5th PQRI/FDA Conference on Advancing Product Quality

Session 2

Advanced Manufacturing Concepts Beyond Continuous Manufacturing

Introduction

Moderators: Robert Meyer, Ph.D., Merck & Co., Inc. and Rajan Jog, Ph.D., FDA

- ***Introduction*** (5 minutes)
- ***A Vision for Agile Manufacturing*** (5 minutes)
  - Celeste Frankenfeld Lamm, Ph.D., Merck & Co.
- ***Pre-Fabricated Solutions for New Facilities*** (5 minutes)
  - Peter Makowenskyj, MEng., G-CON
- ***Decentralized Pharmaceutical Manufacturing: The Next Big Thing?*** (5 minutes)
  - Christine Moore, Ph.D., Organon
- ***Regulatory Perspective on Advanced Manufacturing*** (10 minutes)
  - Sau (Larry) Lee, Ph.D., FDA

INVENTING FOR LIFE

A Vision for Agile Manufacturing

Celeste Frankenfeld Lamm, Ph.D.

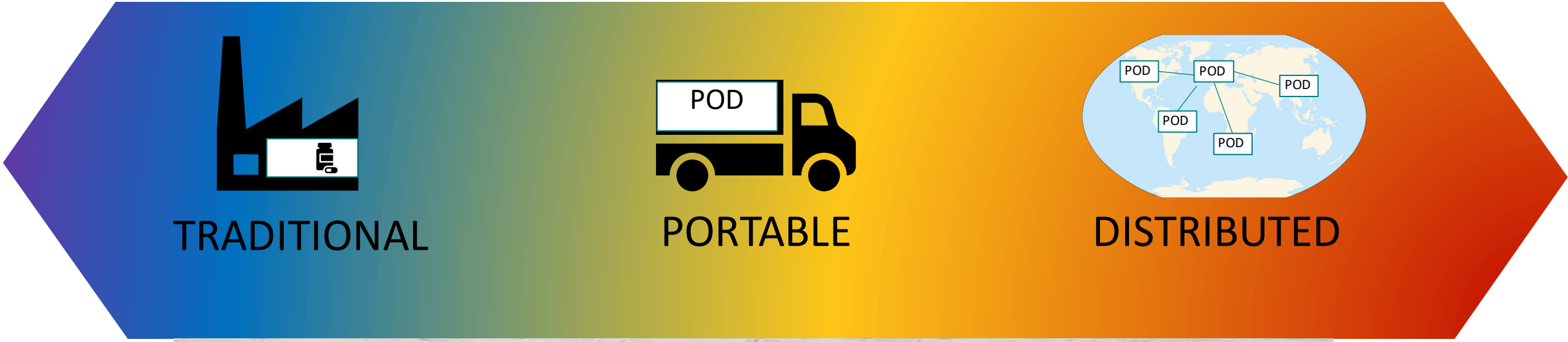
Merck & Co., Inc.

5th PQRI/FDA Conference – December 3, 2021

Industry and Regulators Share the Desire for Agile Manufacturing

A vision of "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight."

- Janet Woodcock, MD



Strong Foundation of Appropriate Regulation and Communication

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Challenges

Regulations authored prior to new technology

Static, physical location is built into the definition of manufacturing site in many global regulations

