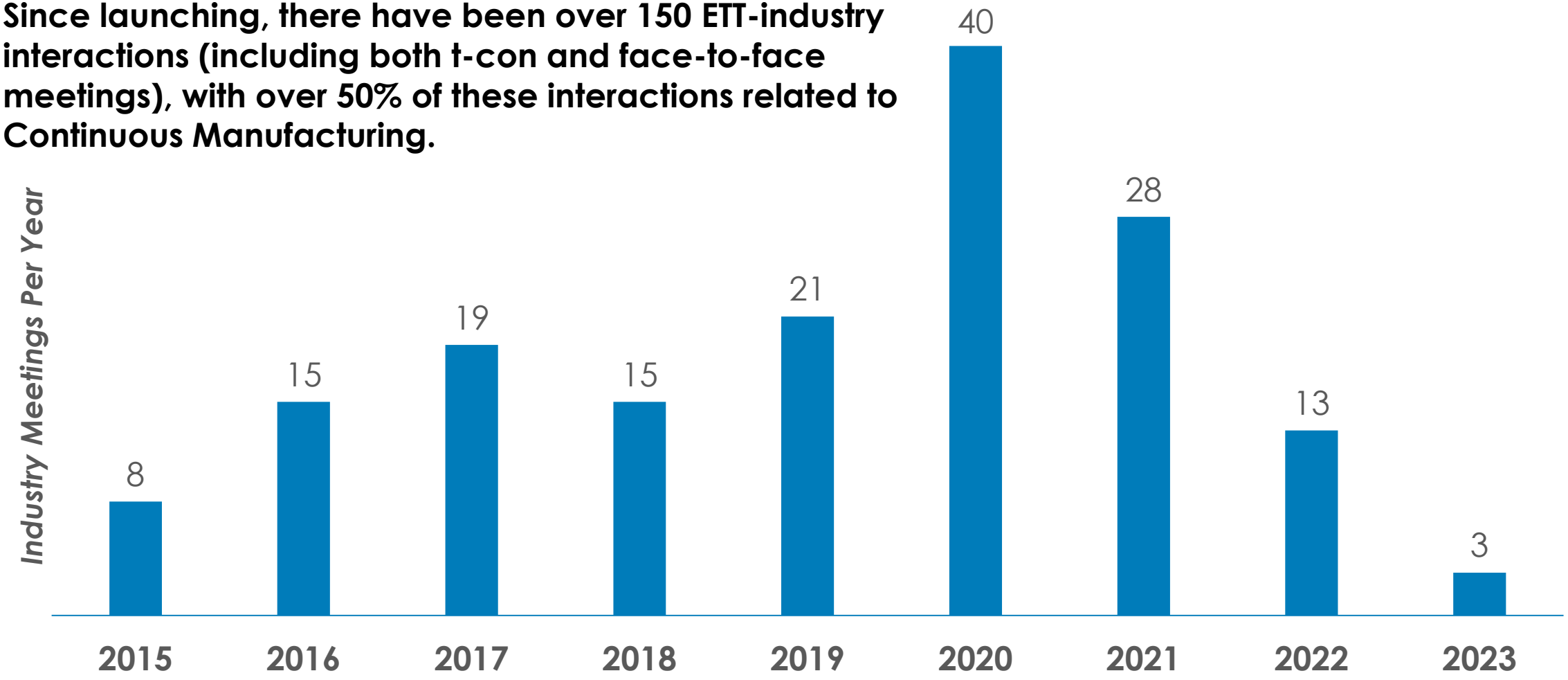
# ETP Accepted Submissions by Technology




*As of April 2023

# Accepted Meeting Requests

**Since launching, there have been over 150 ETT-industry interactions (including both t-con and face-to-face meetings), with over 50% of these interactions related to Continuous Manufacturing.**




*As of April 2023

# How to Apply to ETP

## 01

Start early in development (even potentially without a drug candidate identified)

## 02

Follow procedures described in the ETT guidance found on our website to request participation in the ETP

## 03

Develop proposal

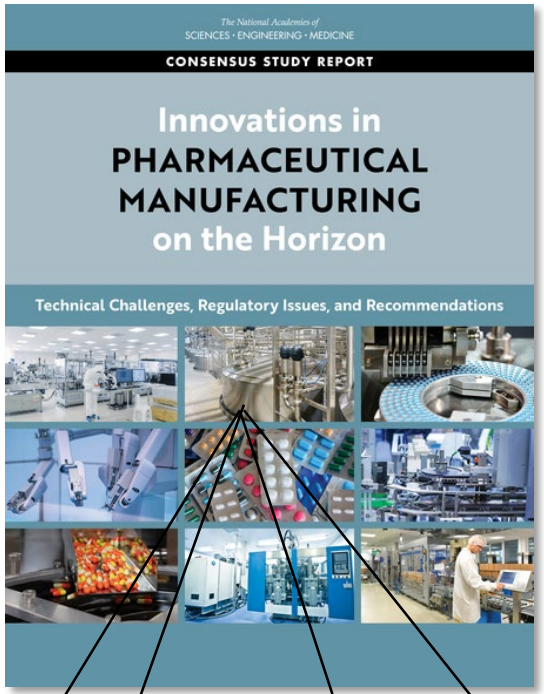
- Describe the technology and explain why it is novel or unique
- Describe how it improves products
- Summarize development plan and implementation roadblocks
- Describe submission timeline

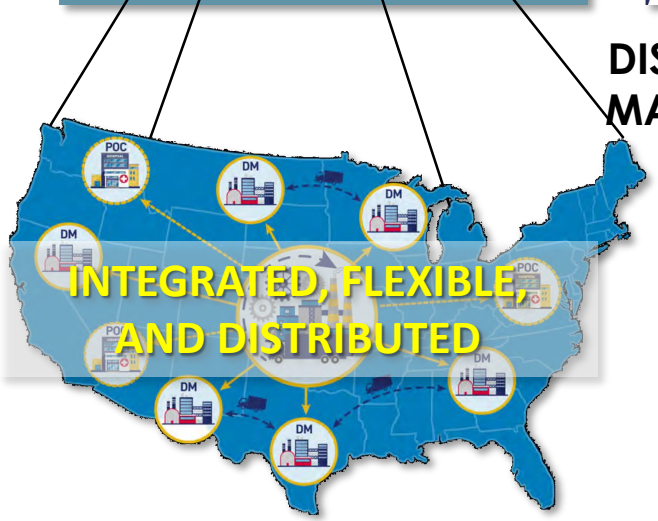
**The sponsor must justify how the proposed emerging technology meet two criteria:**

**(1) Pharmaceutical Novelty**
**(2) Product Quality Advancement**

* Additional procedures are described in the ETT guidance found on our website: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/how-participate-etp

# **FRAME:** **F**ramework for **R**egulatory **A**dvanced **M**anufacturing **E**valuation





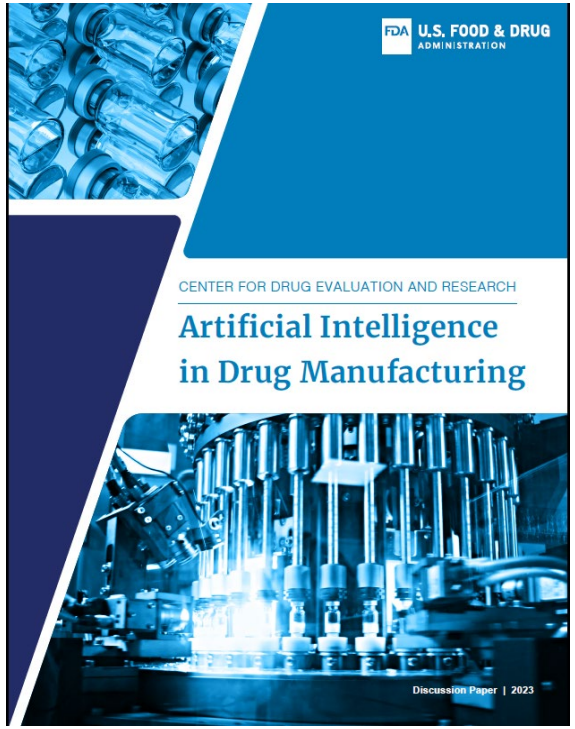
**DISTRIBUTED & POINT-OF-CARE MANUFACTURING DISCUSSION PAPER**

October 13, 2022


**FDA/PQRI**

**DISTRIBUTED & POINT-OF-CARE MANUFACTURING PUBLIC WORKSHOP**

November 14-16, 2022

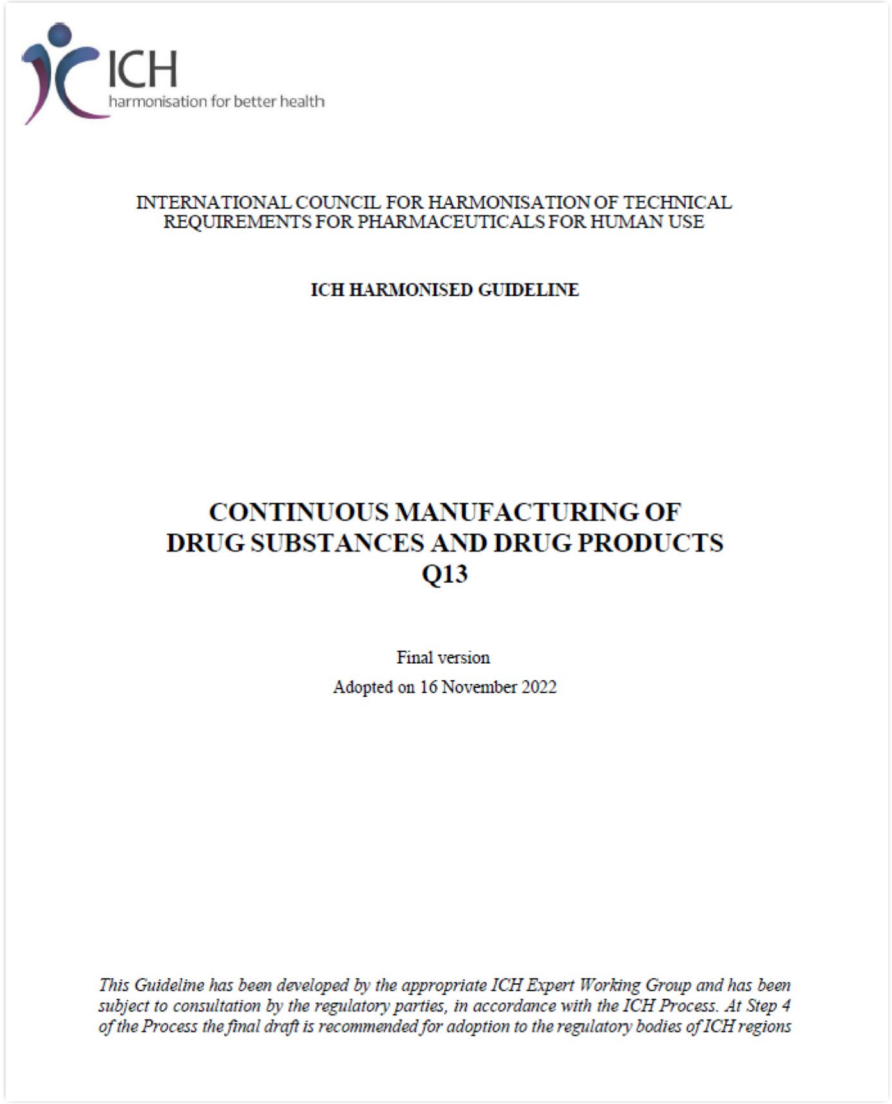



**ARTIFICAL INTELLIGENCE IN MANUFACTURING DISCUSSION PAPER**

March 3, 2023

# ICH Q13

- This document has been signed off as *Step 4* document (16 November 2022) to be implemented by the ICH Regulatory Members
- This document was developed based on a Concept Paper (15 November 2018) and Business Plan (15 November 2018)



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS Q13

Final version

Adopted on 16 November 2022

*This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions*

# OPQ Product Development Science Capabilities

**Continuous perfusion bioreactor**

| Intramural Research |
| --- |
| Novel Manufacturing Methods (10 projects) |
| Precision Analytics (16 projects) |
| Advanced Manufacturing of Biopharmaceuticals (11 projects) |
| Manufacturing of Glycoproteins (3 projects) |
| Manufacturing of Synthetic Nucleic Acid Sequences (1 project) |
| Process Modeling, and Artificial Intelligence (AI)/ Machine Learning (ML) (4 projects) |

| Extramural collaborations via grants and contracts |
| --- |
| Industry 4.0 and Smart Manufacturing (3 projects) |
| Novel Manufacturing Methods (6 projects) |
| Novel Process Analytical Technologies (4 projects) |
| Process Modeling and Simulation (2 projects) |
| Advanced Manufacturing Training (1 project) |

**Projects generated more than 78 internal reports and publications**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ADMINISTRATION
Thank You!

# CBER Advanced Technologies Program

## Promoting the Development and Adoption of Advanced Manufacturing Technologies

**Manuel Osorio, PhD**

*Senior Scientist for Emerging Technologies*

Lead, CBER Advanced Technologies Program

US FDA Center for Biologics Evaluation and Research

**Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches**

June 8, 2023

# What is Advanced Manufacturing?

- Integrating **novel technological approaches**
- Using established techniques in a **new or innovative way**
- Applying production methods in a **new domain** where there are no defined best practices or experience

# Biological Products Regulated by CBER

- Blood, blood components and derivatives
- Vaccines (preventive and therapeutic)
- Tissues
- Cell and gene therapies
- Xenotransplantation
- Allergenics
- Related devices (including IVDs)

# CBER Advanced Technologies Program

**Fund advanced research and development projects to support regulatory science and innovation**

**Build internal scientific and regulatory expertise**

**The CBER Advanced Technologies Team (CATT)**

# Advancing Innovative Manufacturing Technologies through Extramural Funding

Since 2018 CBER has awarded several grants and contracts to support research projects to study improvements for advanced manufacturing of biological products

Funded research addresses knowledge and experience gaps identified for emerging manufacturing and testing technologies and support the development and adoption of such technologies in the biological product sector

# CBER Advanced Technologies Team (CATT)

| | |
|---|---|
| **WHAT** | Established in 2019 to promote dialogue, education, and input among CBER staff and between CBER and prospective developers of advanced manufacturing technologies to encourage their implementation in the manufacturing sector. |
| **WHO** | Consists of a small cross-functional group representing CBER leadership, relevant policy, review and inspection programs.<br>**Offices Represented: OD, OVRR, OTP, OBRR, OCBQ** |
| **HOW** | Provides access to early interactions with CBER, prior to filing a regulatory submission, to discuss technical and regulatory issues related to the implementation of innovative manufacturing and control strategies . |

# Scope of CATT Meetings

**Novel** technologies with significant impact on product development, manufacturing process and control strategies

Manufacturing and analytical methods for which CBER has **limited experience**

**Not for product-specific,** highly technical discussions

# Early Engagement with CBER

Non-binding regulatory advice

**CATT Interaction**

- **CMC**
- **Innovative approaches to product development**

**INTERACT Meeting:**

**Specific product and indication for first-in-human use**

- **CMC**
- **Pharm/tox**
- **Clinical**

Binding regulatory advice

Phase 1 → Phase 2 → Phase 3 → Application (BLA)

- **Pre-IND Meeting:**
  - Manufacturing
  - Lot Release
  - Animal safety & immunogenicity
  - Phase 1 protocol

- **EOP 2 meeting:**
  - Phase 3 protocol(s)
  - Phase 1 & Phase 2 data
  - Animal efficacy protocols & data (if "Animal Rule" used)
  - Update on manufacturing & lot release

- **Pre-BLA/NDA Meeting:**
  - Clinical data summary: Safety & Efficacy data
  - Manufacturing, etc...
  - Outline of BLA/NDA

IND = Investigational New Drug
BLA = Biologics License Application
NDA = New Drug Application

# Submitting CATT Meeting Requests

https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt

- A 2-page (including figures and tables) backgrounder that provides the following information:
  - Description of **technology**
  - Why technology/product class is **novel and unique**
  - **Impact** of technology/product class
  - Summary of **manufacturing or development plan**
  - **Questions** regarding perceived regulatory, technical, or other challenges for implementation

# Review Process

**Evaluation:**

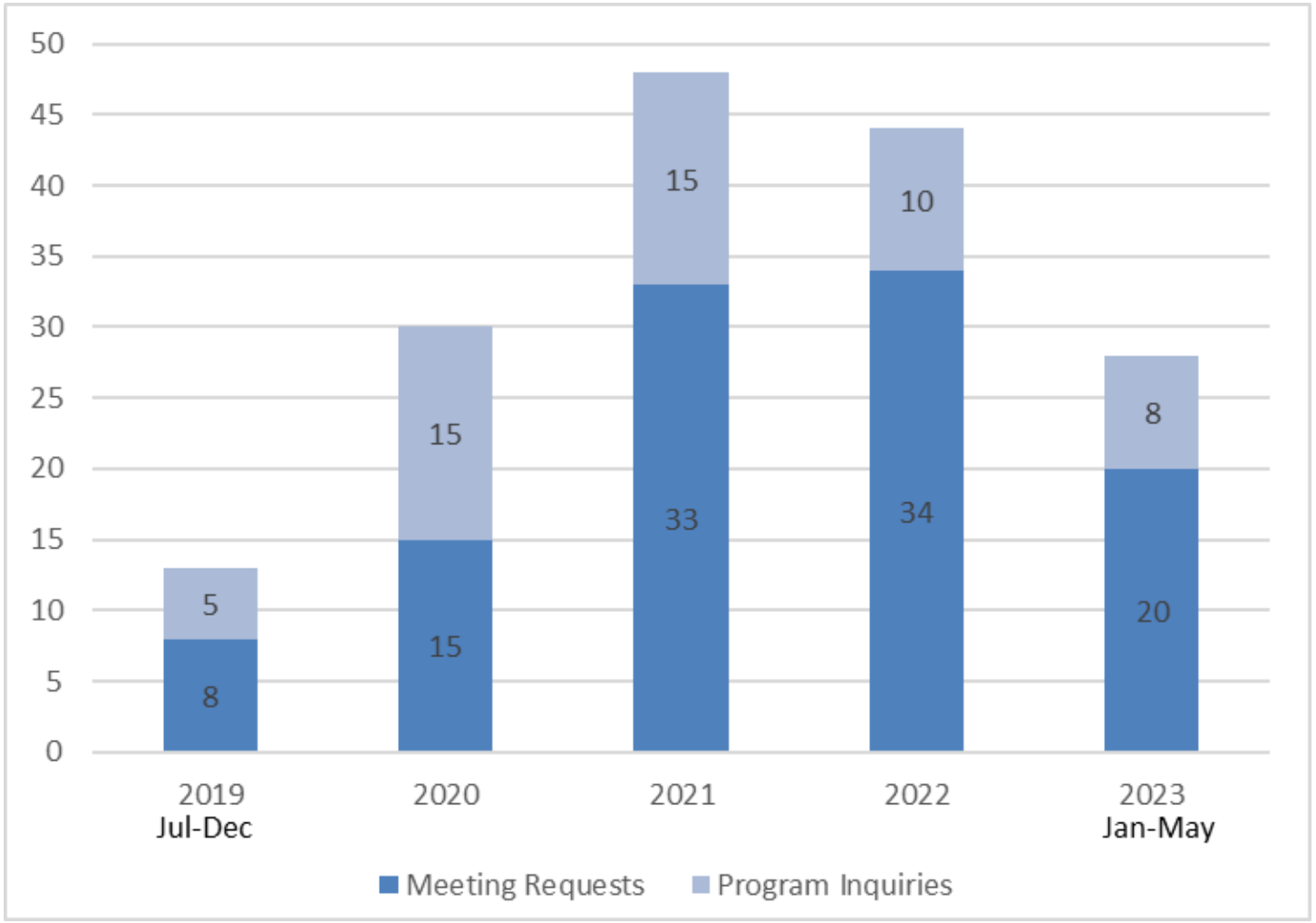
- Initial triage by CATT coordinators
- Assignment to relevant Review Office(s)
- Discussion at recurrent internal CATT meetings

