The Need for Regulatory Flexibility to Support Flexible Manufacturing

NASEM Workshop on Technical and Regulatory Barriers to Innovations in Pharmaceutical Manufacturing

June 2, 2020

Christine M. V. Moore, PhD

Global Head & Executive Director, GRACS CMC-Policy

Merck & Co., Inc., Kenilworth, NJ, USA

Drivers for Flexible Manufacturing

- Smaller volume new products
- Reduced operating costs (e.g., lower inventories)
- Rapid response to changes in demand (e.g., from health emergencies)
- Avoidance of drug shortages
- Rapid launch of new medicines

Ultimate Goal: Availability of quality medicines for patients

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FDA Desired State

CDER's Office of Pharmaceutical Quality created the **Emerging Technology Program** to promote the adoption of innovative approaches to pharmaceutical product design and manufacturing.

The **CATT** was established to promote dialogue, education, and input among CBER staff and between CBER and prospective innovators/developers of advanced manufacturing technologies.

MHRA Regulating Medicines and Medical Devices

Innovation Office

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Process Analytical Technology Team
Innovation Task Force

Pmda 独立行政法人 医薬品医療機器総合機構 Pharmaceuticals and Medical Devices Agency

Innovative Manufacturing Technology Working Group

Synergy For Innovation

Industry

Regulators

Current Environment

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Flexible Manufacturing under Current Regulatory Structure

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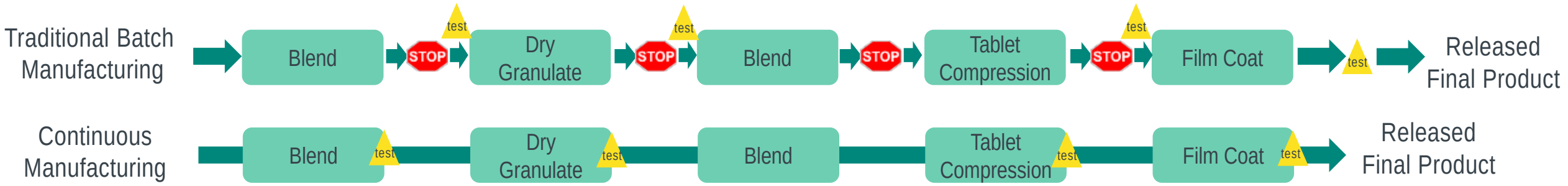
Continuous Manufacturing

Continuous manufacturing is a process in which the input material(s) are continuously fed into and transformed within the process, and the processed output materials are continuously removed from a system which consists of a series of two or more unit operations.



Features of Continuous Manufacturing:

- Shorter processing times
- Integrated unit operations
- Smaller equipment footprint
- Elimination of traditional scale-up
- Enabling of real time analytics & control

Technical & Regulatory Challenges:

- Material traceability
- Effect of disturbances to homogeneity
- Segregation of potential non-conforming material
- Amenable to real time release testing and controls

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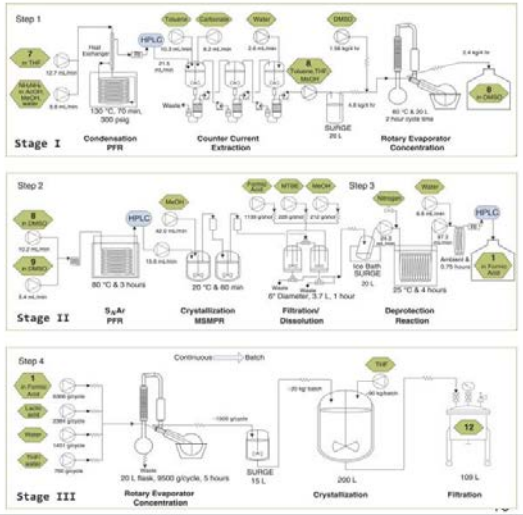
Progress in Continuous Manufacturing (CM)