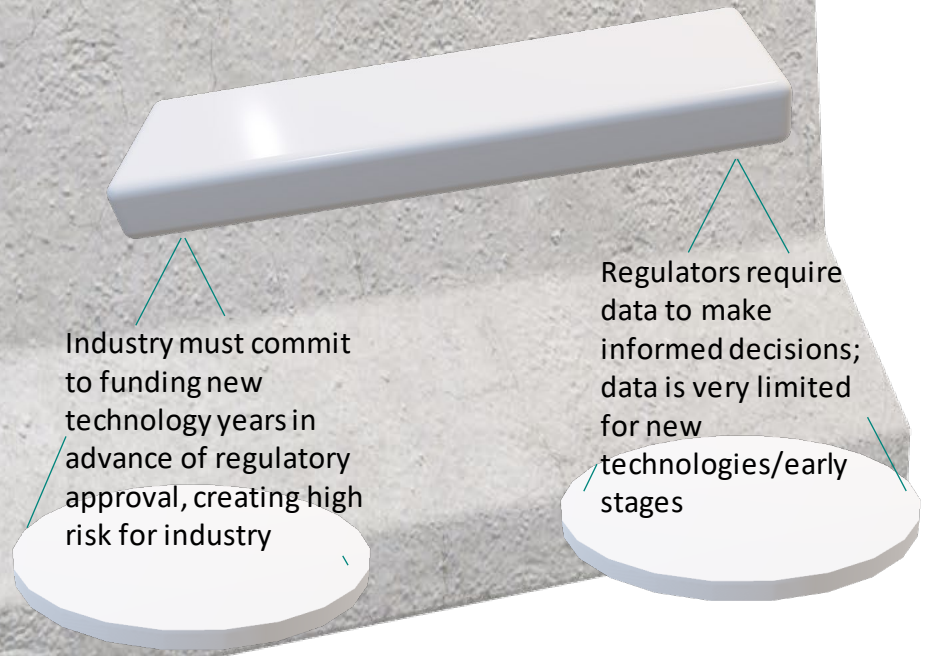
Inspectional authority is tied to physical location (FDA regional offices, countries in the EU etc.)

Additional regulatory expectations may also slow the agility of movement

- Major submissions that require review and approval prior to implementation
- stability studies
- bioequivalence studies
- re-validation of processes

Global Implementation

Decision-Making Timelines



G-CON MANUFACTURING

PQRI Product Quality Research Institute

FDA U.S. FOOD & DRUG ADMINISTRATION

Pre-Fabricated Solutions for New Facilities

Pete Makowenskyj – Director of Design Consulting

12/03/2021

What's the Main Difference to the Traditional Built ?

Prefabricated/Predesigned allows guaranteed full Functionality

The Traditional

Design
(weeks/months)

BoM (weeks)

Ship all parts

Construct
(months)

Qualification
(weeks)

Summary
8-18 months
Unknown functionality

PODs

Design
(days/weeks)

Construct &
Prequalify
(months)

Ship the entire
assembled unit

Install & SAT
(days/weeks)

Summary
3-10 months
Fully functional

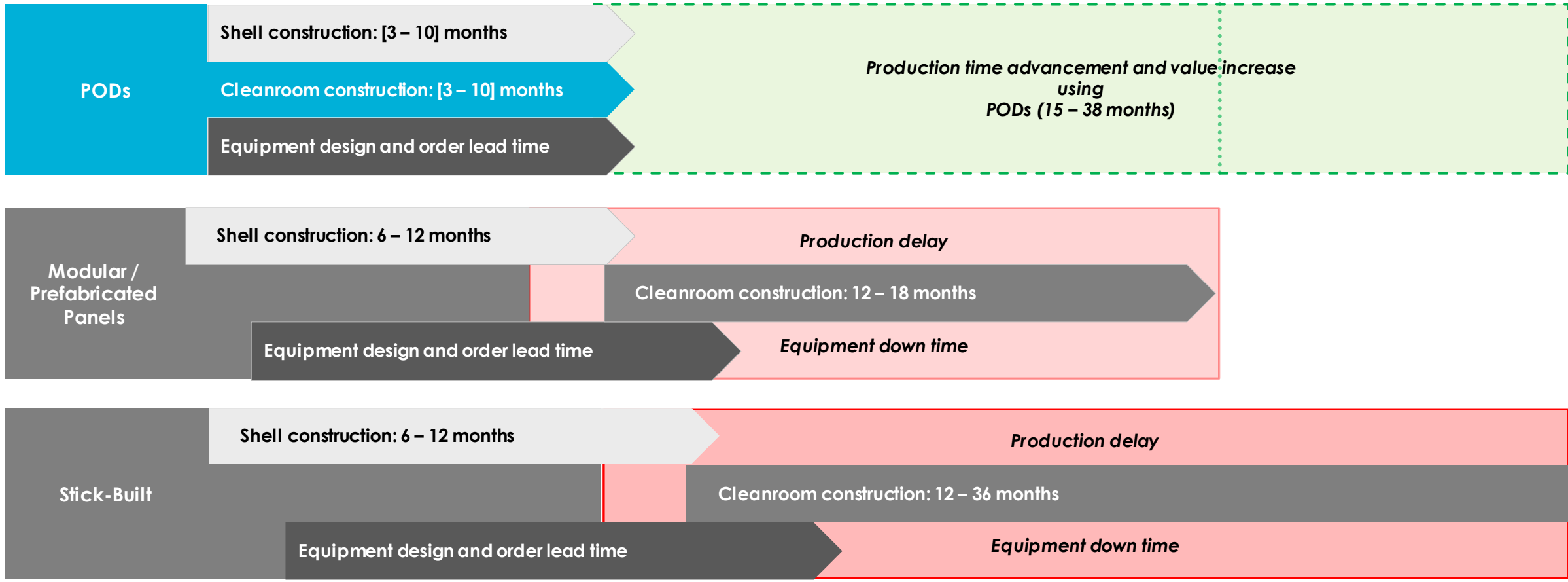
What's the Main Difference to the Traditional Built ?