# Review Process

**Outcomes:**

- CATT meeting granted
- Provide responses to submitted questions
- Recommendation to request other meetings for product-specific discussions

# CATT Meeting Requests/Inquiries Received



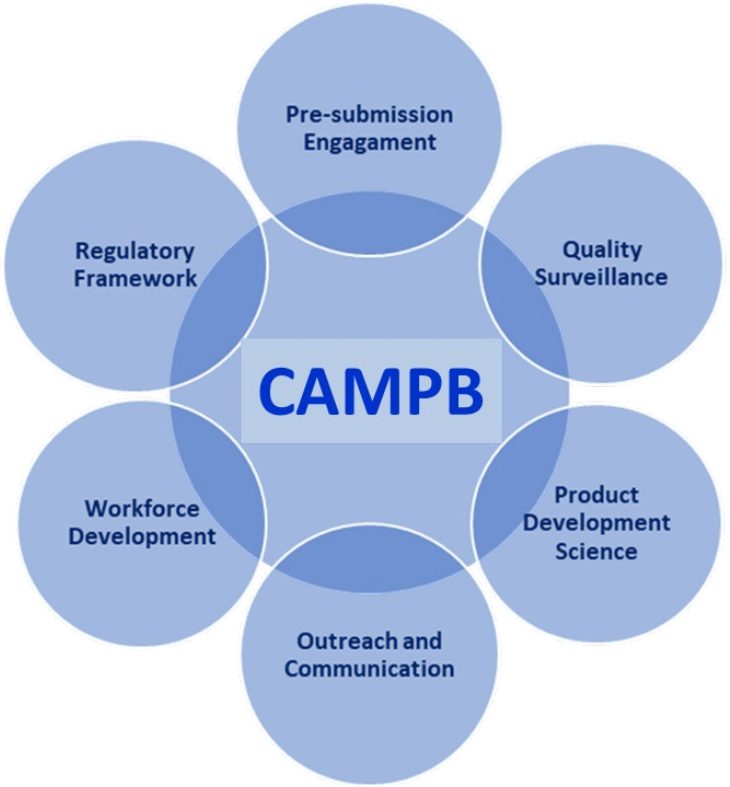
# Examples of Technologies Discussed

- Continuous Manufacturing (vaccines, AAV vectors, exosomes)
- Fully closed, automated, scalable and remote-controlled systems for manufacturing cell therapy products
- Improved cell lines for vaccine antigen production and AAV vector manufacturing
- Use of AI and advanced imaging technologies for real time product quality assessment
- Multi-product manufacturing facility design
- CRISPR/Cas9 Genome editing

# CENTER FOR THE ADVANCEMENT OF MANUFACTURING PHARMACEUTICALS AND BIOPHARMACEUTICALS (CAMPB)

CAMPB Mission:

- Accelerate the development, implementation, and evaluation of advanced manufacturing by establishing science- and risk-based standards and policies
- Advance drug product development science
- Train a world-leading regulatory workforce, through strategic partnership, engagement and communication



# ICHQ13: Continuous Manufacturing of Drug Substances and Drug Products

**Objective**

Provide harmonized guidance for the development, implementation, and assessment of continuous manufacturing (CM) technologies used in the manufacture of drug substances and drug products

**Scope**

Applies to CM of chemical entities and therapeutic proteins, and the conversion of batch manufacturing to CM for existing products. ICH Q13 principles may also apply to other biological/biotechnological entities.

# Summary

- CBER is committed to accelerating the **adoption** of advanced manufacturing technologies - **CATP**
- CBER encourages innovators to engage the Center early to discuss regulatory and technical issues associated with innovative technology implementation - **CATT**
- CBER is collaborating internally and internationally to build the scientific expertise and regulatory framework necessary to evaluate emerging technologies

**CAMPB, FRAME, ICH Q13**

U.S. FOOD & DRUG ADMINISTRATION

# Thank you!

Manuel Osorio
Manuel.Osorio@fda.hhs.gov

https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-program

# Break

Workshop will resume at **10:15 a.m.**

# Case Studies and Lessons Learned

- *Nandita Vishwanathan*, EMD Serono
- *Paul Kirwan*, Amgen
- *Ahmad Almaya*, Eli Lilly and Company
- *Celeste Frankenfeld Lamm*, Merck
- *Kimberly Schultz*, Center for Biologics Evaluation and Research, FDA

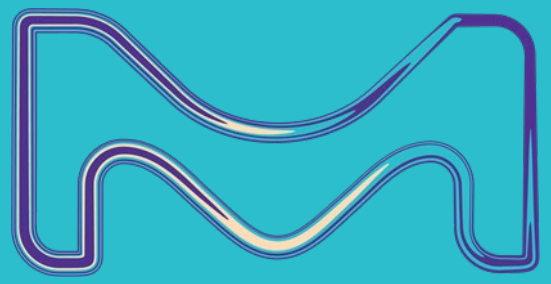
# Case study: Continuous Manufacturing of Biologics

## "Time-To-Results" Analytics Challenge

Nandita Vishwanathan, Andrea Ruggiero & Hervé Broly

FDA convening workshop on *'Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches'*

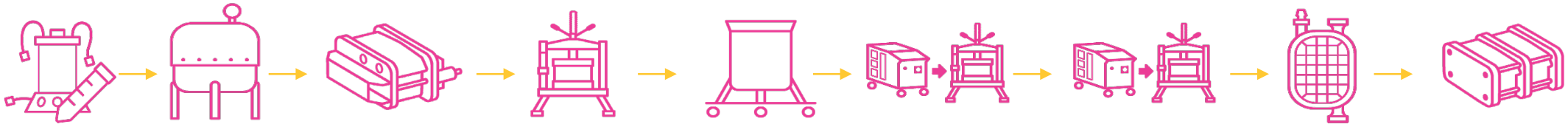
8 June 2023



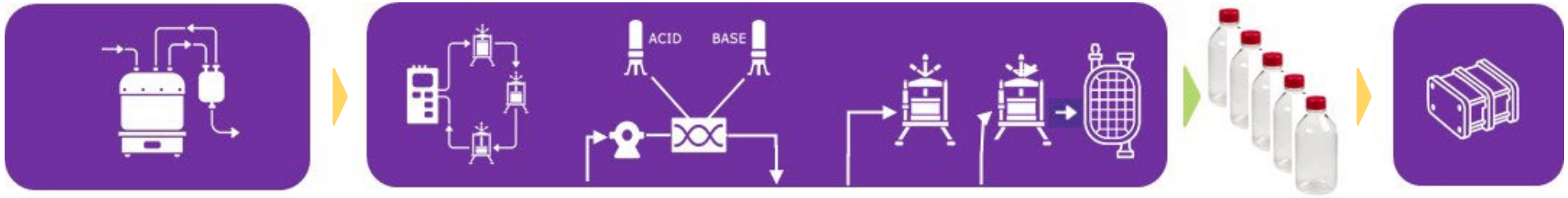
EMD SERONO MilliporeSigma EMD Electronics

# CM of Biologicals
# Segmented to Integrated Continuous Manufacturing

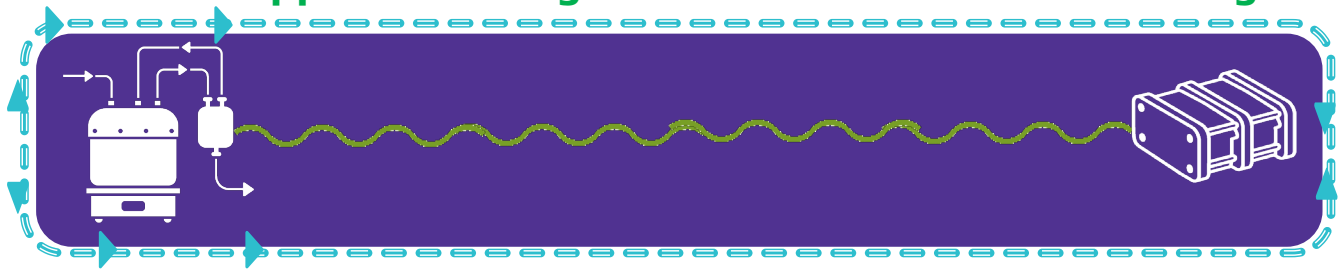
## Historical approach: USP: Fed-batch; DSP: successive independent unit operations




## Current approach: Segmented Continuous Manufacturing




## Future Approach: Integrated Continuous Manufacturing



# CM of Biologicals
# **Concept to implementation journey**

2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023

Pilot scale prototype evaluated for DSP

Mfg scale equipment installed

First GMP process using perfusion and adapted cDSP

Test of cDSP skid

**Type C meeting with FDA ETT**

Qualification of cDSP skid for GMP mfg

1st GMP process using perfusion and cDSP skid

2nd GMP process using perfusion and cDSP skid

ICH Q13 effective

EMA QIG Listen & Learn

Continuous downstream & upstream processes

**cDSP**


**cUSP**

# CM of Biologicals: "Time-To-Results" Analytics Challenge
# **Process Control as described in ICH Q13 cannot be Implemented for Biologics**

***3.1.5. Process Monitoring and Control***

Process monitoring and control support the maintenance of a state of control during production and allow real-time evaluation of system performance. Common approaches to process monitoring and control—including establishment of target setpoints and control limits, design space, and specifications for attributes being measured—are applicable to CM.

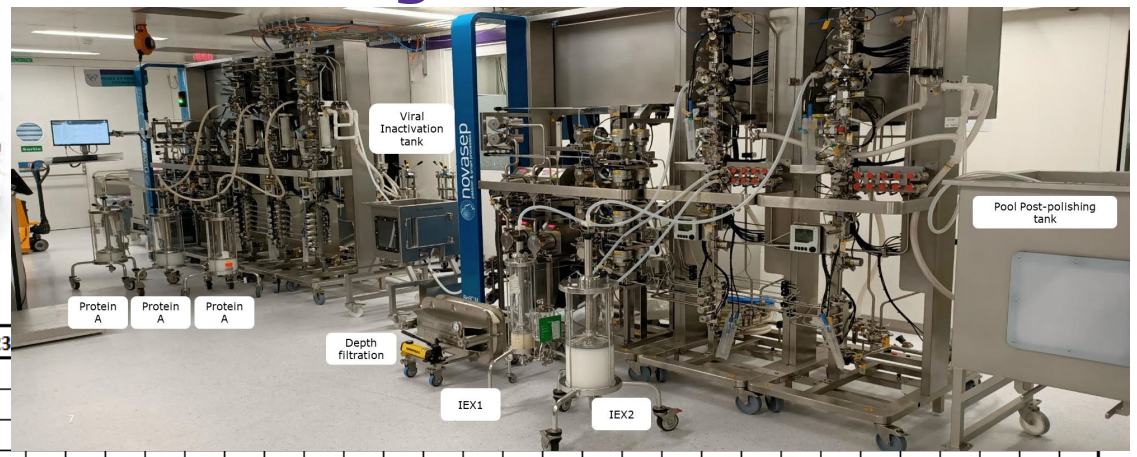
**2.3. Process Monitoring and Real-Time Release Testing**

CM lends itself to various monitoring schemes with different levels of automation. Examples include in-line sensors placed directly in a process vessel or flowing material stream and online analysers that conduct automatic sampling. Regardless of the approach used, appropriate monitoring at suitable stages of the CM process enables timely data analysis to ensure operations are in a state of control. In certain cases, relevant process parameters may be adjusted to ensure the quality of in-process or output materials. Enhancing in-line/online PAT capabilities and development of automation systems for process monitoring enable a continuous monitoring scheme in support of a release testing strategy that may include RTRT for some quality attributes. For example, drug substance in-line release tests for pH, osmolality, protein concentration and online release tests for purity, charge heterogeneity, aggregation, and low-molecular weight impurities can be performed at specific points in the drug substance manufacturing process shown to be critical for control of the product quality attributes.

Today, the lack of PAT or at-line methods with appropriate "time-to-results" does not allow comprehensive monitoring of product quality while the process runs

# CM of Biologicals: "Time-To-Results" Analytics Challenge

## Timing of the Continuous Product Stream through DSP




**Traditional batch approach**

| Step | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clarification | | | | | | | | | | | | | | | | | | | | | | | | |
| Testing | | | | | | | | | | | | | | | | | | | | | | | | |
| Protein A | | | | | | | | | | | | | | | | | | | | | | | | |
| Low pH hold | | | | | | | | | | | | | | | | | | | | | | | | |
| Pooling & testing | | | | | | | | | | | | | | | | | | | | | | | | |
| Polishing 1 | | | | | | | | | | | | | | | | | | | | | | | | |
| Pooling & testing | | | | | | | | | | | | | | | | | | | | | | | | |
| Polishing 2 | | | | | | | | | | | | | | | | | | | | | | | | |
| Nanofiltration | | | | | | | | | | | | | | | | | | | | | | | | |
| UF/DF & formulation | | | | | | | | | | | | | | | | | | | | | | | | |
| Filling | | | | | | | | | | | | | | | | | | | | | | | | |

Time (hour)

**Continuous downstream process**

| Step | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clarification | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Protein A - Colum 1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Protein A - Colum 2 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Protein A - Colum 3 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Low pH hold | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Polishing 1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Polishing 2 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Nanofiltration | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| UF/DF & formulation | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Filling | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

**6 hours from harvest to purified material**

# CM of Biologicals: "Time-To-Results" Analytics Challenge
# **Timing of the Product Stream**

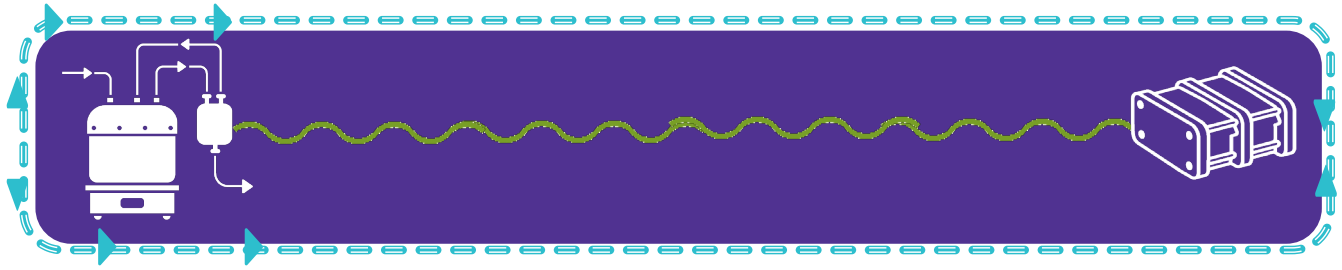
There is a lack of in-line / on-line analytical tools to monitor USP CQAs on a timely manner commensurate with product flow rate through the DSP

| CQA | Sample pre-treatment | Method | Time to result |
|---|---|---|---|
| Endotoxins | No | LAL (qualitative) | 30 min |
| High molecular weight impurities | Yes | SE-HPLC | 3 hours |
| Low molecular weight impurities | Yes | Nred./Red. CE-SDS | 3 hours |
| Charge variants | Yes | IEX-HPLC | 3 hours |
| Host cell proteins | No | ELISA | 3 hours |
| Host cell DNA | No | qPCR | 3 hours |
| **Multiple CQAs (including glycans*)** | **Yes** | **Multi-Attribute Mass Spectrometry** | **6 hours** |
| Bioburden | No | Rapid Microbiological Method | 12 hours |

* Glycans are usually the first quality attributes affected in case of upstream process disturbance

# CM of Biologicals: "Time-To-Results" Analytics Challenge
## **Challenges to Integrated Continuous Manufacturing**

- Could an integrated continuous bioprocess, without USP/DSP segregation, benefit from the regulatory flexibility – i.e., the duration of a run could be variable within the limit of in vitro cell age – even though there is no PAT to monitor CQAs with appropriate "time-to-result" while the process is running?



