Opportunities and Challenges for Decentralized Manufacturing

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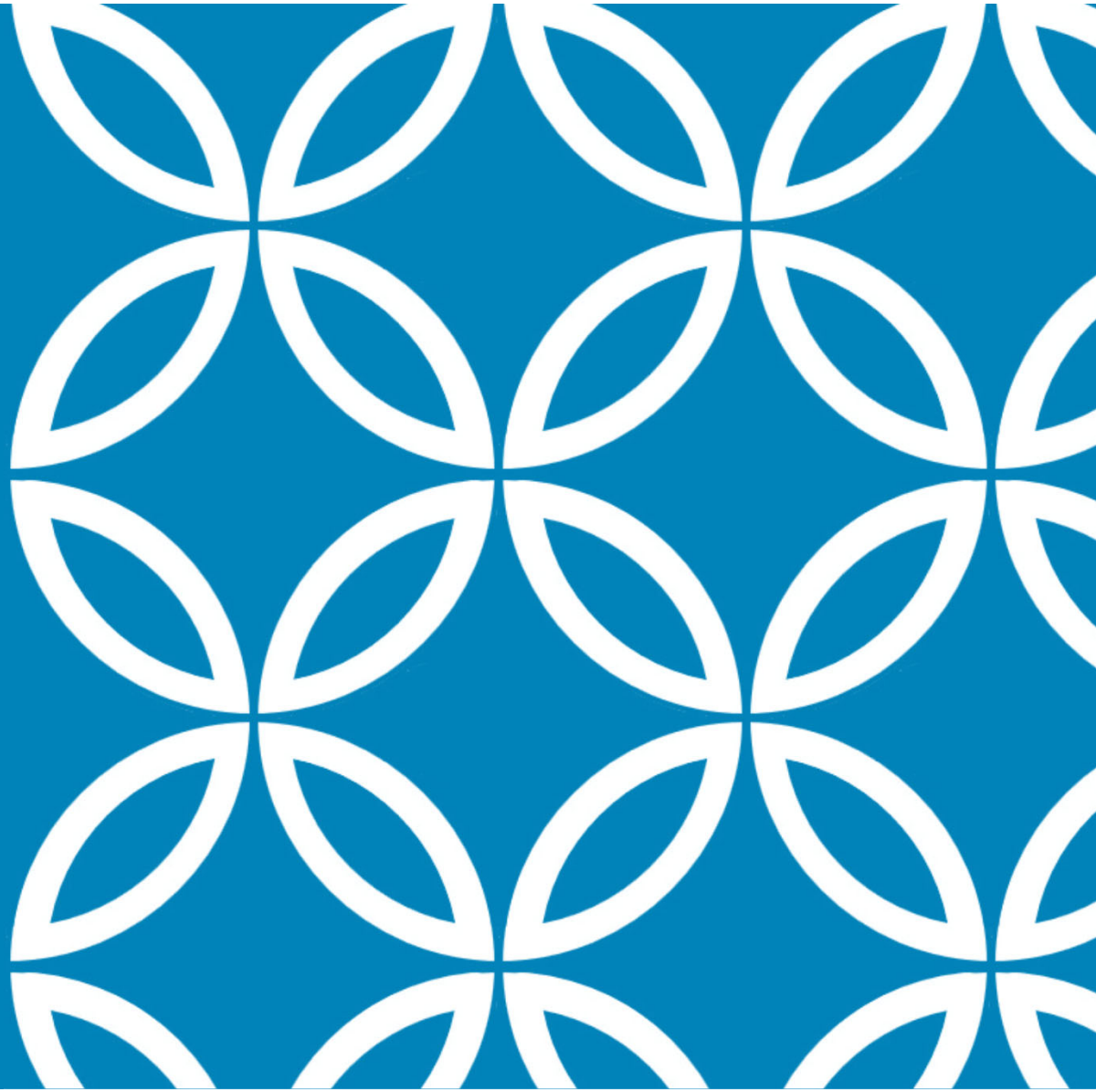