Prefabricated/Predesigned allows guaranteed full Functionality

One would Never Buy a Car like That !

Commitment to Customers – Reliable Speed

- With modular panel and stick-built cleanroom designs, construction of the cleanroom is the rate-limiting step and generally spans 12 - 36 months. POD cleanrooms can be built in 3-10 months.
- While PODs are being built, the host facility can be built or renovated, and the process equipment can be ordered and produced.



Source: LEK Consulting and G-CON Management.

Thank you!

Decentralized Manufacturing: The Next Big Thing?

5th PQRI/FDA Conference on Advancing Product Quality

December 3, 2021

Christine M. V. Moore
Executive Director, External Advocacy & Policy
Global Quality Compliance

ORGANON
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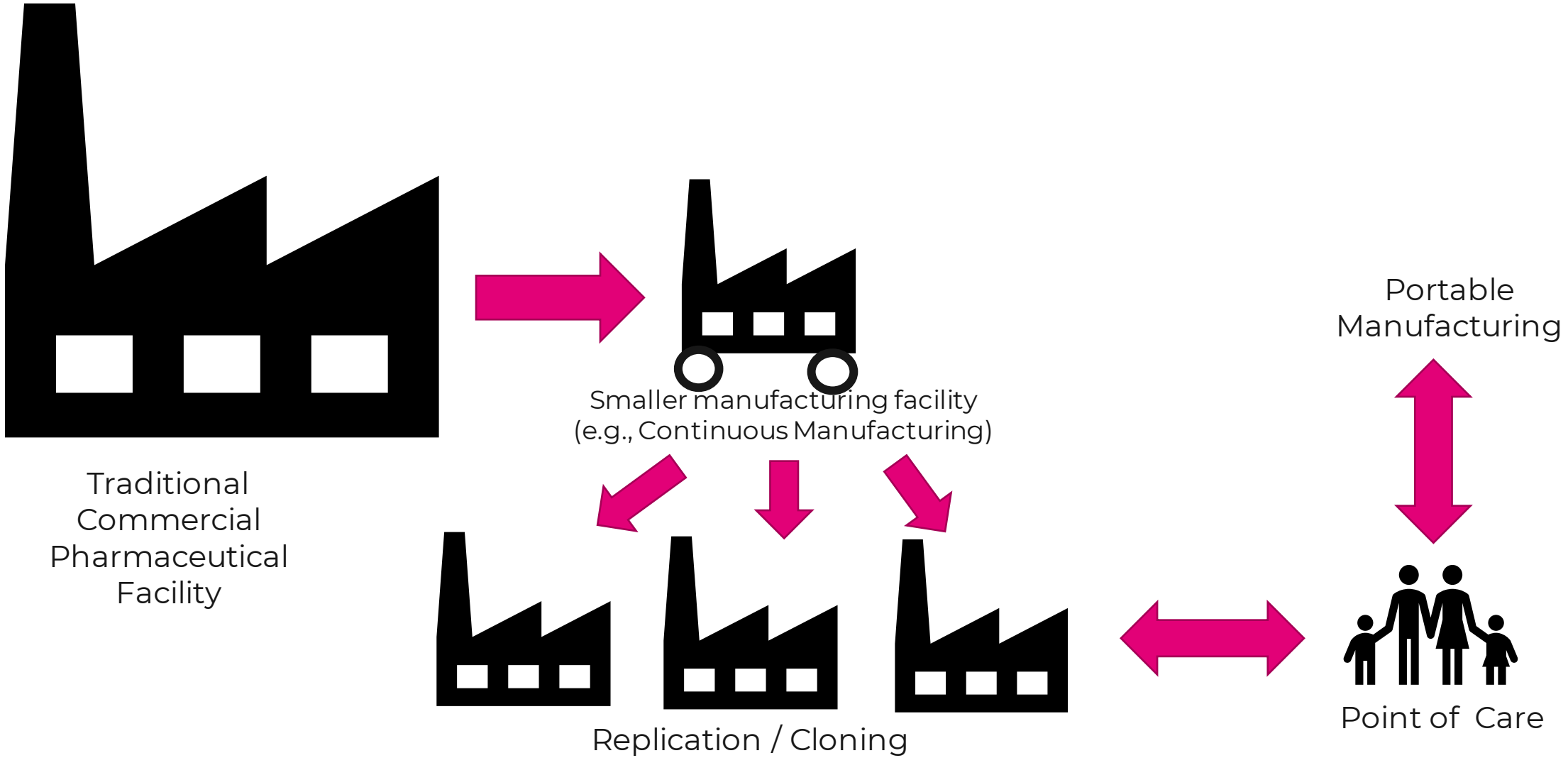
Reimagining Pharmaceutical Manufacturing