# CM of Biologicals: "Time-To-Results" Analytics Challenge
## **Proposal to compensate for lack of CQA-related PAT**

### Upstream process

- Real-time check of process parameters (e.g., temperature, pH, perfusion rate, capacitance)
- Rapid monitoring (e.g., less than 30 min time-to-result) of multiple performance attributes linking cell metabolism and product quality (e.g., cell density, cell viability, volume, $pCO_2$, glucose, lactate, glutamine, glutamic acid, ammonia)

Out of a control range triggers diversion for a period of time based on excursion studies

### Downstream process

- Real-time check of process parameters (time, volume, flow, pH, conductivity, product concentration of substeps) and UV, pH, conductivity profiles

Out of a control range triggers diversion for a period of time based on residence time distribution studies

### Additional process checks

- At-line monitoring of CQAs (USP & DSP) within control ranges
- Purified material is collected in multiple fractions, quality tested for most "sensitive" CQAs to slight variation of process parameters and released prior to further processing (e.g., pooling, pre-formulation, filtration) to generate a batch of multiple batches of drug substance

# CM of Biologicals
# **Experience with FDA ETT**

## Appreciated features

- Option for technology/non-product specific interactions is a good expansion of the original scope.
- Simple & efficient process.
  - Fast acceptance of proposal within a week.
- ETT feedback on questions posed in briefing book obtained 1 week in advance of meeting.
- Pragmatic feedback on company's proposal.
- Clear and concise minutes of meeting provided by ETT.
- ETT interest expressed for a site visit to facilitate discussion of the new technology.

## Features can be improved

- It would be beneficial to amend the current FDA ETT guidance with a view to including more explicit information also on the feasibility of non-product specific interaction (i.e. emerging technology driven rather than product/application specific only).

# Acknowledgements

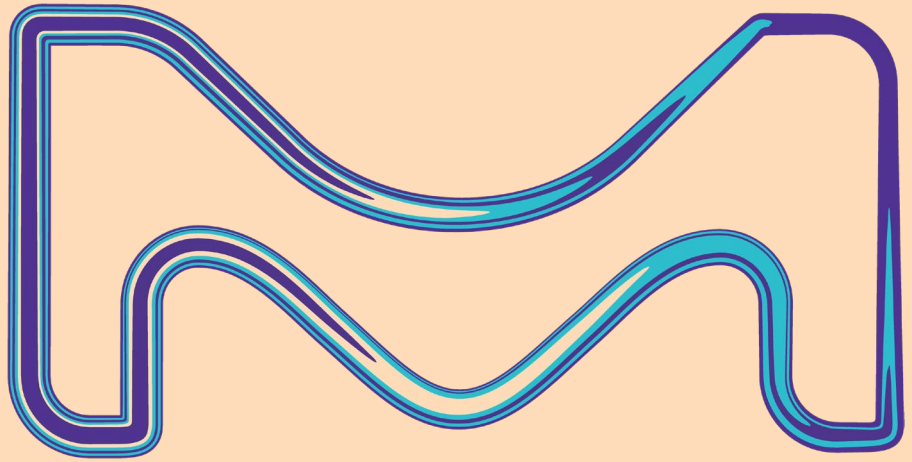

**Global Drug substance development**

- Hervé Broly
- Jonathan Souquet
- Xavier LeSaout
- Kevin Botelho Ferreira

- **Manufacturing Excellence**

**CMC Regulatory Intelligence (GRA CMC & Devices)**

- Andrea Ruggiero
- Wan-Li Liao
- Elodie Charbaut-Taland

# The Multi-Attribute Method: Progression of Advanced Analytical Technology Through the FDA Emerging Technology Program

**J. Paul Kirwan, Ph.D., Senior Manager, Regulatory Affairs CMC**
Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches

June 8, 2023 - FDA Convening - Duke | Margolis Center for Health Policy

# Disclaimer

The views expressed herein represent those of the author and do not necessarily represent the views or practices of the author's employer or any other party.



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# Advancing the Next Generation Of Manufacturing Facilities, Processes, & Integrated Testing

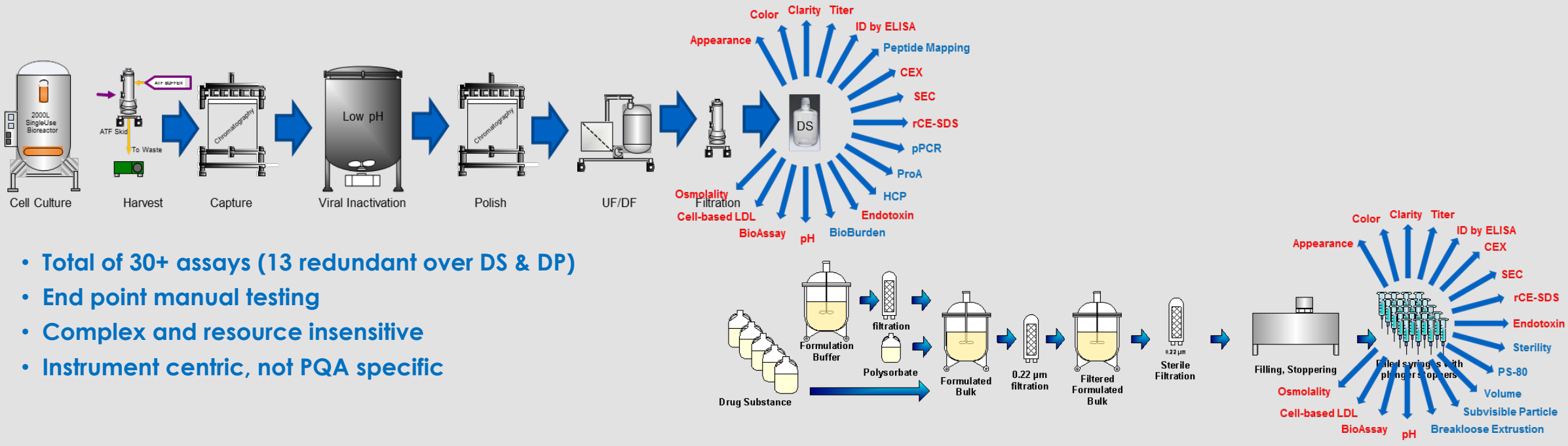
- Continuous manufacturing enables facility footprint reduction and increased efficiency

- Modular facilities construction provides on-demand scaling of biopharmaceutical production and laboratory space

- Testing that provides specificity to measure attributes and increases efficiency of testing and product release

# Numerous Test Methods Are Typically Required For Development, Production & Analytical Assessment

## Conventional Analytical Testing:




- Total of 30+ assays (13 redundant over DS & DP)
- End point manual testing
- Complex and resource insensitive
- Instrument centric, not PQA specific



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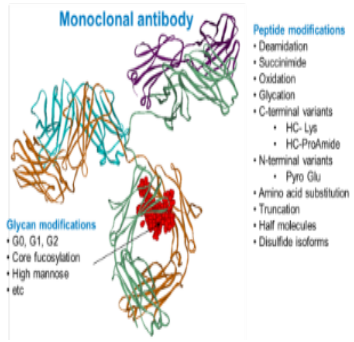
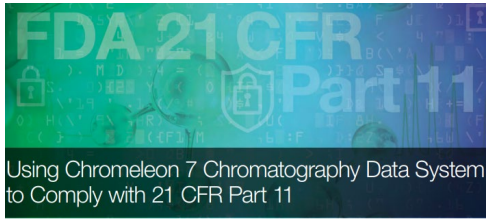
# Multi-attribute-method (MAM) Measures Specific Attributes to Assess 'Fit to Quality Target Product Profile'

**AMG X**




| Attribute | PQAA |
|---|---|
| Sialylation | PK – 7 |
| Oxidation | PK – 5 |
| Oxidation | Potency – 5 |
| Deamidation | Potency – 5 |
| Clips | Potency – 5 |




**Elements of QTPP**

| Category | Attribute | Target Range | Current Observed Range |
|---|---|---|---|
| Strength | Concentration | 126 – 154 mg/mL | 131 – 149 mg/mL |
| Quality | HC Asp Isomerization | ≤ 2% | 0.1 – 0.5% |
| | LC Trp Oxidation | ≤ 5% | 0.1% |
| | HC Met Oxidation | ≤ 5% | 0.3 – 0.9% |
| | HC Met Oxidation | ≤ 5% | 0.4% |
| | Met Oxidation | 1% – 7% | 2.5 – 4.1% |
| | Met Oxidation | ≤ 5% | 0.7 – 1.6% |
| | High Mannose Glycans | 2% – 12% | 6.2 – 8.5% |
| | Protein Dimer/Oligomers (SEC HMW) | ≤ 1% | 0.4 – 0.6% |
| | Protein Fragmentation (rCE LMW+MMW) | ≤ 1% | < 0.6% |
| | Glycation (LC K) | ≤ 5% | 0.8 – 1.5% |
| | Hydroxylysine (HC K) | ≤ 2% | < 0.1% |
| | Hydroxylysine (HC K) | ≤ 2% | 1.0 – 2.0% |
| | Osmolality | 250 – 350 mOsm/kg | 301 – 312 mOsm/kg |
| | Polysorbate 80 | 0.005% – 0.015% | 0.009 – 0.013% |
| | pH | 4.9 – 5.5 | 5.1 – 5.2 |
| Safety | Host Cell Protein | ≤ 100 ppm | 20 – 49 ppm |
| | Residual Protein A | < 6 ppm | < 1 ppm |
| | Endotoxin | ≤ 0.25 EU/mg | ≤ 0.0022 EU/mg |
| | Bioburden | ≤ 10 CFU/10 mL | 0 |


1. A view on the importance of "multi-attribute method" for measuring purity of biopharmaceuticals and improving over control strategy
   Rogers RS, Abernathy MJ, Richardson DD, Rouse JC, Sperry JB, Swann P, Wypych J, Yu C, Zang L, Deshpande R
2. Development of a quantitative mass spectrometry multi-attribute method for characterization, quality control testing and disposition of biologics
   Rogers RS, Nightlinger NS, Livingston B, Campbell P, Bailey R, Balland A. *MAbs*. 2015; 7(5): 881-890
3. An improved trypsin digestion method minimizes digestion-induced modifications on proteins
   Ren D, Pipes GD, Liu D, Shih LY, Nichols AC, Treuheit MJ, Brems DN, Bondarenko PV. *Anal Biochem*. 2009; 392(1): 12-21

# MAM Can Replace Several Methods & Associated Instruments in QC

| Current Method | Attribute | Proposed Method |
|---|---|---|
| rCE-SDS | Purity - Clips | Multi-Attribute Method (MAM) |
| CEX-HPLC | Purity – Charge Variants | |
| Glycan Map | Glycans | |
| Immunoassay | Identity | |

**HPLC-FLD (Glycan-map)** **HPLC-UV (CEX-HPLC)** **CE-UV (rCE-SDS)** **Plate Reader (immunoassay)**

MAM replaces four instrument types

**UPLC/MS (MAM)**

# Initial Regulatory Assumptions to Introduce MAM

- Introduction of MAM methodology required:
  - Data package to **demonstrate advantage of MAM** vs conventional methods
  - Justification to **replace conventional release assays**
  - Justification that **MAM better assesses** and better ensures product **safety & efficacy** profile
  - MAM deemed **suitable for intended use** on a product-specific basis
  - MAM is adequate as a **stability indicating** assay
  - Filing details must be developed to incorporate MAM into ICH CTD module 3 sections
    - **Focus on criticality** of Product Quality Attributes (PQAs) and **emphasize specifications on biologically relevant attributes** and consistency

- MAM details and filing strategy **proactively shared with Health Authorities**
  - Risks minimized with Agency engagement and advocacy

- **Global acceptance brings challenges** based on laws, guidance and historical expectations



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# MAM Regulatory Filing Strategy

- Amgen applied MAM principles to regulatory filings using a stepwise and **phase appropriate risk-based approach**
  - Early-stage clinical products (First in Human)
    - Introduce **MAM as characterization method** as part of S.3.1 Elucidation of Structure
    - Based on successful acceptance, apply MAM as choice method for **product disposition** (S.4 Control of **Drug Substance**)
  - Late-stage pivotal clinical products (Phase 2/3 to Commercial)
    - Based on continued success from early-stage programs, include MAM as choice method for product disposition on specifications (**DS/DP and Stability**) initial
  - Life-cycle products
    - Based on late-stage pivotal acceptance to **replace conventional testing methods with MAM**

- Using MAM on specifications for product disposition
  - Types of modifications reported: **deamidation, oxidation, glycation, glycosylation, sialylation, clipping**, etc.
  - Numerical acceptance criteria determined from experience and data collected



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# MAM Implementation Strategy & ETT Engagement

**Q2 2015** Characterization (IND S.3.1)
Acceptance of MAM as characterization method

**Q3 2015** GMP Release (IND S.3.1, S.4.4)
Acceptance of MAM as release method for ID & Glycan

**Q3 2016** Type C Meeting with US FDA/ETT
Requested additional information on comparability: MAM vs conventional methods
Requested additional information on MAM qualification, robustness, and precision

**Q1 2017** MAM INDa submitted

**Q2 2017** EU CTA (FR & BG)

**Q2 2017** GMP Release

**Q4 2017** Meeting Engagement w/ JP PMDA
5/1/2017- FDA response received requesting additional information on MAM technical capability

**Q1 2018** Meeting Engagement w/ CFDA
7/12/2017 - FDA teleconference: FDA very engaged in moving MAM forward as replacement QC method

**Q2 2018** ATO On-site Engagement w/ FDA ETT
5/29/2018 - Technical Report Submitted to ETT/OBP: Precedent product supporting use of MAM in place of conventional methods

**2019 - 2022** IND/CTA amendments filed and accepted for Phase 2 in 30+ countries

**Challenges**

- In addition to characterization data, prior to replacement of conventional methods, side-by-side testing with MAM was required in a pilot study
- Engagement with FDA ETT required significant time

## Clinical CTAs/INDs

Product 1
Product 2
Product 3
Product 4

Product 1

Product 1

Product 1

Product 1

Product 5
Product 6
Product 7
Product 8
Product 9



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# Summary: Impact of FDA ETT Engagement for MAM

**Detailed interactions with ETT provided helpful guidance:**

Replacement of conventional methods required extensive demonstration of comparability for MAM and conventional methods

Provided additional MAM characterization and qualification data for a single product before submitting MAM for other products

**Submission informed by ETT to support MAM introduction:**

Content from FDA ETT meeting minutes, responses to questions from our technical report, characterization and comparability data were compiled

Most of the information was submitted in a MAM specific 3.2.S.2.6 section

**Positive Outcome:**

Phase 2 accepted, 30+ countries

CEX-UPLC and rCE-SDS testing replaced with MAM for release and stability testing

8 years of development

Productive engagement with ETT but required significant time



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# Overall Impact of Innovation: Global Harmonization

**THE OVERALL IMPACT OF MAM OR ANY INNOVATIVE TECHNOLOGY IS MAXIMIZED WITH GLOBAL HARMONIZATION**

[1]Image: Scientific American



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# Acknowledgements


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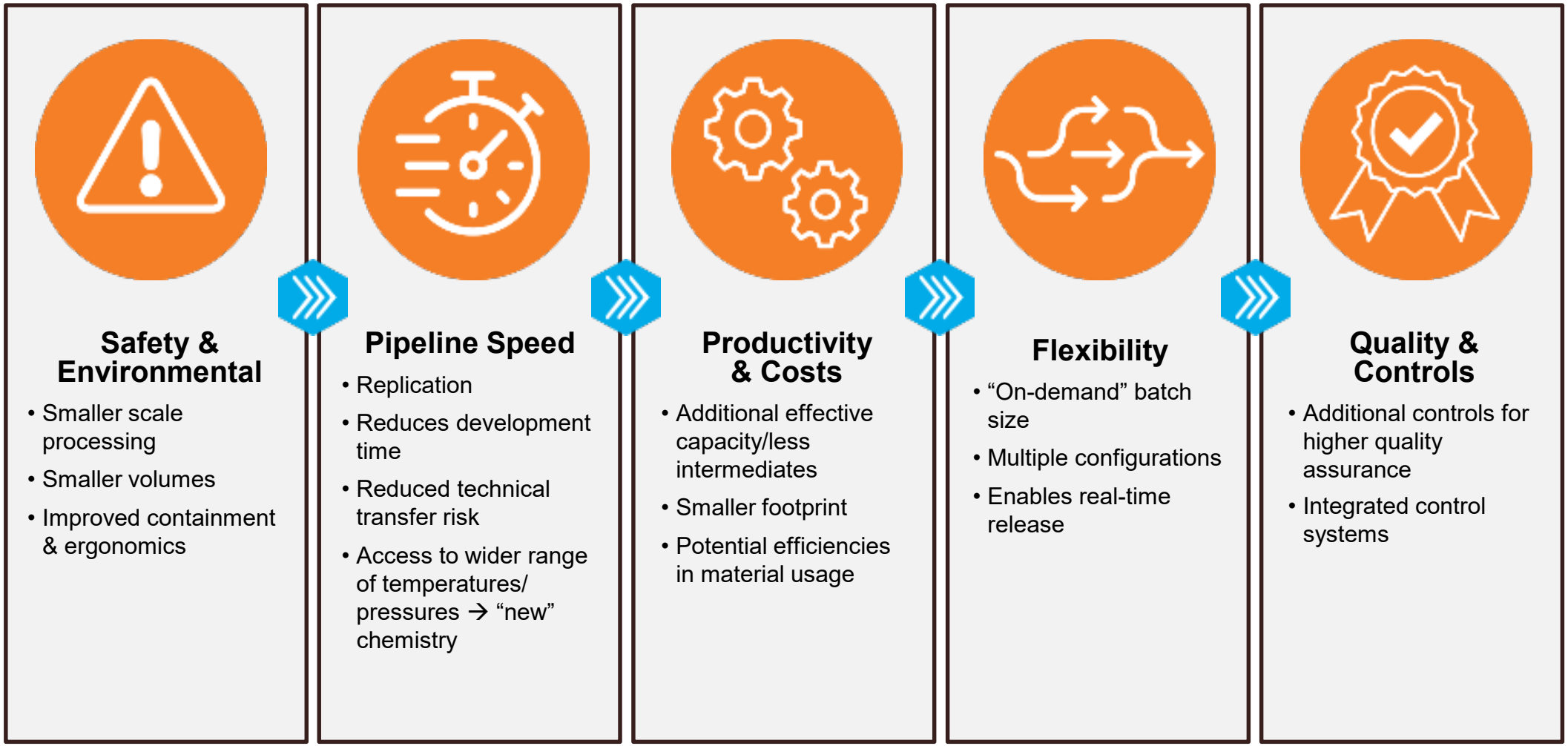
- Rohini Deshpande
- Patrick Swann