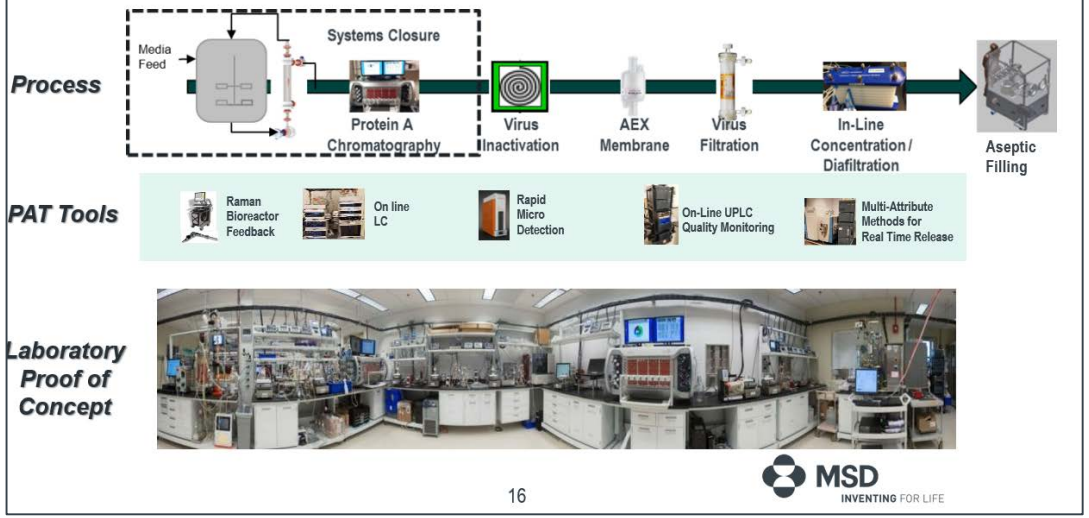
Example of Multistep Small Molecule API Continuous Process



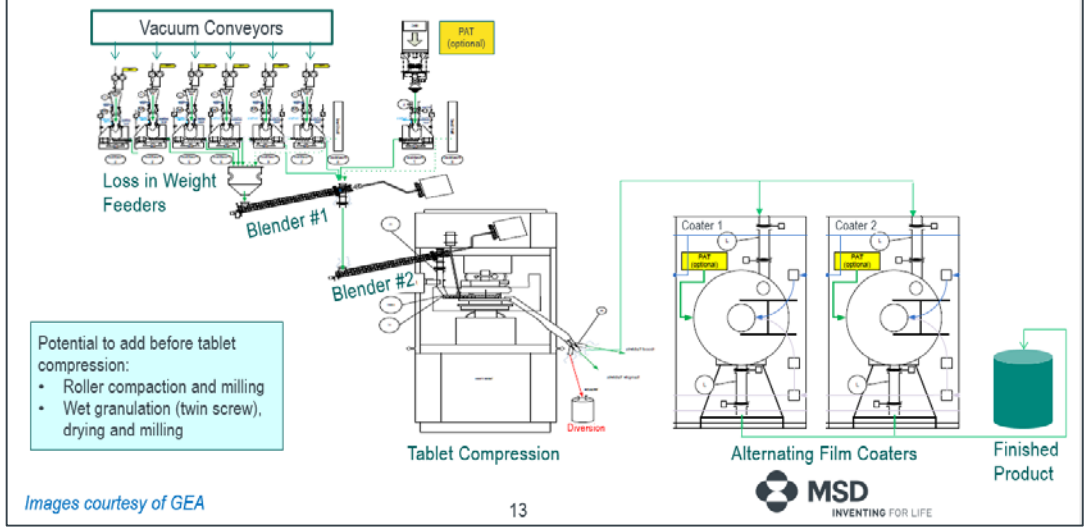
- Continuous preparation of multi-kilogram quantities of a cancer drug candidate
- CGMP operation for clinical trial material
- 5 step synthesis, 8 continuous unit operations
- Around 3 kg per day (total 24 kg)
- Online monitoring

K. Cole, et. al, "Kilgram-scale prexasertib monolactate monohydrate synthesis under continuous flow CGMP conditions", Science, Vol. 356(6343), pp. 1144-160, 2017

Example Continuous Manufacturing for Biologics



Example Continuous Manufacturing for Solid Oral Dosage Forms



To date FDA has approved at least 7 CM applications:

- 6 small molecule drug product
- 1 end to end small molecule drug substance
- Discussions ongoing for CM for biologics

Small molecule CM drug product has been approved in by at least 12 regulatory agencies worldwide