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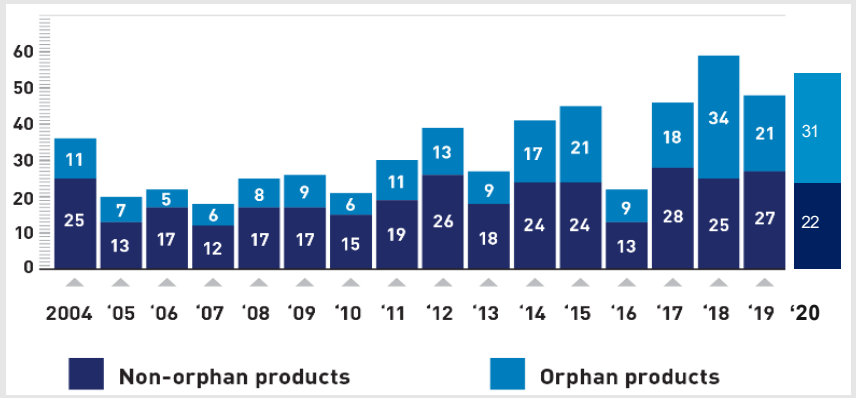
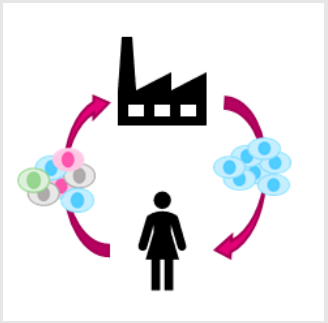
Drivers for Change

More specialized, smaller volume products

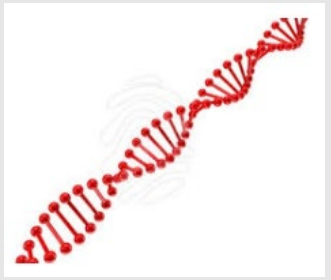


https://www.fda.gov/news-events/fda-voices/innovation-new-drug-approvals-2019-advances-patient-care-across-broad-range-diseases
New Drug Therapy Approvals 2020 | FDA

New modalities



Autologous Cell Therapies



mRNA Vaccines

Availability of smaller equipment

ConsiGma® Direct Compression with Linear Blending (DC-LB) Lines (gea.com)

G-CON Manufacturing Inc. | Cleanroom Products (gconbio.com)

Efforts to on-shore pharmaceutical manufacturing

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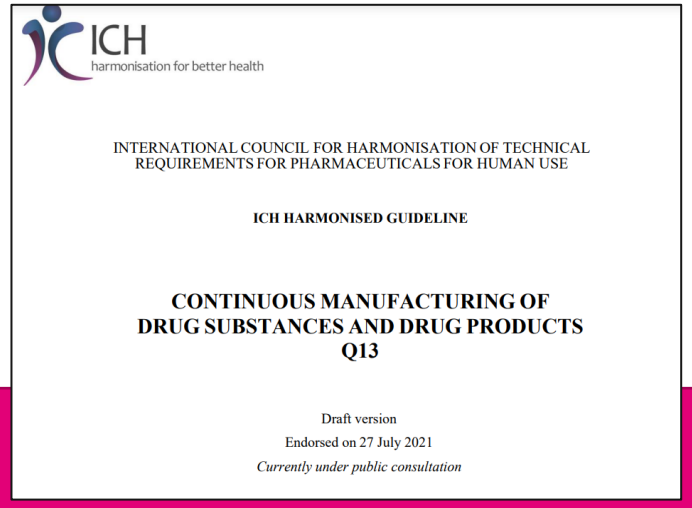
Moving Forward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harmonisation for better health