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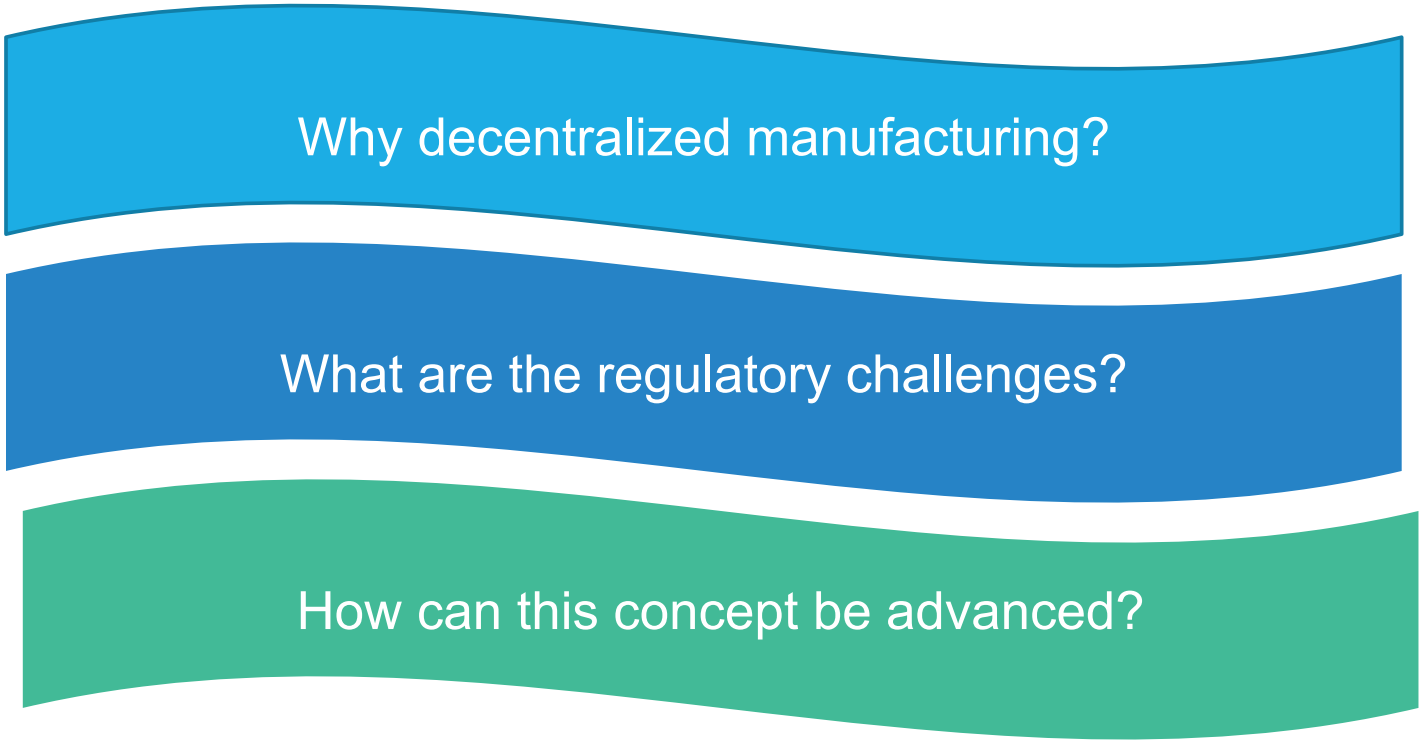
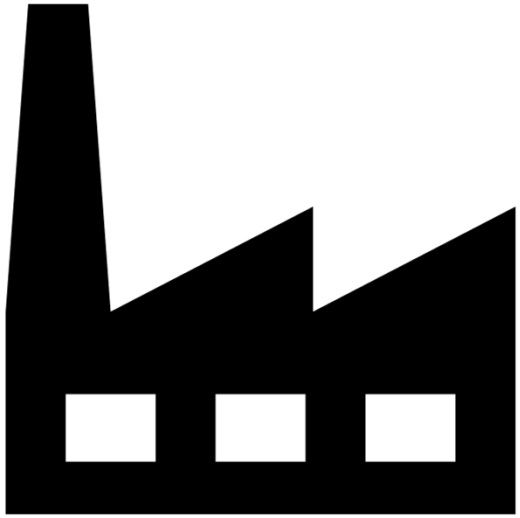
and not of Organon or any other organization

Today's discussion



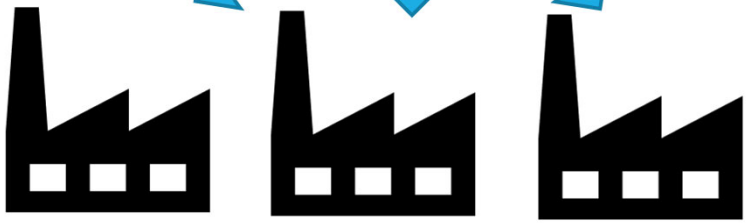
Reimagining Pharmaceutical Manufacturing