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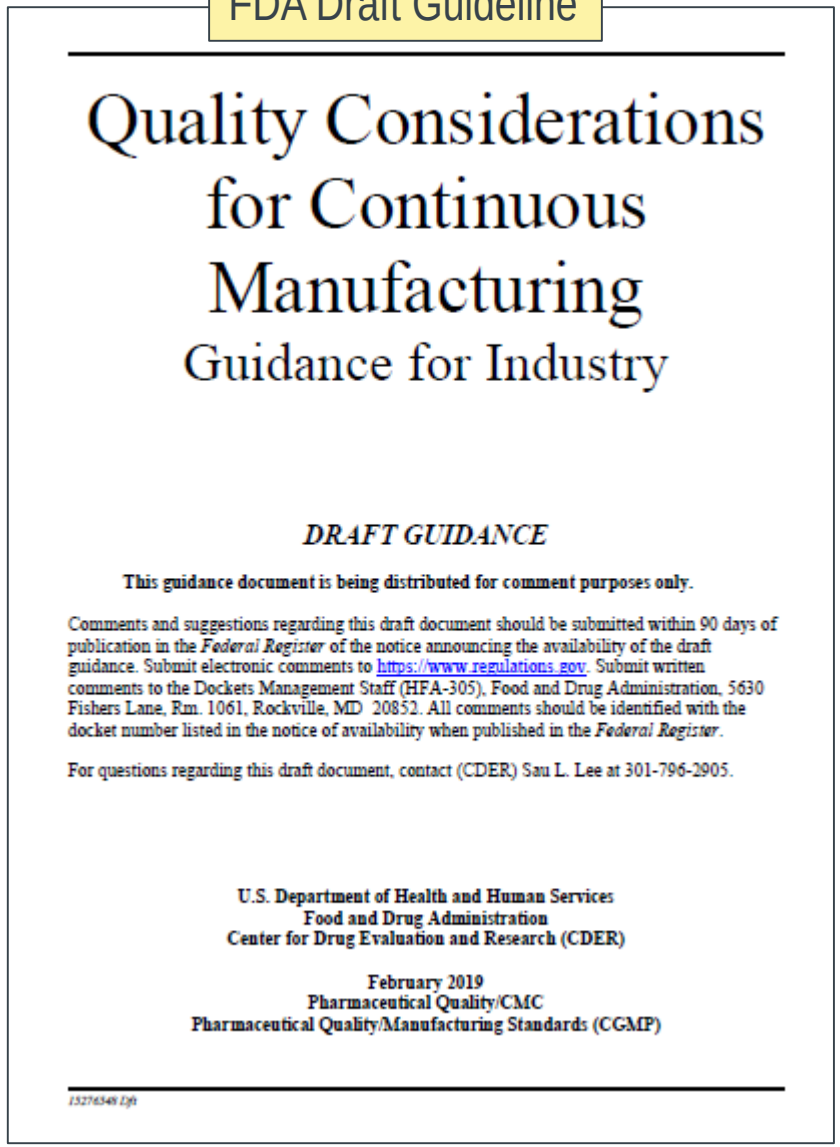
Current Regulatory Status

FDA Draft Guideline



Quality Considerations for Continuous Manufacturing

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability when published in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Sau L. Lee at 301-796-2905.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2019
Pharmaceutical Quality/CMC
Pharmaceutical Quality/Manufacturing Standards (CGMP)

ICH Q13 – In progress

ICH harmonisation for better health

Final Concept Paper

ICH Q13: Continuous Manufacturing of Drug Substances and Drug Products dated 14 November 2018

Endorsed by the Management Committee on 15 November 2018

Type of Harmonisation Action Proposed

New Quality Guideline

Statement of the Perceived Problem:

There is a general consensus that continuous manufacturing (CM) has potential for improving the efficiency, agility, and flexibility of drug substance and drug product manufacturing. Regulatory agencies have seen more companies engaged in the development and implementation of CM in recent years than in the past. Although current regulatory frameworks allow for commercialization of products using CM technology, a lack of regulatory guidelines can make implementation, regulatory approval, and lifecycle management challenging, particularly for products intended for commercialization internationally. An ICH guideline would facilitate international harmonisation and could reduce barriers to the adoption of CM technology.

"Although current regulatory frameworks allow for commercialization of products using CM technology, a lack of regulatory guidelines can make implementation, regulatory approval, and lifecycle management challenging, particularly for products intended for commercialization internationally."

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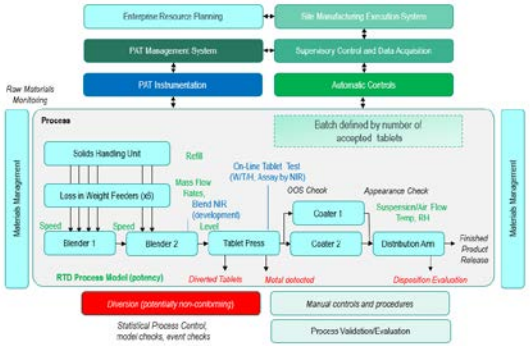
Averting Regulatory Impediments

Use a Science & Risk Based Approach

One size does not fit all!