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

ICH HARMONISED GUIDELINE

CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS Q13

Draft version

Endorsed on 27 July 2021

Currently under public consultation

FDA U.S. FOOD & DRUG ADMINISTRATION

Emerging Technology Team 2.0?
Consultation on Advanced Manufacturing?

Consultation on Point of Care manufacturing

Published 12 August 2021

Medicines & Healthcare products Regulatory Agency

Growing recognition of the regulatory gaps and need to address them!

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Thank you

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US FDA Perspective on Advanced Manufacturing

Sau (Larry) Lee, Ph.D.
Deputy Director of Science
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

5th PQRI FDA Conference on Advancing Product Quality
:Advanced Manufacturing Concepts Beyond Continuous Manufacturing
December 3, 2021

CDER's Regulatory Approaches

Science and risk-based approaches	• CDER supports **Intramural and Extramural Research** to: ▪ Understand key ADM concepts and identify ADM specific risks to product quality ▪ Develop a framework for control strategy considerations
Regulations and guidance	• Existing regulations and ICH guidances (e.g., Q8, Q9, Q10, Q11 and Q12) ▪ Generally applicable to ADM (e.g., continuous manufacturing (CM)) • Emerging Technology Guidance and MAPP • **Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)**
Regulatory Assessment	• Early engagement with CDER's **Emerging Technology Program** to address scientific and regulatory gaps • Pre-operational visits (POVs) • Integrated application and facility assessments including pre-approval inspection
Maturation of regulatory basis	• Evolution of regulatory basis as experience gained with CM regulatory applications • Knowledge management • Regulatory guidance (e.g., FDA on Continuous Manufacturing and/or ICH Q13)

Emerging Technology Program

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

ETT Technology Pipeline: Examples

Small Molecules	Therapeutic Proteins	Multiple Products
• Continuous manufacturing of drug substance and product • End-to-end continuous manufacturing • Pharmacy-on-demand • Model-based control strategy for continuous manufacturing • Continuous aseptic spray drying • 3D printing manufacturing • Pre-fabricated, mobile manufacturing modules • Ultra long-acting oral formulation	• Controlled ice nucleation for lyophilization processes • Advanced process control • Multi-attribute method for quality control • Continuous manufacturing for a downstream process • End-to-end integrated bioprocess • Pre-fabricated, mobile manufacturing modules • Pharmacy-on-demand 	• Closed aseptic filling system • Isolator and robotic arm for aseptic filling • Novel container and closure system for injectable products

ETP 2.0 Roadmap Overview

Priority	Status	Level of Effort	Impact/ Complexity[1]	Nature of Tasks
Graduation	In Progress	To be completed by September 2021	High Impact/High Complexity	Process Development, Communications, Monitoring
Knowledge Management and Transfer	In Progress	To be completed by September 2021	High Impact/High Complexity	Repository, Trainings, Internal Expertise, Documentation
Governance	In Progress	To be completed by September 2021	High Impact/Medium Complexity	Charter, GAP Analysis, Documentation
Intake	Pending	4 months with 0.25 FTE		
Engagement	Pending	6 months with 0.75 FTE		
Communications	Pending	3 months with 0.5 FTE		
Technology and Tools	Pending	4 months with 0.25 FTE		
Skills and Training	Pending	6 months with 0.5 FTE		
Workload Management	Pending	6 months with 0.5 FTE		
Strategy	Pending	4.5 months with 0.5 FTE		
Awareness	Pending	3 months with 0.5 FTE		

1. Graduation

Graduation refers to the transfer of application assessment responsibility from ETP to OPQ sub-offices. A technology achieves graduation when FDA gains enough experience with a technology and it proceeds through the standard assessment process with minimum or no involvement of ETT members. By graduating a novel technology, ETP can realize its mission of promoting the adoption of innovative approaches to pharmaceutical product design and manufacturing.