Traditional Commercial Pharmaceutical Facility

- Small number of large volume facilities
- Often very specialized steps
- Typically, diverse geography & complex supply chains

Smaller manufacturing facility
(e.g., Continuous Manufacturing)



Replication / Cloning

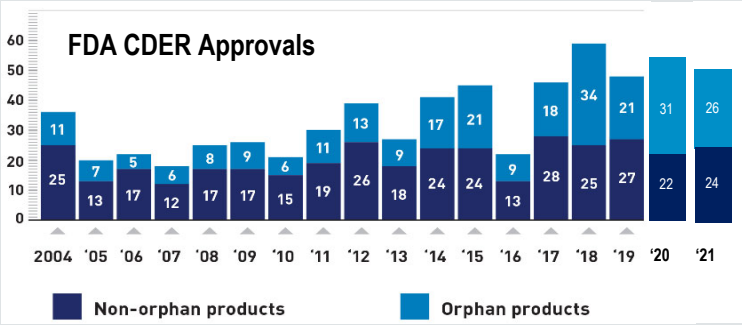
Portable Manufacturing

Point of Care

Potential end to end supply chain

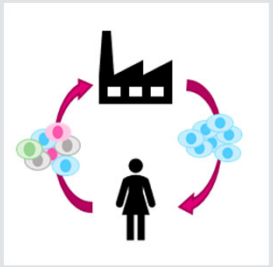
Drivers for Change

More specialized, smaller volume products

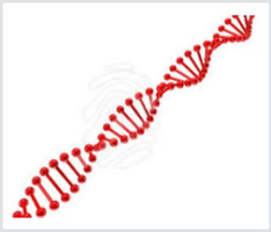


https://www.fda.gov/news-events/fda-voices/innovation-new-drug-approvals-2019-advances-patient-care-across-broad-range-diseases
New Drug Therapy Approvals 2020 | FDA; https://www.fda.gov/media/155227/download

New modalities



Autologous Cell Therapies



mRNA Vaccines

Availability of modular facilities

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

J.POD - Just-Evotec Biologics

Efforts to on-shore pharmaceutical manufacturing

Portable on-Demand (POD) Manufacturing

Constructed at factory

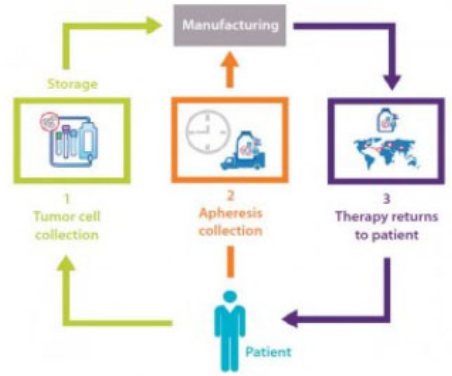
Transported to manufacturing site

Multiple units in a host structure

- Can a manufacturing establishment have a flexible location?
- How is product quality assured when changing locations (e.g., validation, stability)?
- What regulatory oversight is needed when changing locations (e.g., reg filing, inspection)?
- Can a single host facility contain units from multiple clients (i.e., hoteling)?
- How are the quality systems of the manufacturing unit and host facility defined?

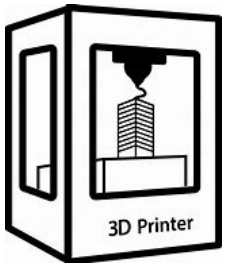
Personalized Medicine – Potential Future Directions

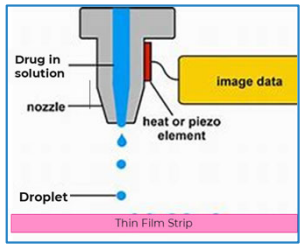
Autologous Immunotherapies



"The Cell Therapy Supply Chain: Logistical Considerations for Autologous Immunotherapies", Dan O'Donnell, 15 Oct 2015, Bioprocess International Supplement

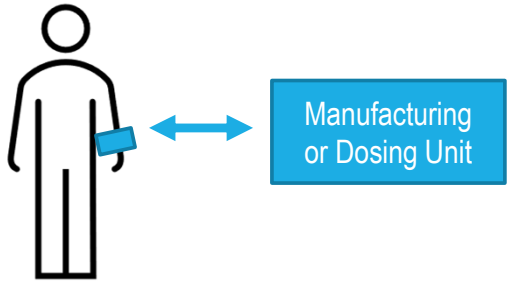
Pharmacy on Demand (additive manufacturing)





Drop on Demand

Auto-titrated Medicines



Wearable monitor

What constitutes pharmaceutical manufacturing vs. pharmacy compounding?