# Case Studies Working with FDA's ETT on Innovative Manufacturing

Ahmad Almaya
Global Regulator Affairs – CMC
Lilly Research Labs

Advancing Innovative Manufacturing Workshop
June 8th, 2023

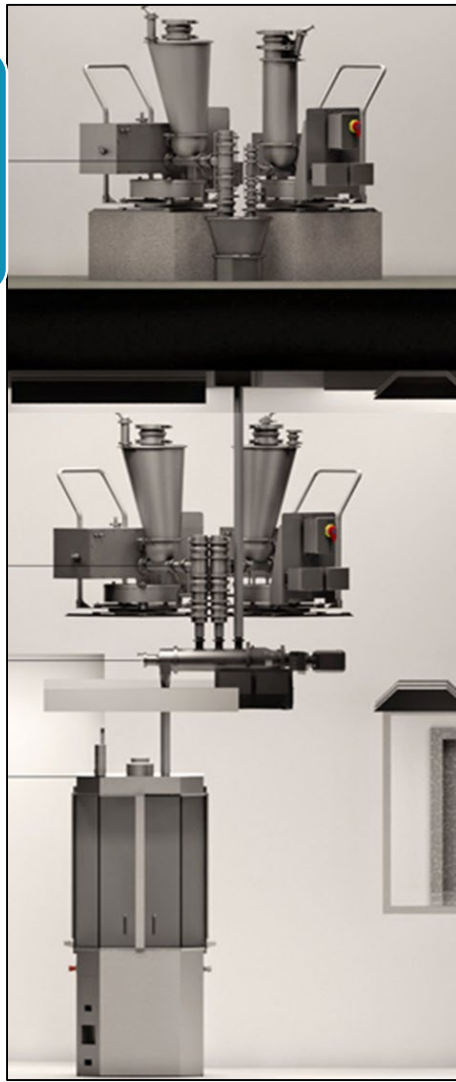
# Continuous manufacturing benefits



# A brief history of drug product continuous manufacturing at Lilly

- Initial implementation – continuous direct compression (cDC)

2012 → 2015 → 2017 ★ → 2023



Development and Optimization of Continuous Direct Compression Line

NCE Development on Lilly Portfolio on cDC

Commercial Experience on cDC

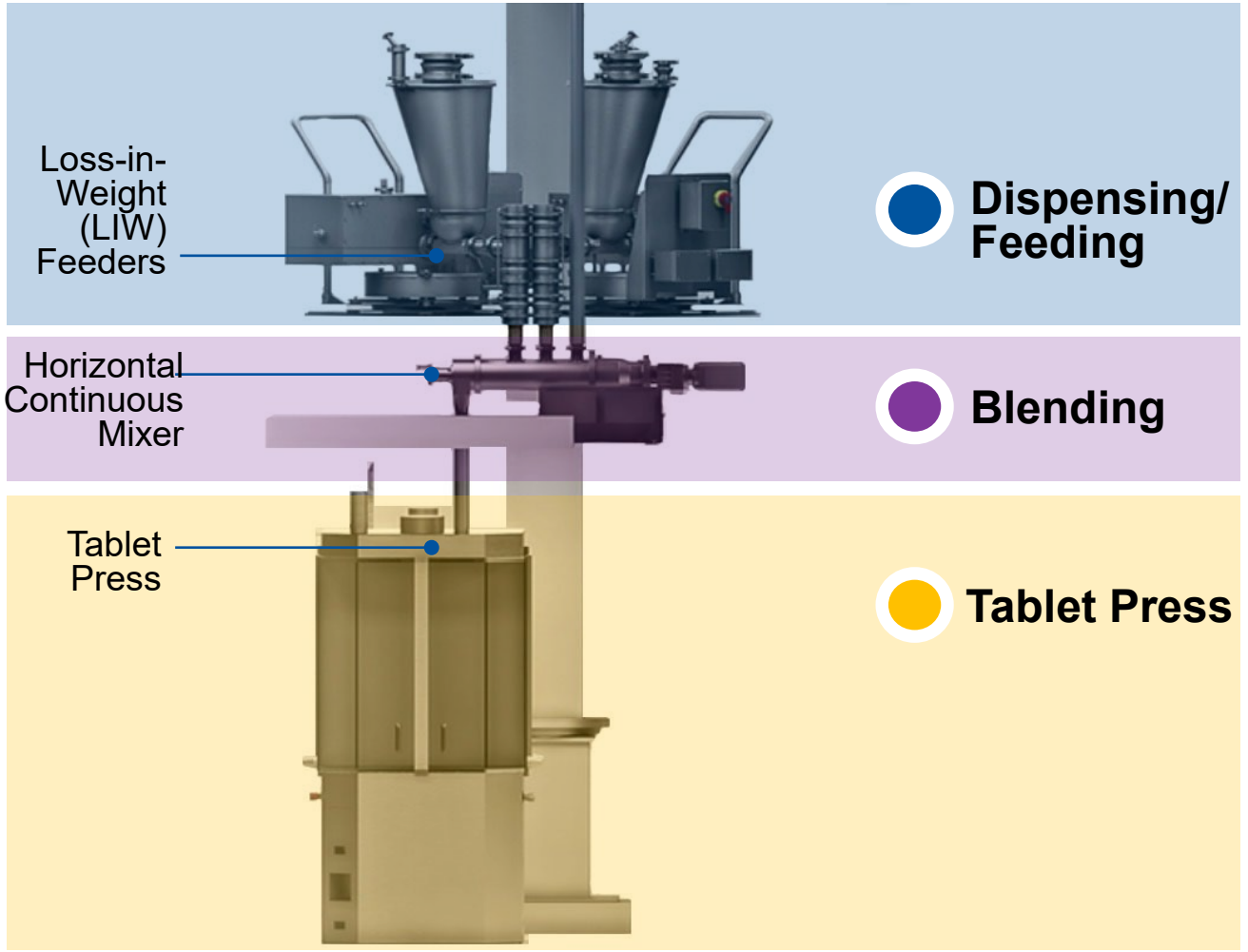
Expand Platforms

★ Verzenio™ approved as Lilly's first continuously manufactured drug product
*Pharmaceutical Engineering* Vol 38:1 Jan/Feb 2018

# Lilly's drug product continuous direct compression platform

- Compact physical design, coupled with optimized automation software and integrated PAT for process monitoring/control and RTRT.

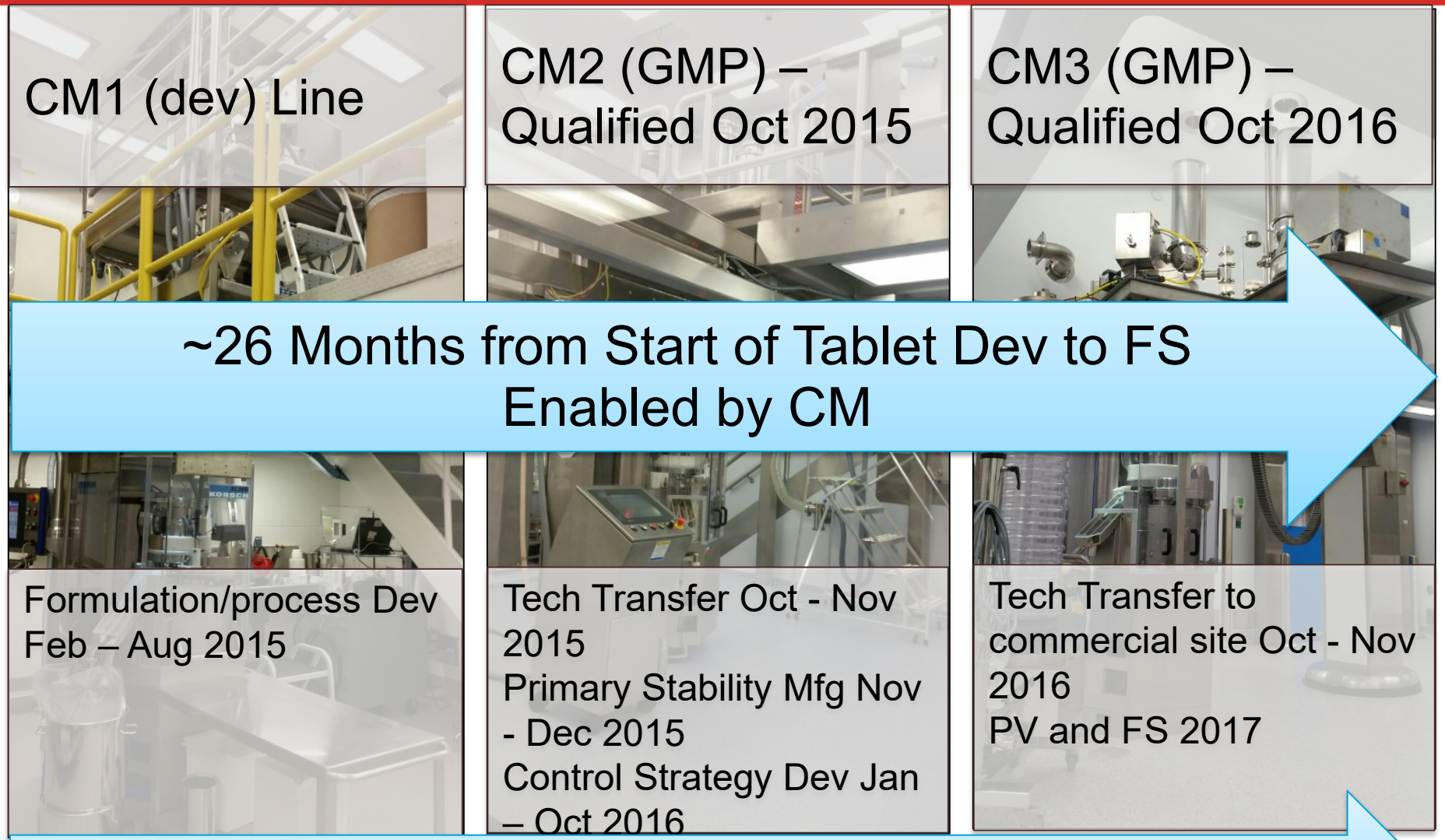
- Real time process monitoring, multiple feedforward and feedback control loops, and automated product collection/rejection decisions.



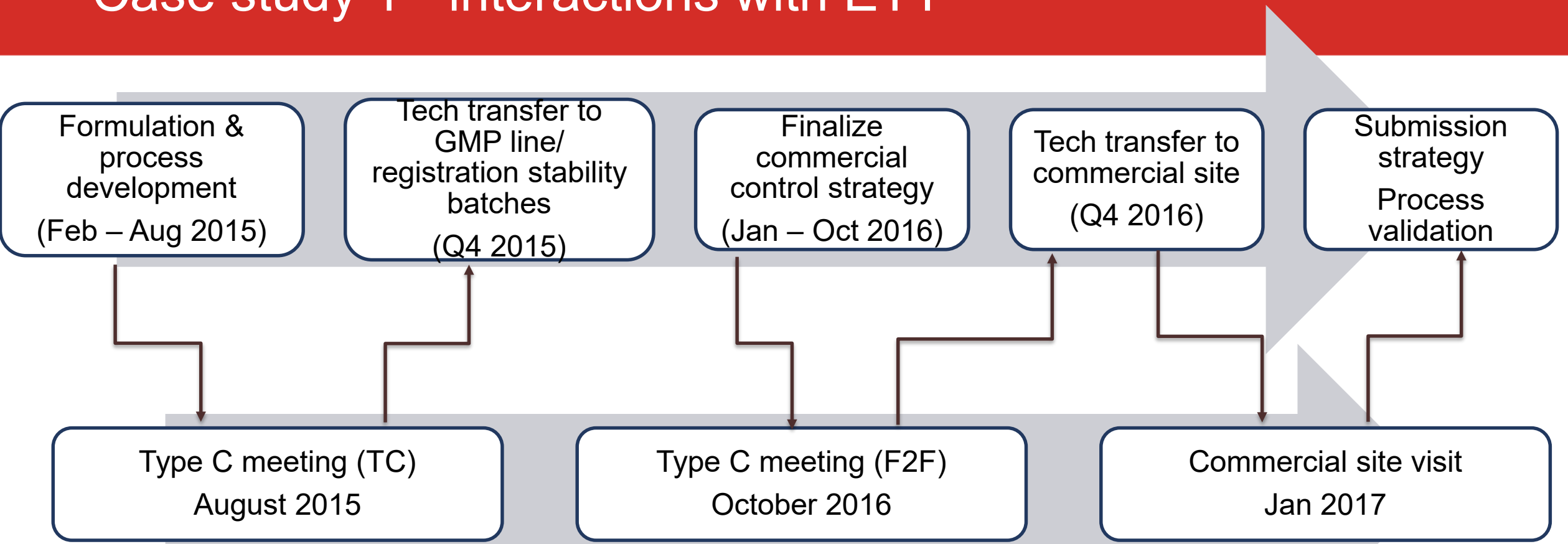
# Case study 1 – drug product with continuous direct compression

- New chemical entity.
- Only one DP was approved in US/EU with CM at the time dev with CM started (2015).
- Differences in Lilly's CM unit design and control approaches from other companies' at that time.
- This necessitated a regulatory interaction plan prior to MAA filing.

# Case study 1 – drug product with continuous direct compression



# Case study 1 - interactions with ETT




- Lilly CM platform introduction
- Batch definition plans
- Batch size flexibility with CM
- Preliminary control strategy plans

- Final control strategy
- Tech transfer/process validation plans

- FDA reviewers and GMP inspectors.
- 2-day meeting. Presentations, discussions, and tours.
- Comprehensive, in-depth discussions of technical, regulatory, and quality topics.
- Discussed unresolved topics from earlier meetings

# Case study 1 - interactions with ETT

US Approval 2017

Commercial production since 2017

Global submissions/approvals in more than 50 markets with CM and RTRT

*(3rd CM approval in US; 1st CM approval in Japan/China)*

Informal TC – 2017

Lessons Learned

Written only Type C meeting – 2018

Proposed approaches to expand RTRT to additional CQAs

Written only Type C Meeting – 2020

Proposed post approval reporting category for batch size increases

Written Only Type C meeting - 2023

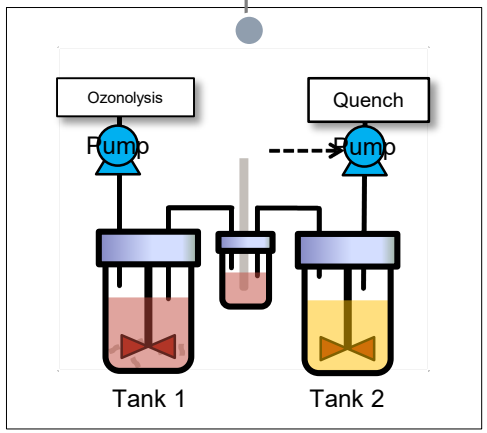
Proposed plans for a post approval change

# Case study 2 – drug product with continuous wet granulation

- Lilly's DP CM platform was expanded to include a fluid bed granulation option (semi-continuous).
- The dried granules from the fluid bed are forward processed onto Lilly's existing continuous direct compression platform.
- This platform was used to develop drug product for a high drug load asset.
- Interaction with ETT:
  - Type C Meeting (TC) – March 2022
  - Leveraged prior internal experience with cDC; focused Type C meeting discussion topics on new control strategy elements related to semi-continuous fluid bed granulation processing.

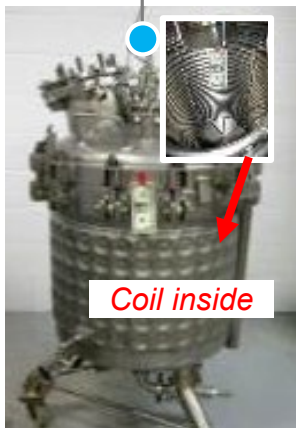
# DS continuous manufacturing history at Lilly

## 1970's-80's




Continuous Unit Operation (Mfg)

## 2006-10




Platform & Technology Development in R&D

## 2013

3 Hybrid Processes in Manufacturing at Kinsale

## 2014

Small Volume Continuous (SVC) Manufacturing in Fumehood at Kinsale

## 2017+

CM Facility at Kinsale

**Hybrid CM** → **Multiple Steps in CM**

# Case study 3 – drug substance continuous manufacturing

- Hybrid drug substance process - integrated batch and continuous operations.
- ETT interactions:
  - Type C meeting (TC)
  - Virtual site visit
    - A site visit was not possible due to Covid travel restrictions
    - Virtual visit consisted of presentations, videos, and on-line meetings/discussions.
  - Topics included state of control definition, start-up/shutdown concepts, product collection decisions, and batch definition plans.

# Closing remarks

- FDA's Emerging Technology Program has been instrumental in facilitating the implementation of new innovative manufacturing technologies.
- ETP provides the mechanisms for early dialogue and alignment on technical and regulatory aspects of new technologies.
- Such a mechanism will continue to be critical for implementation of future new innovative technologies.