Expected Level of Effort	To be completed by September 2020
Expertise Required	Project Management, Process Improvement, Change Management, Communication Strategy, Subject Matter Expertise
Potential Contributors	ETT Project Manager, Quality Assessors, OPQ Learning and Professional Development, ETT Chair, Technology Leads
Impact Complexity	High Impact, High Complexity

Tasks to Achieve ETP 2.0

Tasks	Actions
Define graduation with ETP approval	• Draft a definition to formally describe what it means for a technology to graduate from ETP. • Gather and incorporate feedback from ETT members on graduation definition. • Confirm the approved graduation definition supporting ETP 2.0 operating model.
Define the criteria for a technology to graduate and the associated processes for implementation	• Identify requirements for current ETP technologies to qualify for graduation. • Create a decision tree to track a technology's path through graduation. • Create a Working Instruction that details the processes and frameworks for graduating a technology. • Create formal approval process to officially transfer assessment responsibility to the receiving OPQ sub-office(s).
Create the communication plan associated with a graduating technology	• Document ETT's roles and responsibilities regarding communications when graduating a technology. • Identify goals for planned communications. • Identify audience(s) who will be impacted by graduating a technology. • Develop messaging for target audiences.

- **Step-by-step guide to achieve ETP 2.0**
- Describes priorities, tasks, actions, expected level of effort, expertise required, potential contributors, impact/complexity, risks, and mitigation tactics

Priority Areas

- **Graduation**
- **Knowledge Management and Transfer**
- **Governance**
- **Intake**
- **Engagement**
- **Communications**
- **Technology and Tools**
- **Skills and Training**
- **Workload Management**
- **Strategy**
- **Awareness**

Regulatory and Policy Initiatives

- FDA draft guidance on continuous manufacturing for solid oral products (Published in February 2019)
- FDA is working on the development of ICH Q13 on continuous manufacturing of drug substances and drug products – both small and large molecules
  - Reached Step 2 in June 2021

ICH Q13 Expert Working Group

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Draft version

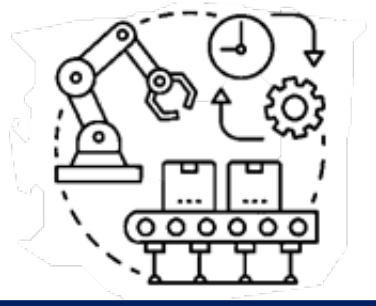
Endorsed on 14 June 2021

Currently under public consultation

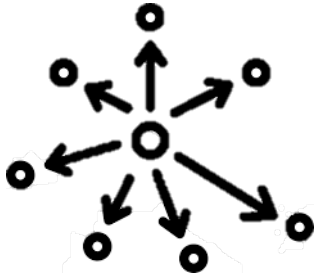
At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)

End to End Continuous Manufacturing (E2E CM)



Distributed Manufacturing (DM)



Point of Care (POC) Manufacturing

Artificial Intelligence (AI)

Phase I

Building the Foundation

Phase II

Planning Implementation

Phase III

Setting Things in Motion

Beginning Fall 2021

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

Moving Forward…

- Enhancement of Emerging Technology Program (ETP 2.0)
  - Refine the operating model to meet increasing workload
  - Strengthen knowledge management and transfer
- Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)
  - If necessary, make changes to our current regulatory framework or create a new regulatory framework to facilitate the adoption of advanced manufacturing
- CDER Research Manufacturing Pilot Plant
  - Increase FDA's capability to generate knowledge and train FDA staff to support assessment, inspection, and policy and guidance development for advanced manufacturing
- Synergize with other CDER/OPQ efforts or initiatives to improve the effectiveness and efficiency of regulatory oversight of drug quality
  - Quality Management Maturity (QMM)
  - ICH Q12 – Pharmaceutical Product Lifecycle Management

Acknowledgement

- Michael Kopcha, Director, OPQ/CDER/FDA
- Joel Welch, Associate Director of Science and Biosimilar Strategy, OBP/OPQ/CDER/FDA
- Adam Fisher, Director for Science and Research Staff, OPQ/CDER/FDA
- Thomas O'Connor, Director, Division of Product Quality Research, OTR/OPQ/CDER/FDA
- Emerging Technology Team

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Thank You!