How to regulate "variable dose" medicines?

Can a platform be licensed rather than a specific product?

Health Authority Engagement

FDA/CDER Efforts to Advance Manufacturing

Innovations in Pharmaceutical Manufacturing on the Horizon | The National Academies Press (nap.edu)

Objective (task statement)
Identify emerging and upcoming technology with potential to advance pharmaceutical quality and modernize pharmaceutical manufacturing that FDA/CDER will need to be prepared for in 5-10 years

Workshop #1: Feb 27-28, 2020
Workshop #2: June 2-3, 2020

Key Manufacturing Innovations on the Horizon:
- New routes to drug substances
- Co-processed APIs
- Process intensification (including continuous manufacturing)
- Additive manufacturing
- Advanced process control and automation
- Modular systems

Recommendations to FDA:
- Strengthen expertise in innovative manufacturing
- Advance innovative mechanisms for evaluating technology outside product approvals
- Expand the scope and capacity of the Emerging Technology Program/Team
- Increase external engagement to facilitate innovation and increase awareness of readiness of CDER to evaluate innovative technology
- Expand the leadership role in global regulatory harmonization efforts

US FDA Response

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

FDA

ETP 2.0 Priority Areas

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

FRAME Focus Areas:

- **E2E Continuous Manuf.**
- **Distributed Manufacturing**
- **Point of Care Manuf.**
- **Artificial Intelligence**

CDER Internal Research (partial list):

- Precision Analytics
- Adv Manuf - Biopharmaceuticals
- Manuf of Glycoproteins
- Manuf Synthetic Nucleic Acid
- Process Models, AI/ML

Sau (Larry) Lee, "US FDA Perspective on Advanced Manufacturing", PQRI-FDA Conference, Dec 2021

MHRA Consultation

" New types of innovative products are increasingly being manufactured at the point where a patient receives care e.g. personalised medicines made for the patient either within or very close to the healthcare setting."

Control Site Concept:

- A physical site that will be named on the clinical trial or marketing authorisation application
- Responsible for overseeing all aspects of the POC manufacturing system including the control of each manufacturing location and their activities, including (partial list):
  - Maintain POC master file , including adding and decommissioning sites
  - Oversee pharmaceutical quality system - including incidents, issue, compliance and quality events
  - Provide Qualified Person (QP) oversight
  - Train central and local staff
  - Control and maintenance of manufacturing equipment and control strategy
  - Supply of raw and starting materials and consumables used in manufacture
  - Act as central point for inspections

Consultation on Point of Care manufacturing - GOV.UK (www.gov.uk)

Solicitation closed 23 Sept 2021

EMA QIG Solicitation

EMA plans to create the Quality Innovation Group (QIG)

- Multi-disciplinary group comprising experts from QWP, BWP, and GMDP IWG, with other network or academic experts as needed
- Focus on facilitating innovation in CMC
- Provide a platform for engagement with developers and academia to discuss any new methods, materials, approaches
- Aim to facilitate uptake and remove any technical and regulatory barriers
- Knowledge generated will be shared throughout the EU regulatory network to increase awareness and ensure that assessors and inspectors develop the required capabilities