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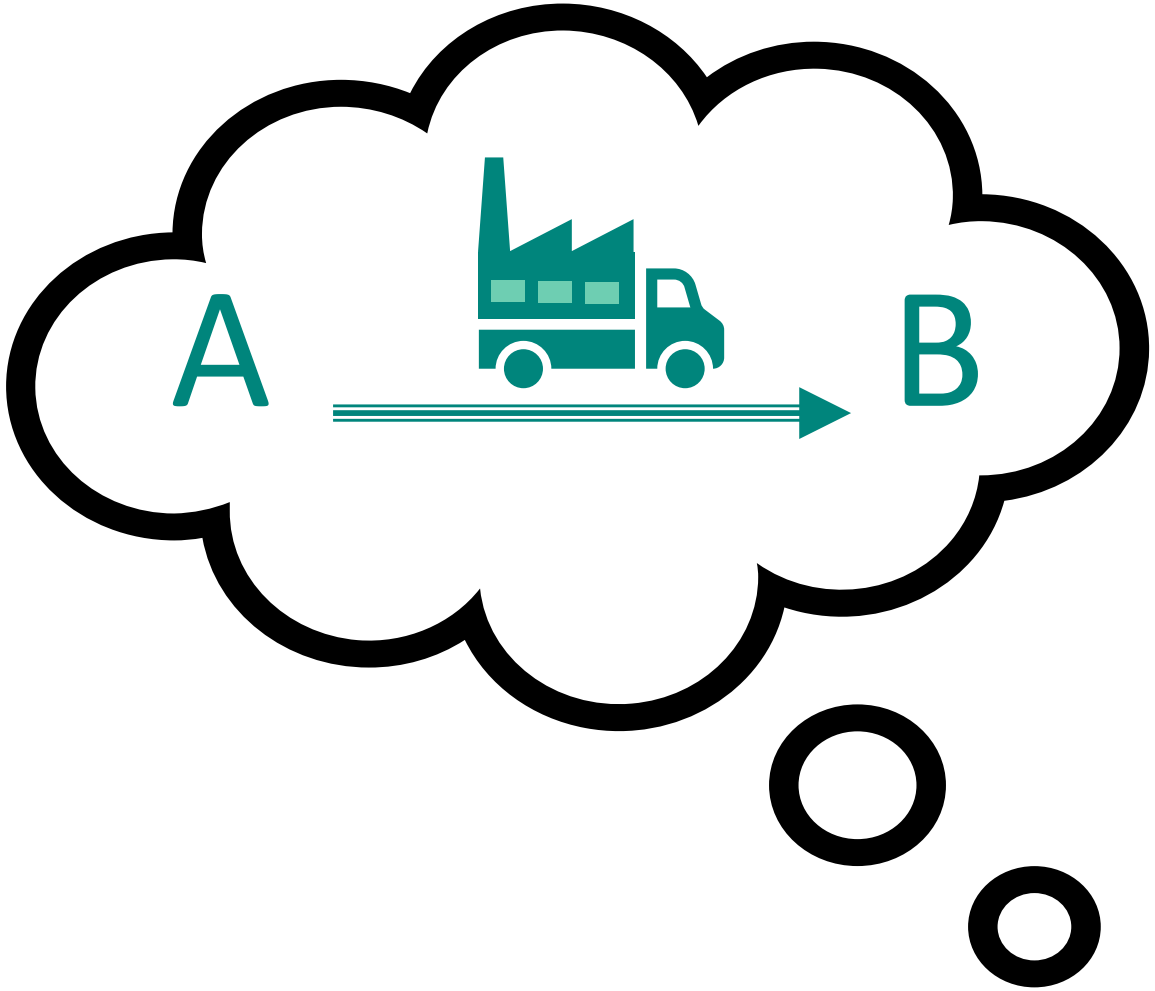
Almaya_ahmad@lilly.com

# ETP Case Study: Distributed Manufacturing (DM)

Celeste Frankenfeld Lamm

(June/08/2023)

# DM is Gaining Global Acceptance, and It Started with the ETT




**The challenge:**

We had a small molecule drug with a long-acting formulation in development. Changing manufacturing sites is quite complex, potentially introducing risk to the product, and incurring long delays (BE studies that are even longer for long-active products, stability studies, tech transfer, validation, inspections etc.)

**The solution:**

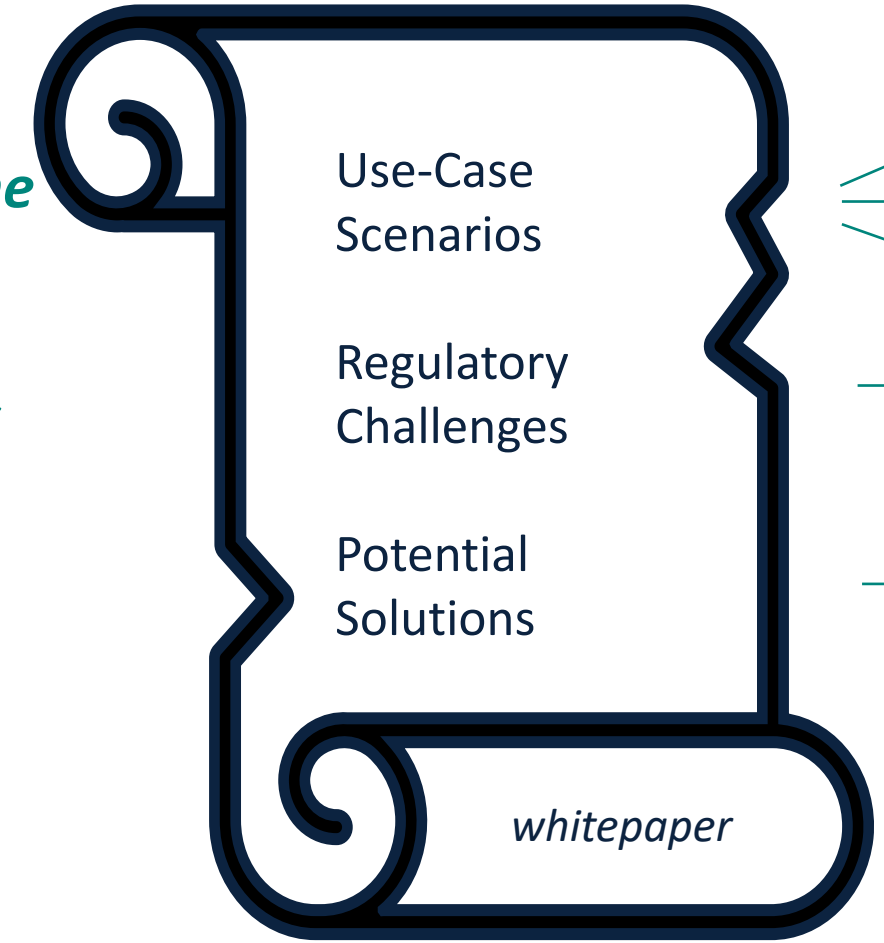
Could we move the location without changing the site?

**Application to ETP for Mobile Manufacturing**

- 3.5 pages for initial application
- 13 pages for background document after acceptance

# At our first Face-to-Face, the ETT Gave Surprising Advice

***If we're going to change the regulatory framework, we want it to be robust - think about all of the ways you might use this technology***

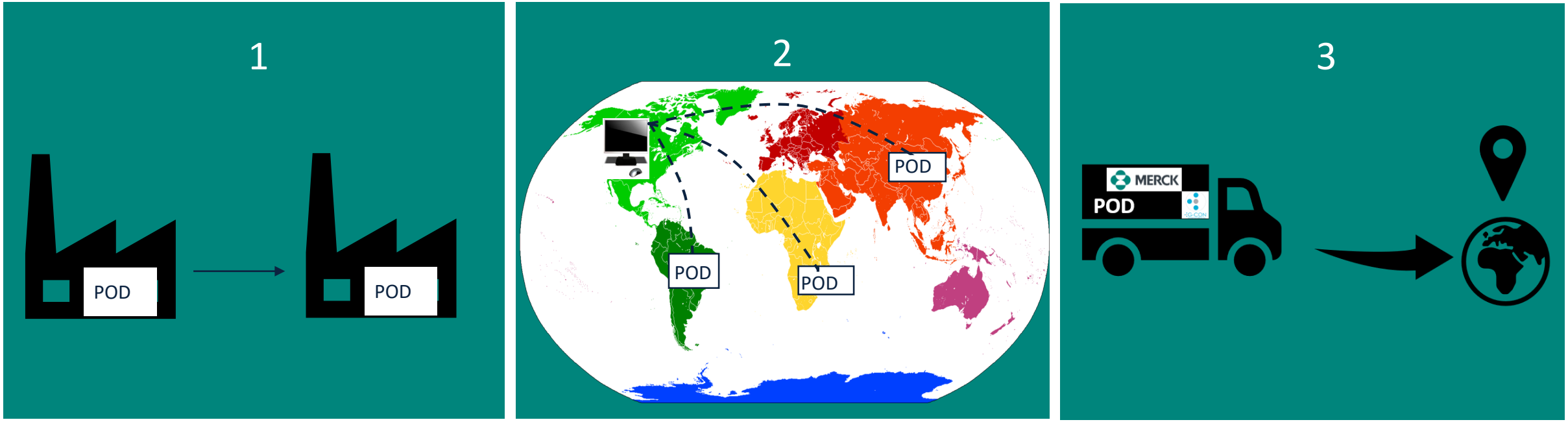



→ Moving unit from point A to point B
→ A network of identical units
→ A unit always on wheels

→ Combed through CFR and guidelines to ID challenges

→ Proposed solutions – which have continued to develop with FDA and industry engagement

# A Second Meeting with the ETT Enabled Frank Discussion




We posed questions regarding acceptability of our proposals, and fielded additional questions

How frequently would a unit move?

What if there is an inspectional finding in one unit? How would that be managed across the network of units?

What considerations and factors would be evaluated when moving?

# The Concept Continues to Progress….What More is Needed?

ETT

FDA FRAME

Discussion Paper 3Q 2022

Public Workshop Nov 2022

Globally aligned approach for global supply chain!

Risk-Based Guidance that provides clarity in expectations

# Thank you

**Merck & Co., Inc.**

**E-mail:** celeste.frankenfeld@merck.com

**Address:** Rahway, NJ, USA

# Break

Workshop will resume at **12:35 p.m.**

# Regulatory Challenges to Adoption

*Riley Myers,* Center for Drug Evaluation and Research

U.S. Food and Drug Administration

U.S. FOOD & DRUG ADMINISTRATION

# Mitigating Regulatory Challenges to Adoption of Advanced Manufacturing

**Riley C. Myers, Ph.D.**
Chief, Advanced Pharmaceutical Manufacturing Laboratory
Office of Testing and Research
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Advancing the Utilization and Supporting the Implementation of Innovative Manufacturing Approaches

June 8, 2023

# Examples of Historical FDA Leadership in AM

Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach

- Encourage the early adoption of new technological advances by the pharmaceutical industry
- Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science

# Identifying and Mitigating Regulatory Challenges

- CDER's Emerging Technology Program
- CBER's Advanced Technologies Program
- International Harmonization
- FDA Guidance
- FDA Research
- Workforce Development
- Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)

# FDA Supports International Harmonization for AM

- ICH Q13—Continuous Manufacturing
- ICH Q5A(R2)—Viral Clearance for Biotech CM
- ICH Q14—Multivariate Models for Analytical Procedures and Real Time Release Testing
- ICH Q12—Lifecycle Management

# FDA Guidance Provides Recommended Approaches to Enable Adoption of AM

- PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance
- Q8, Q9, & Q10 Questions and Answers
- Development and Submission of Near Infrared Analytical Procedures
- Comparability Protocols for Postapproval Changes to CMC Information in an NDA, ANDA, or BLA
- Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization

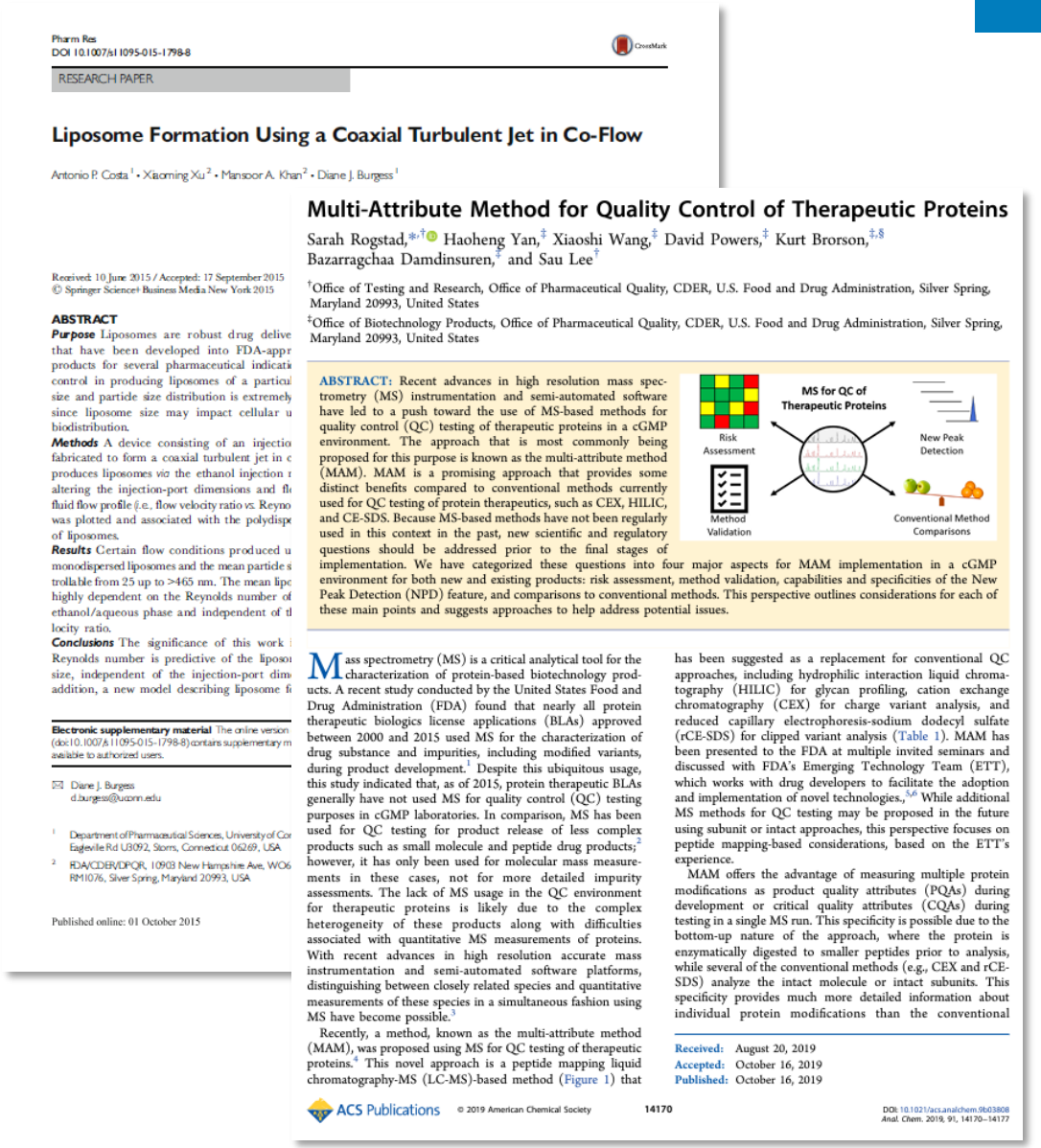
# Impact of CDER Research on Regulatory Outcomes

- Directly supported ETT feedback and application assessment for over 12 ETP projects
- Policy and guidance development
  - Informed development of ICH Q13 Continuous Manufacturing of Drug Substances and Drug Products
  - Supporting development and implementation for FRAME
- Workforce development

# FDA Research Mitigates Regulatory Barriers

- Costa et. al.—Continuous production of liposomes for drug products and vaccines

- Rogstad et. al.—Data driven considerations for supporting performance of biopharmaceutical MAM



Pharm Res
DOI 10.1007/s11095-015-1798-8

RESEARCH PAPER

**Liposome Formation Using a Coaxial Turbulent Jet in Co-Flow**

Antonio P. Costa[1] • Xiaoming Xu[2] • Mansoor A. Khan[2] • Diane J. Burgess[1]

Received: 10 June 2015 / Accepted: 17 September 2015
© Springer Science+Business Media New York 2015

**ABSTRACT**

***Purpose*** Liposomes are robust drug delive
that have been developed into FDA-appr
products for several pharmaceutical indicati
control in producing liposomes of a particul
size and particle size distribution is extremely
since liposome size may impact cellular u
biodistribution.

***Methods*** A device consisting of an injectio
fabricated to form a coaxial turbulent jet in c
produces liposomes *via* the ethanol injection r
altering the injection-port dimensions and fl
fluid flow profile (i.e., flow velocity ratio *vs.* Reyno
was plotted and associated with the polydispe
of liposomes.

***Results*** Certain flow conditions produced u
monodispersed liposomes and the mean particle s
trollable from 25 up to >465 nm. The mean lipo
highly dependent on the Reynolds number of
ethanol/aqueous phase and independent of tl
locity ratio.

***Conclusions*** The significance of this work
Reynolds number is predictive of the liposo
size, independent of the injection-port dim
addition, a new model describing liposome fi

**Electronic supplementary material** The online version
(doi:10.1007/s11095-015-1798-8) contains supplementary m
available to authorized users.

✉ Diane J. Burgess
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RM1076, Silver Spring, Maryland 20993, USA

Published online: 01 October 2015

**Multi-Attribute Method for Quality Control of Therapeutic Proteins**

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**ABSTRACT:** Recent advances in high resolution mass spectrometry (MS) instrumentation and semi-automated software have led to a push toward the use of MS-based methods for quality control (QC) testing of therapeutic proteins in a cGMP environment. The approach that is most commonly being proposed for this purpose is known as the multi-attribute method (MAM). MAM is a promising approach that provides some distinct benefits compared to conventional methods currently used for QC testing of protein therapeutics, such as CEX, HILIC, and CE-SDS. Because MS-based methods have not been regularly used in this context in the past, new scientific and regulatory questions should be addressed prior to the final stages of implementation. We have categorized these questions into four major aspects for MAM implementation in a cGMP environment for both new and existing products: risk assessment, method validation, capabilities and specificities of the New Peak Detection (NPD) feature, and comparisons to conventional methods. This perspective outlines considerations for each of these main points and suggests approaches to help address potential issues.



Mass spectrometry (MS) is a critical analytical tool for the characterization of protein-based biotechnology products. A recent study conducted by the United States Food and Drug Administration (FDA) found that nearly all protein therapeutic biologics license applications (BLAs) approved between 2000 and 2015 used MS for the characterization of drug substance and impurities, including modified variants, during product development.[1] Despite this ubiquitous usage, this study indicated that, as of 2015, protein therapeutic BLAs generally have not used MS for quality control (QC) testing purposes in cGMP laboratories. In comparison, MS has been used for QC testing for product release of less complex products such as small molecule and peptide drug products;[2] however, it has only been used for molecular mass measurements in these cases, not for more detailed impurity assessments. The lack of MS usage in the QC environment for therapeutic proteins is likely due to the complex heterogeneity of these products along with difficulties associated with quantitative MS measurements of proteins. With recent advances in high resolution accurate mass instrumentation and semi-automated software platforms, distinguishing between closely related species and quantitative measurements of these species in a simultaneous fashion using MS have become possible.[3]

Recently, a method, known as the multi-attribute method (MAM), was proposed using MS for QC testing of therapeutic proteins.[4] This novel approach is a peptide mapping liquid chromatography-MS (LC-MS)-based method (Figure 1) that has been suggested as a replacement for conventional QC approaches, including hydrophilic interaction liquid chromatography (HILIC) for glycan profiling, cation exchange chromatography (CEX) for charge variant analysis, and reduced capillary electrophoresis-sodium dodecyl sulfate (rCE-SDS) for clipped variant analysis (Table 1). MAM has been presented to the FDA at multiple invited seminars and discussed with FDA's Emerging Technology Team (ETT), which works with drug developers to facilitate the adoption and implementation of novel technologies.,[5,6] While additional MS methods for QC testing may be proposed in the future using subunit or intact approaches, this perspective focuses on peptide mapping-based considerations, based on the ETT's experience.

MAM offers the advantage of measuring multiple protein modifications as product quality attributes (PQAs) during development or critical quality attributes (CQAs) during testing in a single MS run. This specificity is possible due to the bottom-up nature of the approach, where the protein is enzymatically digested to smaller peptides prior to analysis, while several of the conventional methods (e.g., CEX and rCE-SDS) analyze the intact molecule or intact subunits. This specificity provides much more detailed information about individual protein modifications than the conventional

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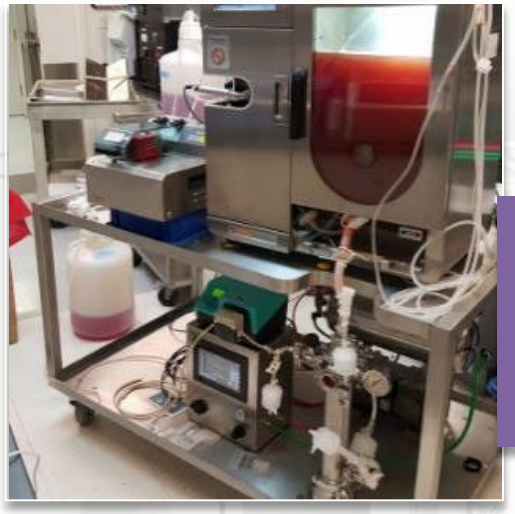
DOI: 10.1021/acs.analchem.9b03808
Anal. Chem. 2019, 91, 14170−14177

# CDER-funded Research Supports Innovation

| Intramural Research |
| --- |
| Novel Manufacturing Methods (10 projects) |
| Precision Analytics (16 projects) |
| Advanced Manufacturing of Biopharmaceuticals (11 projects) |
| Manufacturing of Glycoproteins (3 projects) |
| Manufacturing of Synthetic Nucleic Acid Sequences (1 project) |
| Process Modeling, and Artificial Intelligence (AI)/ Machine Learning (ML) (4 projects) |



Continuous perfusion bioreactor

| Extramural collaborations via grants and contracts |
| --- |
| Industry 4.0 and Smart Manufacturing (3 projects) |
| Novel Manufacturing Methods (6 projects) |
| Novel Process Analytical Technologies (4 projects) |
| Process Modeling and Simulation (2 projects) |
| Advanced Manufacturing Training (1 project) |

**Projects generated more than 78 internal reports and publications**

# Examples of Supported CBER Projects

- 3D Bioprinting for tissue engineering
- Novel manufacturing approaches for cell therapy products
  (CQA discovery, purification, continuous production)
- Continuous Manufacturing
  (Vaccines, AAV vectors for gene therapy)
- Process modeling/simulation
- Non-destructive analytics (NMR) for evaluating product quality

https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-program-extramural-research-funding

# FDA Routinely Reviews the Impact of Intramural and Extramural Research on Adoption of AM


International Journal of Pharmaceutics 491 (2015) 2–7

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/ijpharm

Mini review

FDA pharmaceutical quality oversight

Lawrence X. Yu*, Janet Woodcock

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ARTICLE INFO

ABSTRACT

1. Introduction


J Pharm Innov (2015) 10:191–199

DOI 10.1007/s12247-015-9215-8

REVIEW ARTICLE

Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production

Sau L. Lee · Thomas F. O'Connor · Xiaochuan Yang · Celia N. Cruz · Sharmista Chatterjee · Rapti D. Madurawe · Christine M. V. Moore · Lawrence X. Yu · Janet Woodcock

Published online: 19 March 2015

© Springer Science+Business Media New York (outside the USA) 2015

Abstract The Food and Drug Administration (FDA) regu-

1. Introduction


The AAPS Journal, Vol. 17, No. 4, July 2015 (© 2015)

DOI: 10.1208/s12248-015-9754-4

Meeting Report

Advancing Product Quality: a Summary of the Inaugural FDA/PQRI Conference

Lawrence X. Yu,[1,5] Jeffrey Baker,[1] Susan C. Bertam,[2] Ashley Boam,[1] E. J. Brandreth,[2] Lucinda Buhse,[1] Thomas Cosgrove,[1] David Doleski,[1] Lynne Ensor,[1] Joseph Famulare,[4] Mohan Ganapathy,[2] Gustavo Grampp,[2] David Hussong,[1] Robert Iser,[1] Gordon Johnston,[2] Filippos Kesisoglou,[3] Mansoor Khan,[1] Steven Kozlowski,[1] Emanuela Lucaya,[1] Sau L. Lee,[1] Stephen Miller,[1] Sarah Pope Miksinski,[1] Christine M. V. Moore,[1] Theresa Mullin,[1] G. K. Raju,[4,5] Andre Raw,[1] Susan Rosencrance,[1] Mark Rosolowsky,[10] Paul Stinavage,[11] Hayden Thomas,[12] Russell Wesdyk,[1] Joerg Windisch,[13] and Sivakumar Vaithiyalingam[14]

Received 24 January 2015; accepted 16 March 2015; published online 4 April 2015

Abstract. On September 16 and 17, 2014, the Food and Drug Administration (FDA) and Product Quality Research Institute (PQRI) inaugurated their Conference on Evolving Product Quality. The Conference is conceived as an annual forum in which scientists from regulatory agencies, industry, and academia may exchange viewpoints and work together to advance pharmaceutical quality. This Conference Summary Report highlights key topics of this conference, including (1) risk-based approaches to pharmaceutical development, manufacturing, regulatory assessment, and post-approval changes; (2) FDA-proposed quality metrics for products, facilities, and quality management systems; (3) performance-based quality assessment and clinically relevant specifications; (4) recent developments and implementation of continuous manufacturing processes, question-based review, and European Medicines Agency (EMA)-FDA pilot for Quality-by-Design (QbD) applications; and (5) breakthrough therapies, biosimilars, and international harmonization, focusing on ICH M7 and Q3D guidelines. The second FDA/PQRI conference on advancing product quality is planned for October 5–7, 2015.

INTRODUCTION

The purpose of the Conference on Evolving Product Quality, under the sponsorship of the Food and Drug Administration (FDA) and Product Quality Research Institute (PQRI), is to bring regulators, industry professionals, and academic researchers together and advance pharmaceutical quality. The FDA/PQRI 2014 conference consisted of a plenary session and 12 breakout sessions arranged in four major tracks: risk management and quality metrics; performance-based quality assessment; innovation in manufacturing and regulatory assessment; and emerging


COMMENTARY

Regulatory and Quality Considerations for Continuous Manufacturing
May 20–21, 2014 Continuous Manufacturing Symposium

GRETCHEN ALLISON,[1] YANXI TAN CAIN,[2] CHARLES COONEY,[3] TOM GARCIA,[4] TARA GOOEN BIZJAK,[5] OYVIND HOLTE,[6] NIRDOSH JAGOTA,[7] BEKKI KOMAS,[8] EVDOKIA KORAKIANITI,[9] DORA KOURTI,[10] RAPTI MADURAWE,[2] ELAINE MORTEFIELD,[11] FRANK MONTGOMERY,[12] MOHEB NASR,[13] WILLIAM RANDOLPH,[14] JEAN-LOUIS ROBERT,[15] DAVE RUDD,[9] DIANE ZEZZA[16]

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[9]EMA, London, UK
[10]Global Manufacturing and Supply, GSK, Ware, UK
[11]Pharmaceutical Development, Vertex Pharmaceuticals Incorporated, Boston, Massachusetts
[12]Global Medicines Development, J
[13]Research and Development, Glaxo
[14]Janssen Supply Group, Janssen, Ik
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Received 10 October 2014; revised

Published online 14 January 2015

ABSTRACT: This paper assesses the manufacturing. It summarizes curre regulatory aspects, including contin key Good Manufacturing Practice (G forward to facilitate implementation 2015

Keywords: continuous manufactur cessing; bioequivalence

INTRODUCTION

In a continuous manufacturing p or mixtures are fed into a proce the processed output materials a though the amount of material h instance may be relatively small ing process, the process may be generate quantities of finished p quality. In an end-to-end continu

Correspondence to: Mohsh Nasr (Telep 4704; E-mail: mohsh.m.nasr@gsk.com)

The views expressed in this paper by p personal views and do not represent the offi academic institution, trade associations, or not a regulatory guideline and the order c paper does not reflect agreements among in the regulatory files and what should be quality system (PQS) and becoms subject t

Journal of Pharmaceutical Sciences, Vol. 1 © 2016 Wiley Periodicals, Inc. and the Ame


International Journal of Pharmaceutics 528 (2017) 354–359

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

The future of pharmaceutical quality and the path to get there

Lawrence X. Yu*, Michael Kopcha

Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD 20993, United States

ARTICLE INFO

ABSTRACT

1. Introduction

The U.S. Food and Drug Administr Quality for the 21 st Century Initiative efficient, agile, flexible pharmaceutical reliably produce high quality drugs oversight (FDA, 2004a). Over the year been made toward this vision, in technology (PAT) (FDA, 2004b), Cu Practices (CGMPs) for the 21 st centu Design (QbD) (FDA, 2009a), and E 2015a) initiatives. Overall product/p significantly higher, concerns over pha have continued due to unacceptably hi shortages. Largely driven by legacy product recalls has actually increase 2015b) (Fig. 1). Alarming drug short product quality remains a primary driv improve quality and address shortages the patient and consumer. These recen

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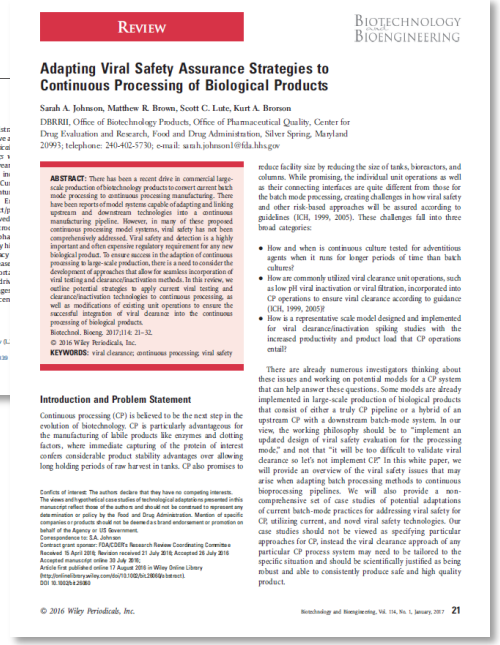
http://dx.doi.org/10.1016/j.ijpharm.2017.06.039 0378-5173/Published by Elsevier B.V.


REVIEW

BIOTECHNOLOGY BIOENGINEERING

Adapting Viral Safety Assurance Strategies to Continuous Processing of Biological Products

Sarah A. Johnson, Matthew R. Brown, Scott C. Lute, Kurt A. Bronson

DBRRII, Office of Biotechnology Products, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland 20993; telephone: 240-402-5730; e-mail: sarah.johnson1@fda.hhs.gov

ABSTRACT: There has been a recent drive in commercial large-scale production of biotechnology products to convert current batch mode processing to continuous processing manufacturing. There have been reports of model systems capable of adapting and linking upstream and downstream technologies into a continuous manufacturing pipeline. However, in many of these proposed continuous processing model systems, viral safety has not been comprehensively addressed. Viral safety and detection is a highly important and often expensive regulatory requirement for any new biological product. To ensure success in the adoption of continuous processing to large-scale production, there is a need to consider the development of approaches that allow for seamless incorporation of viral testing and clearance/inactivation methods. In this review, we outline potential strategies to apply current viral testing and clearance/inactivation technologies to continuous processing, as well as modifications of existing unit operations to ensure the successful integration of viral clearance into the continuous processing of biological products.

Biotechnol. Bioeng. 2017;114: 21–32.

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KEYWORDS: viral clearance; continuous processing; viral safety

Introduction and Problem Statement

Continuous processing (CP) is believed to be the next step in the evolution of biotechnology. CP is particularly advantageous for the manufacturing of labile products like enzymes and clotting factors, where immediate capturing of the protein of interest confers considerable product stability advantages over allowing long holding periods of raw harvest in tanks. CP also promises to reduce facility size by reducing the size of tanks, bioreactors, and columns. While promising, the individual unit operations as well as their connecting interfaces are quite different from those for the batch mode processing, creating challenges in how viral safety and other risk-based approaches will be assured according to guidelines (ICH, 1999, 2005). These challenges fall into three broad categories:

- How and when is continuous culture tested for adventitious agents when it runs for longer periods of time than batch cultures?
- How are commonly utilized viral clearance unit operations, such as low pH viral inactivation or viral filtration, incorporated into CP operations to ensure viral clearance according to guidance (ICH, 1999, 2005)?
- How is a representative scale model designed and implemented for viral clearance/inactivation spiking studies with the increased productivity and product load that CP operations entail?

There are already numerous investigators thinking about these issues and working on potential models for a CP system that can help answer these questions. Some models are already implemented in large-scale production of biological products that consist of either a truly CP pipeline or a hybrid of an upstream CP with a downstream batch-mode system. In our view, the working philosophy should be to "implement an updated design of viral safety evaluation for the processing mode," and not that "it will be too difficult to validate viral clearance so let's not implement CP." In this white paper, we will provide an overview of the viral safety issues that may arise when adapting batch processing methods to continuous bioprocessing pipelines. We will also provide a non-comprehensive set of case studies of potential adaptations of current batch-mode practices for addressing viral safety for CP, utilizing current, and novel viral safety technologies. Our case studies should not be viewed as specifying particular approaches for CP, instead the viral clearance approach of any particular CP process system may need to be tailored to the specific situation and should be scientifically justified as being robust and able to consistently produce safe and high quality product.

Conflicts of interest: The authors declare that they have no competing interests.

The views and hypothetical case studies of technological adaptations presented in this manuscript reflect those of the authors and should not be construed to represent any determination or policy by the Food and Drug Administration. Mention of specific companies or products should not be deemed as a brand endorsement or promotion on behalf of the Agency or US Government.

Correspondence to: S.A. Johnson

Contract grant sponsor: FDA/CDER's Research Review Coordinating Committee

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Biotechnology and Bioengineering, Vol. 114, No. 1, January, 2017 21


Trends in Biotechnology

CellPress REVIEWS

Review

The Current Scientific and Regulatory Landscape in Advancing Integrated Continuous Biopharmaceutical Manufacturing

Adam C. Fisher,[1,3] Mark-Henry Kamga,[2,3,*] Cyrus Agarabi,[1] Kurt Brorson,[1,*] Sau L. Lee,[1] and Seongkyu Yoon[2,4,*]

There is a trend across the pharmaceutical sector toward process intensification and continuous manufacturing to biotechnology products. For biotech manufacturing technology behind upst has the potential to reduce product s production flexibility, simplify scale-up p reduce facility footprints, increase produ On the upstream side of biotechnology cell cultures are fairly well established. H biomanufacturing requires the uninterru operations (upstream and downstream) steps occurring between them. This work regulatory landscape surrounding the im ous biomanufacturing.

Highlights

Advancing Integrated Continuous Biopha Biologics Landscape

The application of recombinant DNA technology pharmaceutical landscape. The era of commerci October 28, 1982, with the U.S. FDA base Glossia insulin [1]. Today, the majority of the top 10 best recombinant biopreosses [2] and monoclonal growing drug product classes on the market [3] the U.S. under the Food Drug and Cosmetic Act Service (PHS) Act. As such, their clinical developm **Drug Applications (INDs)**, while the actual prod **Biologics License Application**, including those Act (i.e., **biosimilars**). In the U.S., the era of biosi first biosimilar products: two filgrastim products etanercept, two adalimumab products, trastuzu era, the major market drivers of pharmaceutical b ment time and maximizing cost control. This natu products rather than processes, especially postm


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Industry 4.0 for pharmaceutical manufacturing: Preparing for the smart factories of the future

N. Sarah Arden, Adam C. Fisher *, Katherine Tyner, Lawrence X. Yu, Sau L. Lee, Michael Kopcha

Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD 20993, United States

ARTICLE INFO

ABSTRACT

1. Introduction

The term Industry 4.0 refers to the fourth industrial re brings together rapidly evolving technologies such as i things (IoT), artificial intelligence (AI), robotics, computing to dramatically change the landscape of man dustry 4.0 is characterized by integrated, autonomo organizing production systems. New thinking will b realize Industry 4.0 for pharmaceuticals and overcome current manufacturing infrastructure, operations, and reg implementing many of the advanced technologies and approaches needed to enable Industry 4.0 may not be ea be worthwhile as they bring the potential for higher ou manufacturing safety, improved quality, better value, in additional flexibility, and reduced waste (Beg, 2016; Boor and Wee, 2018; Clemens, 2016; Tilley, 2017).