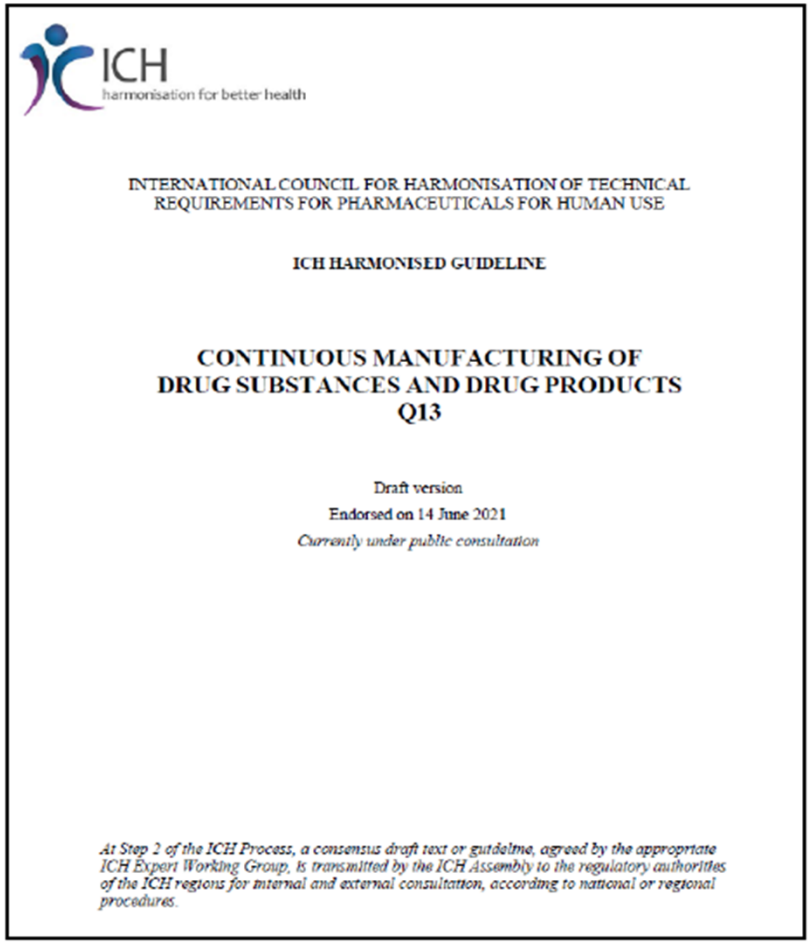
Questionnaire:
Which novel technologies are you working on that will be used to manufacturing medicinal products in the next 5-10 years?
What are the potential barriers in the legislation or current guidance that could slow down or prevent their implementation?
What would be needed in the legislation or current guidance to facilitate their introduction?

Novel Technologies:
manufacturing technology, analytical technology, control strategy approaches, drug delivery systems, devices and/or digital solutions, materials, manufacturing facility designs or design concepts

EUSurvey - Survey (europa.eu)

Deadline for questionnaire 11 Feb 2022

ICH Q13 – Continuous Manufacturing



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

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.

Scope:
Drug substance and drug products of chemical entities and therapeutic proteins; and potentially other biological entities

Includes:

- General continuous manufacturing (CM) concepts
- Scientific approaches for control strategy, production output, process verification
- Regulatory considerations for process description, control strategy, batch description, models, stability, process validation, quality system, etc.
- Annexes with examples including protein drug substance (Annex III)


CALL FOR ACTION

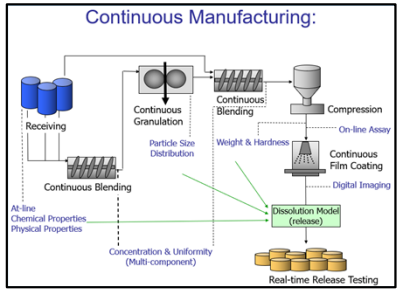
Considerations for the Future Regulations

Use a Science & Risk Based Approach

One size does not fit all!

- Flexible regulatory approaches to adapt to different manufacturing schemes

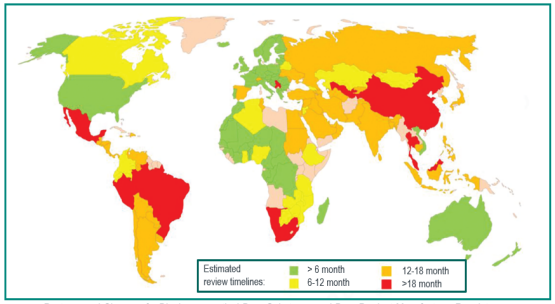
Keep Patient Needs in Mind



Manufacturing Complexity ≠ **Regulatory Commitments**

- What elements are needed for patient safety& efficacy vs manufacturability?

Cultivate International Convergence



Postapproval Changes for Biopharmaceutical Drug-Substance and Drug-Product Manufacture: Regulatory Complexity and Impact - BioProcess InternationalBioProcess International (bioprocessintl.com)

Alignment needed on:

- Dossier content (established conditions)
- Post approval change data requirements & timelines
- Inspectional approaches & reliance

Concluding Thoughts

- Regulators want new technologies
- Change won't happen by itself!
- Proactive engagement and partnership with regulators is needed

Thank you