1.1. Industry 1.0

If Industry 4.0 is the future, then Industry 1.0 is the st the modern pharmaceutical industry. The application

* Corresponding author at: Food and Drug Administration, Ce States.

https://doi.org/10.1016/j.ijpharm.2021.120554

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journal homepage: www.elsevier.com/locate/ijpharm

An audit of pharmaceutical continuous manufacturing regulatory submissions and outcomes in the US

Adam C. Fisher, William Liu, Andreas Schick, Mahesh Ramanadham, Sharmista Chatterjee, Raphael Brykman, Sau L. Lee, Steven Kozlowski, Ashley B. Boam, Stelios C. Tsinontides *, Michael Kopcha

Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD 20993, United States

ARTICLE INFO

ABSTRACT

1. Introduction

Continuous manufacturing (CM) is a technology that sends materials produced during each process step directly and continuously to the next step for further processing. In such a process, input materials are continuously fed into production and transformed, and processed output materials are continuously removed. CM has been adopted in many industries (e.g., petroleum, commodity chemicals), while the pharmaceutical industry has been slower to adopt CM (Lee et al., 2015; Rossi, 2012). The U.S. landscape of prescription drug products made using a CM process was roughly $3.09B in 2020 (Fig. 1), representing a small but growing portion of the $172B total market for branded, solid oral prescription drugs. The leading firm in the CM sector captures around 60% of total sales, with 20% of sales captured by the next largest firm. Many have pointed to the slow adoption of advanced manufacturing technologies, including CM, as one of the reasons that the pharmaceutical industry has not achieved the consistent six sigma manufacturing capability (i.e., <3.4 errors per million opportunities) common in other industries (Politis and Rekkas, 2011; Yu and Kopcha, 2017).

The United States Food and Drug Administration (FDA) has long championed the development and implementation of advanced manufacturing technologies like CM for drug substances and finished drug products because of the potential to improve product quality and reliability, lower manufacturing costs, reduce waste, decrease inventory, and increase manufacturing flexibility and agility in response to fluctuations in product demand. The cumulative effects of CM adoption could reduce or mitigate drug shortages (Lee et al., 2015). CM can be applied to all classes of products: new drugs submitted in New Drug Applications (NDAs) (Fernandes, 2019), generic drugs filed in Abbreviated New Drug applications (ANDAs) (Chaudhary et al., 2017), drug substances filed in Drug Master Files (DMFs) (Stauffer et al., 2019), biotechnology products filed in Biologics License Applications (BLAs) (Fisher et al., 2019), and nonprescription drugs (Griffin et al., 2016). There is now a rich source of scientific literature describing the benefits of CM in pharmaceutical manufacturing relating mostly to decreases in production/operating costs and improvements in product quality and reliability (Rossi, 2022; Badman et al., 2019). Perhaps most importantly for patients and consumers, CM has the potential to impact product availability; for example, by avoiding drug shortages due to manufacturing problems or expediting patient access through improved

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# FDA Workforce Development Streamlines AM Assessment

- Continuous Direct Compression (CDC)
  - Sufficient experience to transfer review responsibilities out of ETP
  - ETP trained future CDC assessors on the technology
  - Future CDC applications within FDA's experience will be reviewed through the standard quality assessment process
- Advanced Manufacturing Assessor Training—New Ammendale Research Facility

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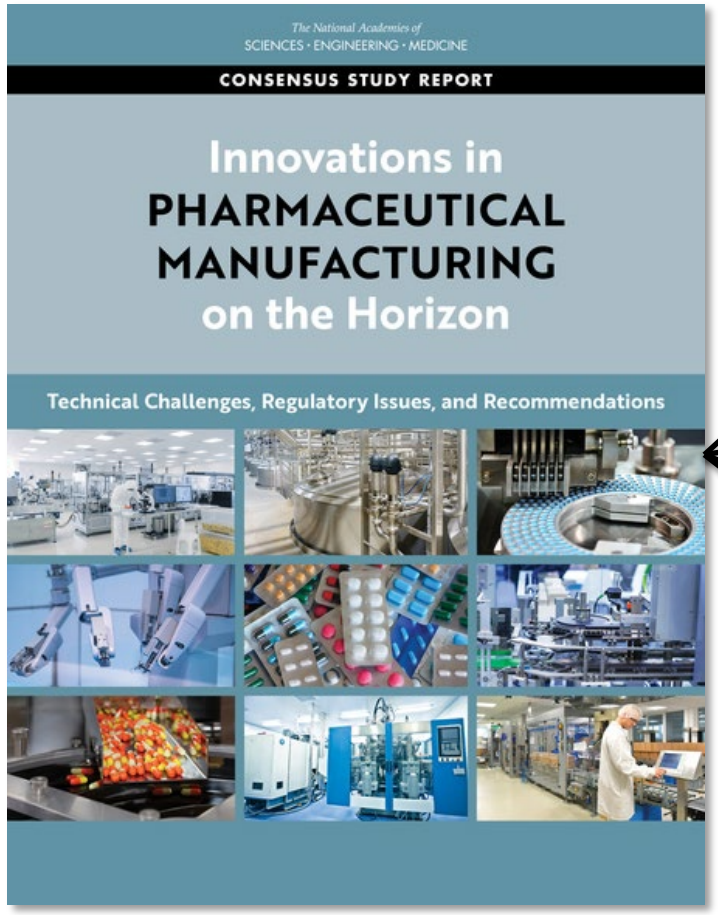
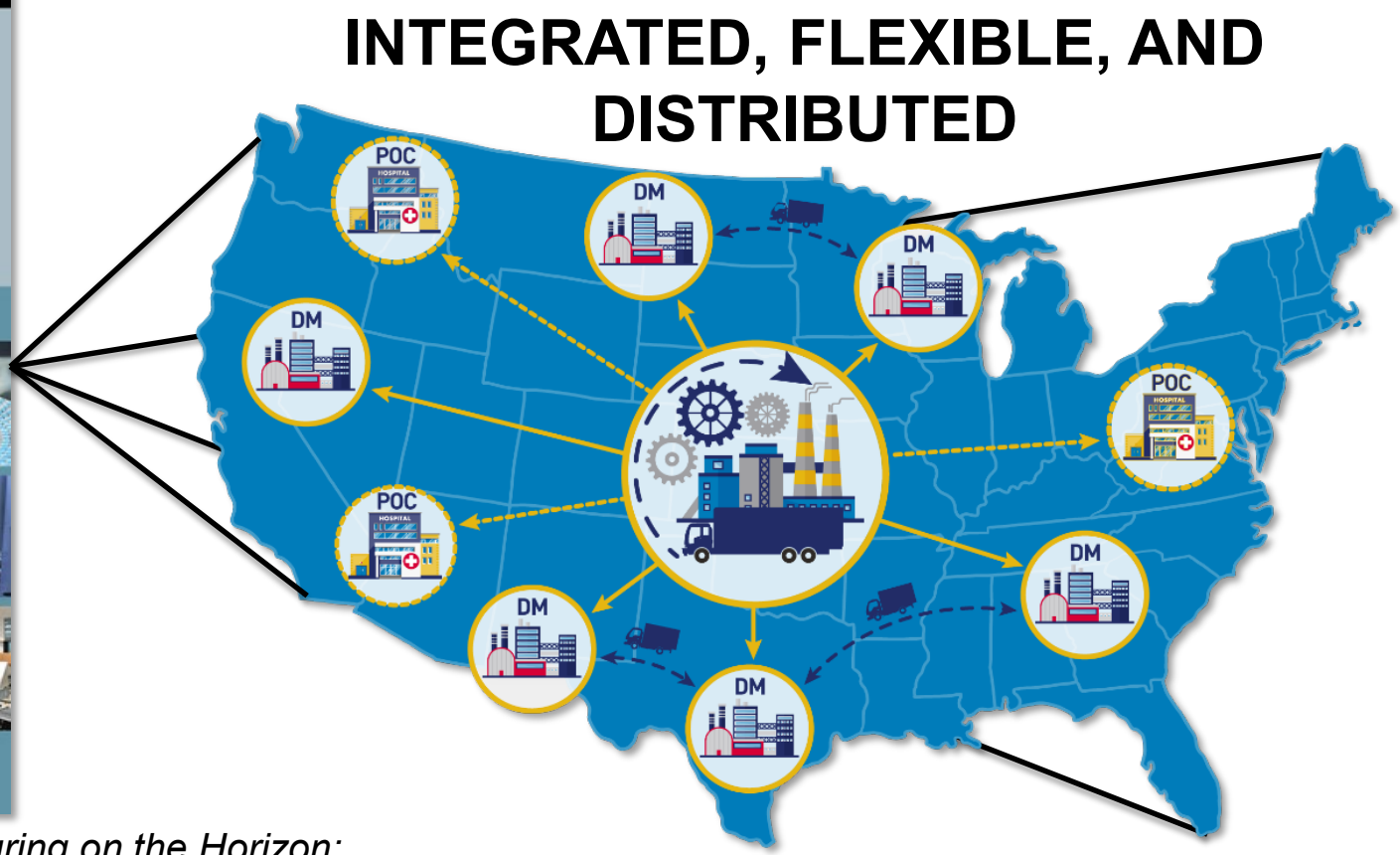
# Framework for Regulatory Advanced Manufacturing Evaluation (**FRAME**)

# FRAME: Framework for Regulatory Advanced Manufacturing Evaluation

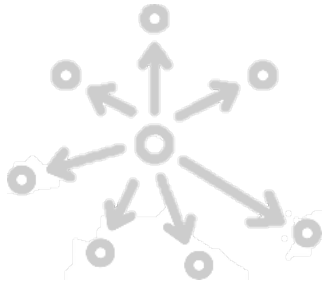


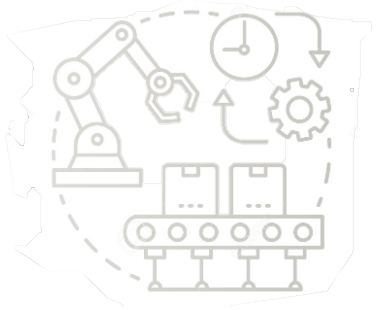

*NASEM *Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations* (2021)

# FRAME Priority Technologies

## Distributed Manufacturing (DM)



## End to End Continuous Manufacturing (E2E CM)



## Point of Care (POC) Manufacturing

## Artificial Intelligence (AI)

# FRAME Priorities

| Seek and Analyze Input | Address Risks | Clarify Expectations | Harmonize Internationally |
|---|---|---|---|
| Ensure CDER's understanding of advanced manufacturing technologies is thorough and its analysis of the regulatory framework is science- and risk-based. | Ensure regulations and policy are compatible with future advanced manufacturing technologies. | Explain the current thinking on a regulatory issue via new or updated guidance as needed. | Ensure global regulatory practice is clear to stakeholders implementing advanced manufacturing. |

**Cohesive regulatory framework for drugs**

## Facilitated Stakeholder Input:

- **Distributed and Point-of-Care Manufacturing Discussion Paper in Federal Register** Published 10/14/22
- **FDA/PQRI Distributed and Point-of-Care Manufacturing Public Workshop** (November 14-16, 2022)

## Facilitated Stakeholder Input:

- **Artificial Intelligence Discussion Paper in Federal Register** (Published March 1, 2023)
- **FDA/PQRI Artificial Intelligence Public Workshop** (September 26-27, 2023)

# Regulatory Challenges to Adoption

- **Operating within existing regulatory frameworks**
  - CGMPs
  - Validation
- **Post-approval issues**
  - Inspecting new technologies
  - Lifecycle management
- **International harmonization**
  - Regulatory convergence needed

# Regulatory Hurdles and FDA Actions

| Manufacturers were hesitant to adopt CM… | FDA Actions |
|---|---|
| **Without additional engagement from FDA** | **2014**: Created the Emerging Technology Program (ETP) |
| **Before FDA approved a product manufactured with CM** | **2015**: Approved the first product manufactured with CM (and have since accepted 50 proposals from industry into the ETP and approved 13 additional submissions) |
| **For existing products before the FDA approved a switch from batch manufacturing to CM** | **2016**: Approved the first switch from batch to CM for a drug product. |
| **Without guidance from FDA** | **2019**: Draft guidance *Quality Considerations for Continuous Manufacturing*<br><br>**2022**: Draft revision to the guidance *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* (includes viral safety evaluation for CM) |
| **Because they feared the timelines for FDA approval might be longer** | **2022**: Showed that applications using CM were approved faster than similar applications using batch manufacturing |
| **Without internationally harmonized guidance** | **2023**: Internationally harmonized guidance *Q13 Continuous Manufacturing of Drug Substances and Drug Products*. |

# Regulatory Challenges to Adoption

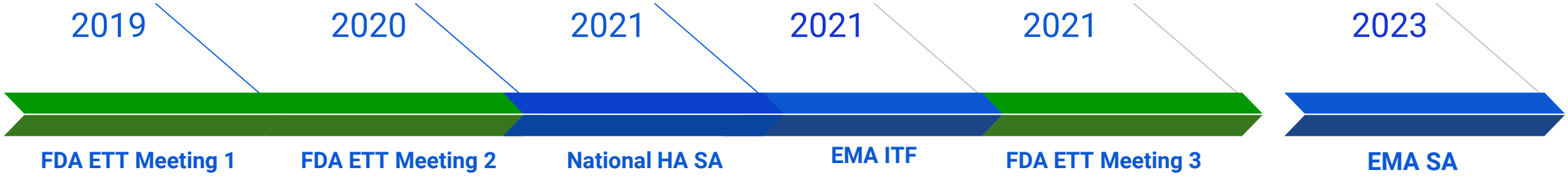
- *Ingrid Markovic*, Center for Biologics Evaluation and Research, FDA
- *Roger Nosal*, International Society for Pharmaceutical Engineering
- *Ahmad Almaya*, European Federation of Pharmaceutical Industries and
- Associations
- *Gert Thurau*, Roche
- *Fernando Muzzio*, Rutgers University

# The Journey to Regulatory Acceptance

## From Technology to Registration

At the start of the project in 2017 the novelty of the robotic gloveless filler concept necessitated Health Authority engagement

- Starting with engagement with «Technology Innovation Teams» with FDA and EMA
- Expand to regional authorities (if not FDA or EMA) where systems would be located




Different regional guidance on sterile manufacturing are applicable

- **FDA** Sterile Drug Products Produced by Aseptic Processing — cGMP -**21 CFR parts 210 and 211** Oct 2004
- **EU** GMP **Annex 1**: Manufacture of Sterile Medicinal Products – recently updated (2023)

***There are currently regional differences remaining in the regulatory acceptance of the type of system Roche is planning to use.***

# Break

Workshop will resume at **2:20 p.m.**

# Advanced Manufacturing Technologies Designation Program

*Ranjani Prabhakara,* Center for Drug Evaluation and Research

U.S. Food and Drug Administration

# Advanced Manufacturing Technologies Designation Program

**Ranjani Prabhakara, Ph.D.**
Policy Lead
Office of Policy for Pharmaceutical Quality
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

**Innovative Manufacturing Public Workshop**
June 8, 2023

# The Omnibus or "The Consolidated Appropriations Act, 2023"

- $1.7 trillion omnibus spending bill
- Signed by President Biden on December 29, 2022
- Funded the US government for the 2023 fiscal year and addressed a range of domestic and foreign policy priorities

# Selected Quality-Related Provisions

- "PREVENT Pandemics Act" (Title II)
  - Sec. 2503 – Platform Technologies
  - Sec. 2511 - Ensuring Registration of Foreign Drug and Device Manufacturers
  - Sec. 2512 Extending Expiration Dates for Certain Drugs
- "Food and Drug Omnibus Reform Act of 2022" (FDORA, Title III)
  - Sec. 3203 Emerging Technology Program
  - Sec. 3204 National Centers of Excellence in Advanced and Continuous Pharmaceutical Manufacturing
  - Sec. 3213 Advanced Manufacturing Technologies Designation Program
  - Sec. 3613 Improving Food and Drug Administration Inspections

# What is an Advanced Manufacturing Technology (AMT)?

- Applies to methods of manufacturing drugs, including biological products and active pharmaceutical ingredients
- "A method of manufacturing, or a combination of manufacturing methods, is eligible for designation as an advanced manufacturing technology if such method or combination of methods incorporates a novel technology, or uses an established technique or technology in a novel way, that will substantially improve the manufacturing process for a drug while maintaining equivalent, or providing superior, drug quality, including by—
  - "(1) reducing development time for a drug using the designated manufacturing method; or
  - "(2) increasing or maintaining the supply of—"(A) a drug that is life-supporting, life sustaining, or of critical importance to providing health care; or "(B) a drug that is on the drug shortage list under section 506E.

# Advanced Manufacturing Technologies Designation Program

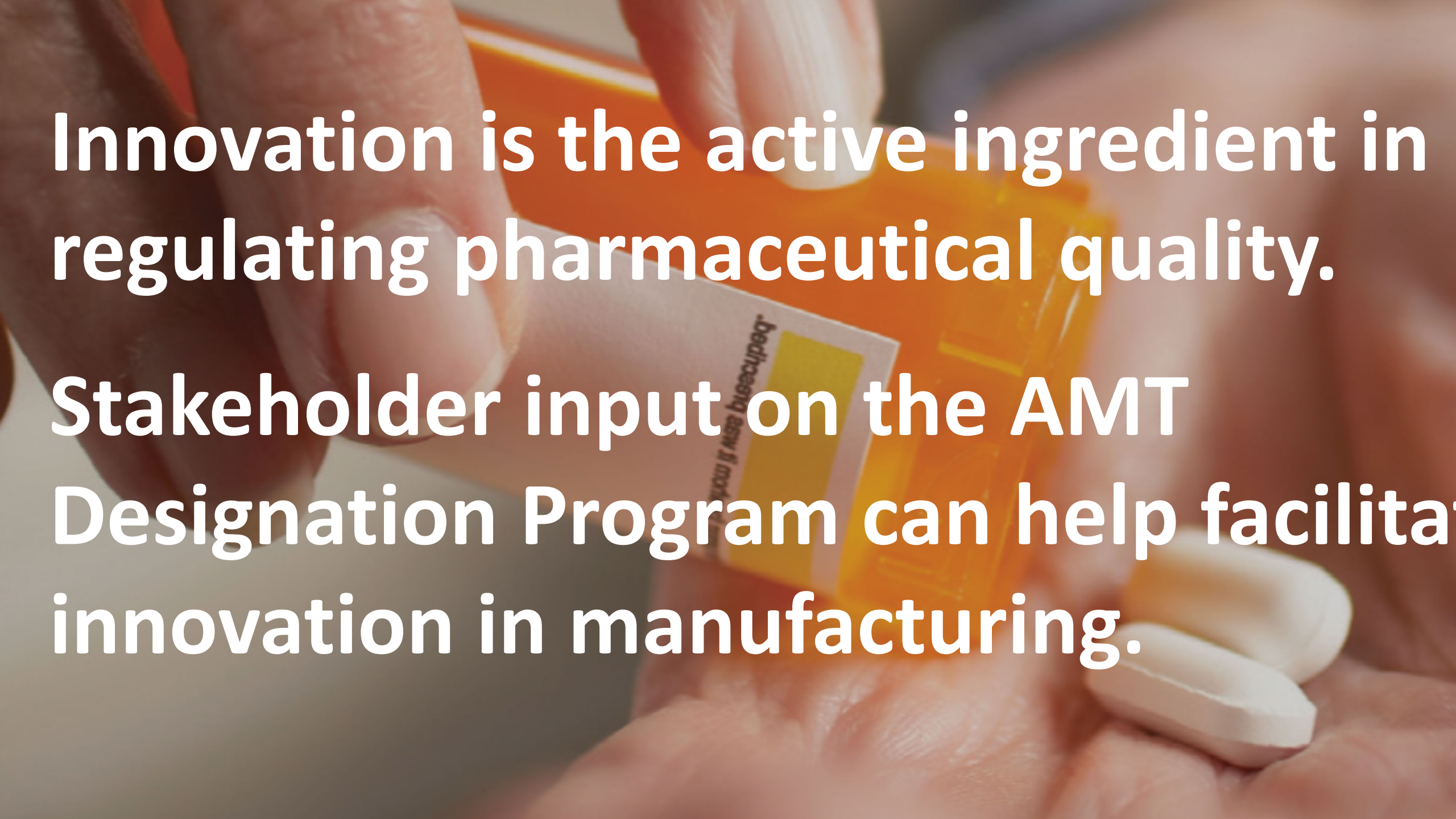
- ‘‘(a) IN GENERAL.—Not later than 1 year after the date of enactment of this section, the Secretary shall initiate a program under which persons may request designation
- “(b) DESIGNATION PROCESS.—The Secretary shall establish a process for the designation under this section of methods of manufacturing drugs, including biological products, and active pharmaceutical ingredients of such drugs, as advanced manufacturing technologies...
- ‘‘(c) EVALUATION AND DESIGNATION OF AN ADVANCED MANUFACTURING TECHNOLOGY.—
  - ‘‘(1) SUBMISSION.—A person who requests designation of a method of manufacturing as an advanced manufacturing technology under this section shall submit to the Secretary data or information demonstrating that the method of manufacturing meets the criteria described in subsection (b) in a particular context of use. The Secretary may facilitate the development and review of such data or information by—
    - ‘‘(A) providing timely advice to, and interactive communication with, such person regarding the development of the method of manufacturing; and
    - ‘‘(B) involving senior managers and experienced staff of the Food and Drug Administration, as appropriate, in a collaborative, cross disciplinary review of the method of manufacturing, as applicable.

# AMT Designation Guidance

- ‘‘(2) PROGRAM GUIDANCE .—
  - ‘‘(A) IN GENERAL.—The Secretary shall—
    - ‘‘(i) not later than 180 days after the public meeting under paragraph (1), issue draft guidance regarding the goals and implementation of the program under this section; and
    - ‘(ii) not later than 2 years after the date of enactment of this section, issue final guidance regarding the implementation of such program.
  - ‘‘(B) CONTENT.—The guidance described in subparagraph (A) shall address—
    - ‘‘(i) the process by which a person may request a designation under subsection (b);
    - ‘‘(ii) the data and information that a person requesting such a designation is required *to* submit under subsection (c), and how the Secretary intends to evaluate such submissions;
    - ‘‘(iii) the process to expedite the development and review of applications under subsection (d); and
    - ‘‘(iv) the criteria described in subsection (b) for eligibility for such a designation.

# Important AMT-Related Questions Being Considered

- How best to “expedite,” as it relates to drug development time and manufacturing of critical drugs?
- What does the term “novel” mean, as it relates to a proposed AMT?
- What types of timely advice and means of communication most effectively shorten drug development times?
- What data and information are needed to support AMT designation?
- How can this program link effectively to the Emerging Technologies Program or CBER Advanced Technologies Team?



# Innovation is the active ingredient in regulating pharmaceutical quality.

# Stakeholder input on the AMT Designation Program can help facilitat innovation in manufacturing.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# Regulatory Strategies for Adoption and Next Steps

- *Joel Welch*, Center for Drug Evaluation and Research, FDA
- *Ben Stevens*, GlaxoSmithKline
- *Celeste Frankenfeld Lamm,* Merck
- *Cornell Stamoran*, Catalent
- *Andrew Kuzmission*, Vertex Pharmaceuticals

# Considerations for Advanced Manufacturing Technologies (AMT) Designation

- **Scope of AMT definition under the statute is very broad**
  - FDA and industry should work together to establish a *reasonable basis* for granting designation.
    - Overly broad – may tax Agency resources, minimize ability of FDA to meaningfully accelerate development/review.
    - Overly narrow – no meaningful impact on development or implementation of AMT (i.e., will not satisfy the intent of the legislation).

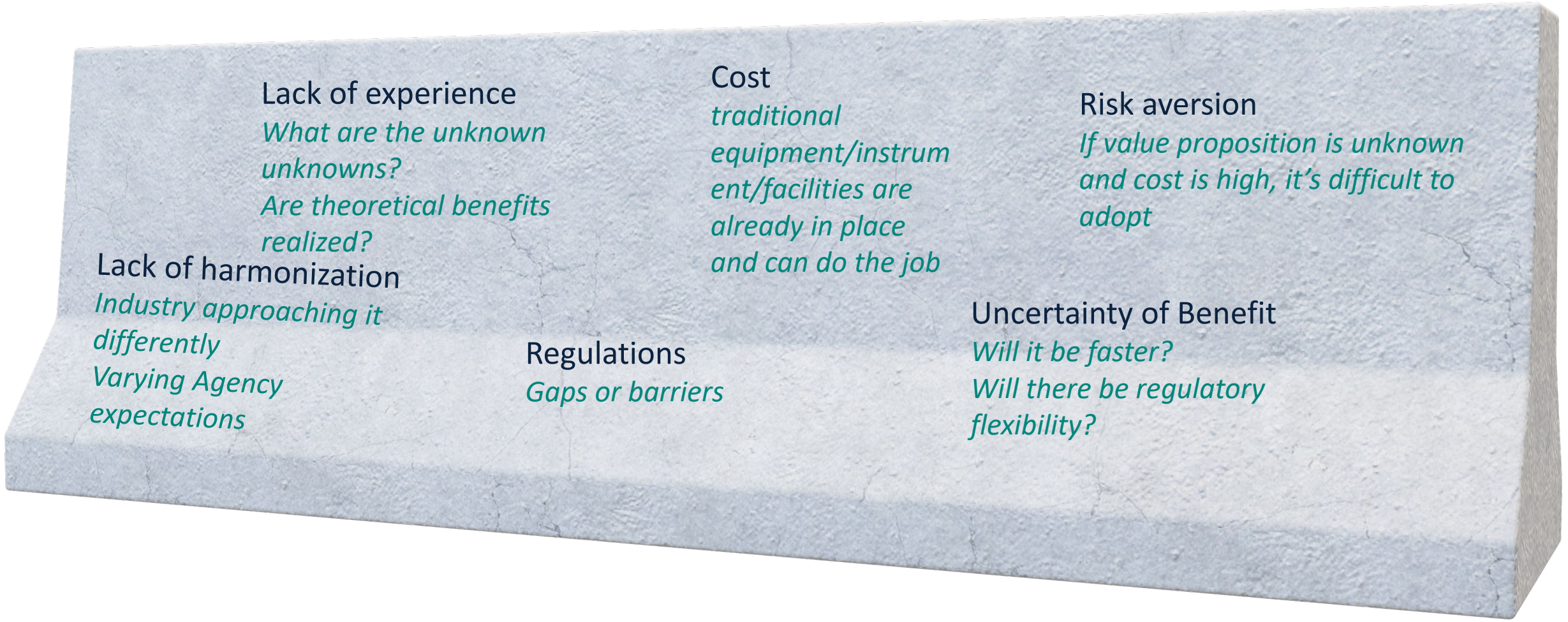
- **Important that AMT designation be granted for innovation beyond the applications enumerated under subsection (b)**
  - Applications outside of subsection (b) may be especially valuable since some technologies are not incentivized through other pathways by FDA, but are nevertheless critical.
  - E.g., "green" AMT that will reduce carbon footprint or have positive environmental impact.

- **"Context of use" – similar challenge for scope of AMT**
  - Should be defined by the dataset and justifications provided in request for designation.
  - Revisions to the context of use for which the designation is granted should be permitted based on additional data (i.e., scope of the context of use should evolve over time).

- **Consider a tiered approach for expediting development and review under AMT designation**
  - FDA should be able to provide significant acceleration under this pathway for highly impactful technologies.
  - Consider flexibilities under the recently released MAPP 5015.13 for expedited programs.

GSK

# Barriers to Innovation are Multi-Faceted



# Reaching Towards Implementation of Innovative Technology


## Consider Distributed Manufacturing

**Forward looking focus**

**Concrete Incentives (e.g. via Advanced Manufacturing Designation):**

- Accelerated review *within X months*
- Continuity of reviewer knowledge between initial application and supplements

**Risk-Based Approach**

- Accept alternative approaches to demonstrate bioequivalence (where needed), stability, etc. – use of comprehensive risk assessments to determine level of risk

**Global Conversations**

- Invitation to other regulators to observe ETT/CATT meetings
- Engage in global forums/conversations

MERCK

# Thank you

**Merck & Co., Inc.**

**E-mail:** celeste.frankenfeld@merck.com

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Advanced Manufacturing Technologies pathway

# Implementation considerations

- **Evidence requirements to support program qualification, particularly in advance of product filings**

  "substantially improved manufacturing process", "maintaining equivalent, or providing superior, quality", and "novel technology… or established techniques or technology used in a novel way"

- **Initial use context potentially broader than a single drug, such as to a class of drugs or a specific modality**

  Potential for conflict/alignment with "platform technology" designation process (Sec. 2503)

- **Clear identification of incentives for sponsors who reference a designation in a product filing**

  To what extent dependent upon flexibility options, individual reviewer expectations

- **Co-ownership of designations**
- **Ease of continuous improvements of designated AMTs**

Catalent

VERTEX

THE SCIENCE *of* POSSIBILITY


VERTEX

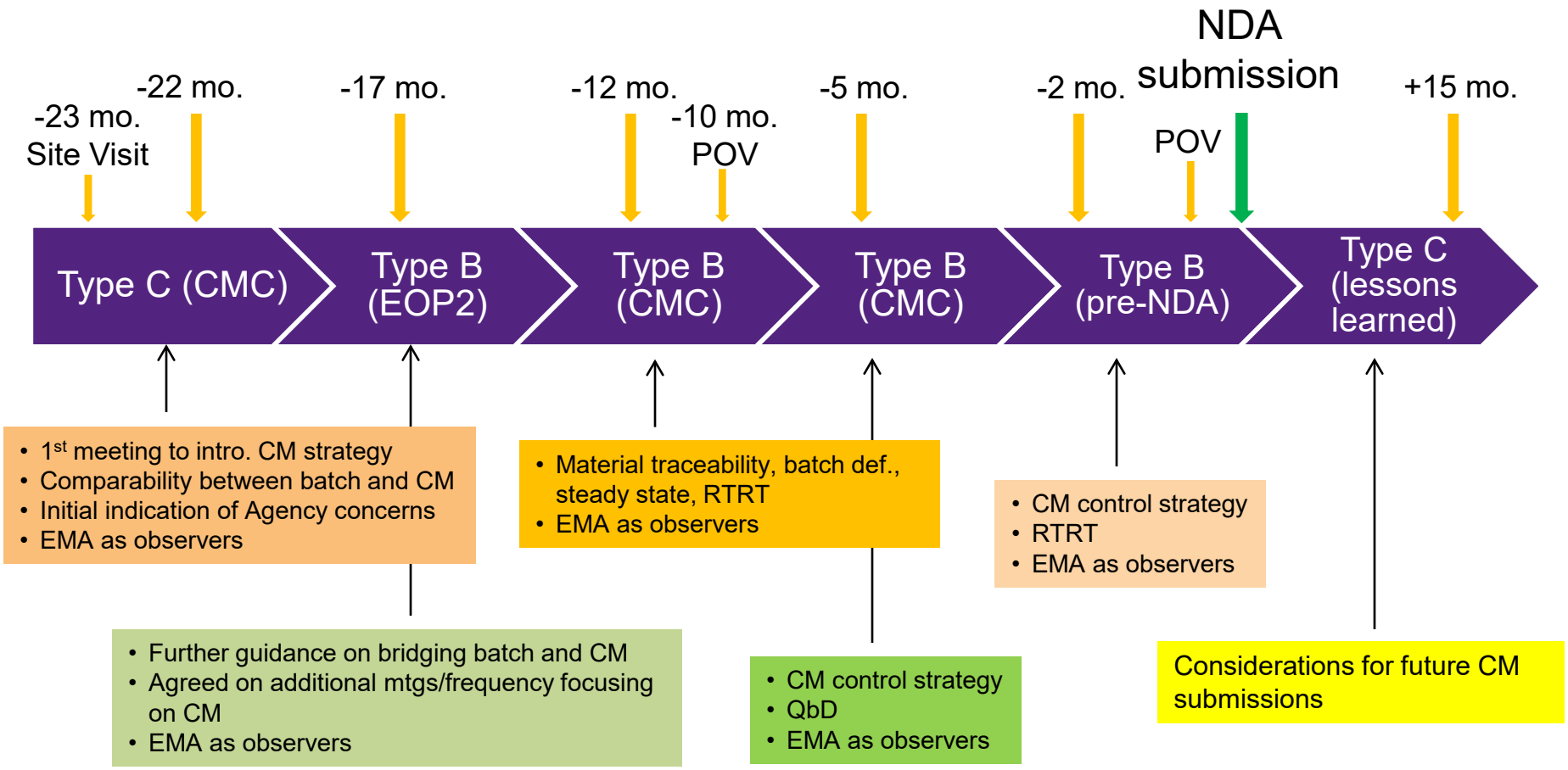
# Implementation of Continuous Manufacturing

- Innovation in a regulated environment requires careful planning and Agency interactions: Preparation = success
- Early and often communication

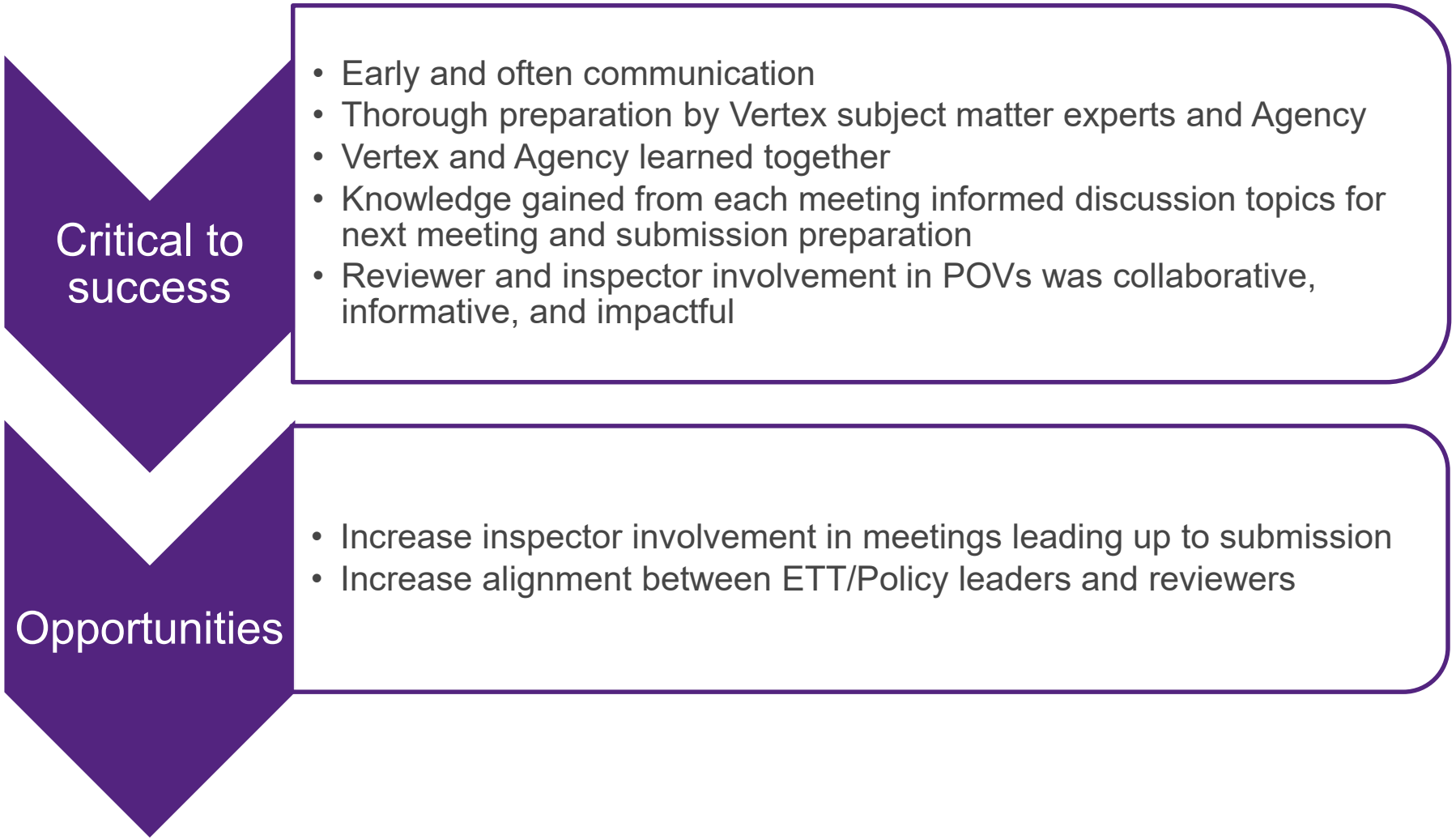
**Multiple options for FDA interactions used**

- Site visits
- Pre-Operational Visits (POV)
- Consultative Advice
- Type B meetings
- Type C meetings

# Implementation of CM – Agency Interactions



# Implementation of Continuous Manufacturing



# Closing Remarks

*Gerrit Hamre*

Research Director, Duke-Margolis Center for Health Policy

# Thank You!

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