- Control strategy elements need to be appropriate to specific product and process risks

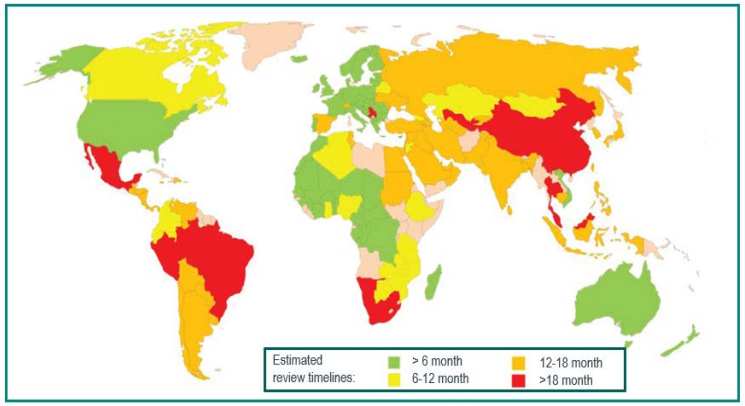
Keep Patient Needs in Mind



Manufacturing Complexity ≠ Regulatory Commitments

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

Cultivate International Convergence



Alignment needed on:

- Dossier content (established conditions)
- Post approval change data requirements
- Post approval change timelines

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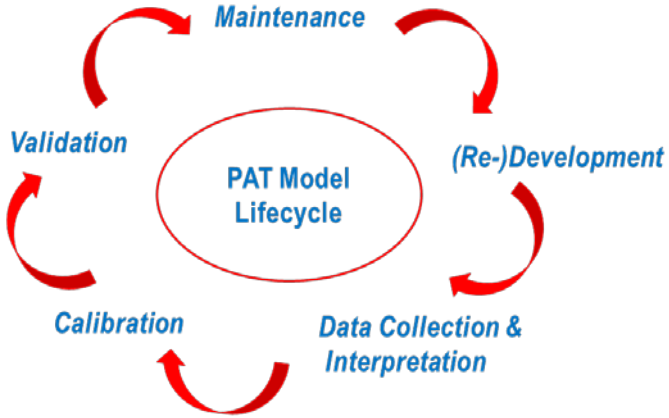
Technology & Regulation Example - NIR Spectroscopy

Model maintenance is a normal and necessary part of lifecycle management for PAT models as new variability is introduced



Regulatory expectations for post-approval changes (including maintenance) are provided:

- FDA draft guideline: https://www.fda.gov/media/91343/download
- EMA Guideline on NIRs data requirements
- Addendum to EMA NIRs guideline

Current Approach

Little differentiation of regulatory reporting for changes

NIR Procedure Components		Potential Approach
Measurement Method	Instrument	"Fixed" components – require supplement to change
	Measurement Mode	
	Scan rate/number	
	Sample presentation	
Model Construct	Reference Method	
	Chemometric Algorithm	
	Calibration range	
Performance Criteria	Specificity	
	Linearity	
	Accuracy	
	Measurement precision	
	Robustness	
Calibration Parameters	Calibration samples	"Flexible" components – managed within PQS
	Spectral range	
	Spectral preprocessing	
	# of latent variables	
	Loadings	
Monitoring	Spectral quality check algorithm & threshold	
	Outlier diagnostics	

(aligned with ICH Q12 – perform based approaches)

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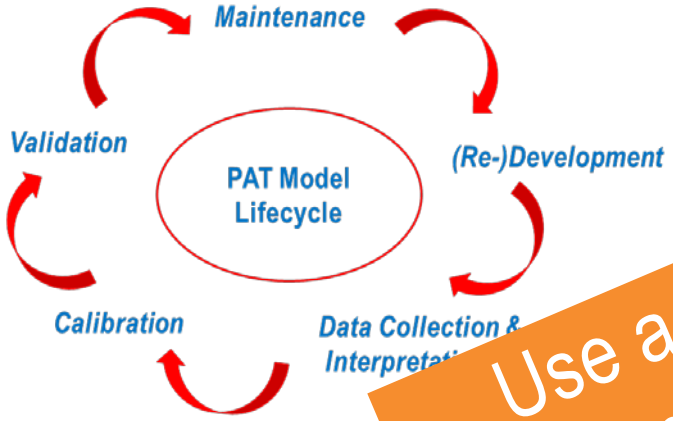

Regulatory expectations

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Use a science & risk based approach
Keep patient needs in mind
Cultivate international convergence

NIR Procedure Components

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Existing Regulatory Tools – Design Space

2005 & 2008

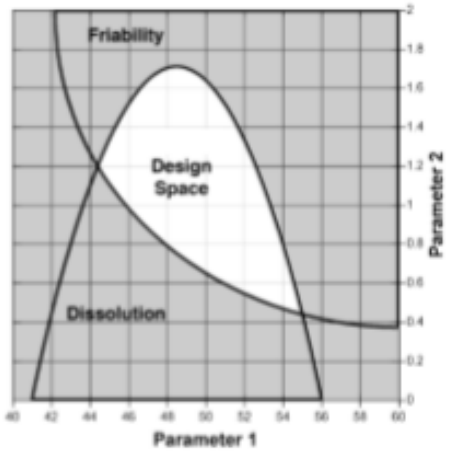
INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL DEVELOPMENT
Q8(R2)

Current *Step 4* version
dated August 2009

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 the European Union, Japan and USA.



2012

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

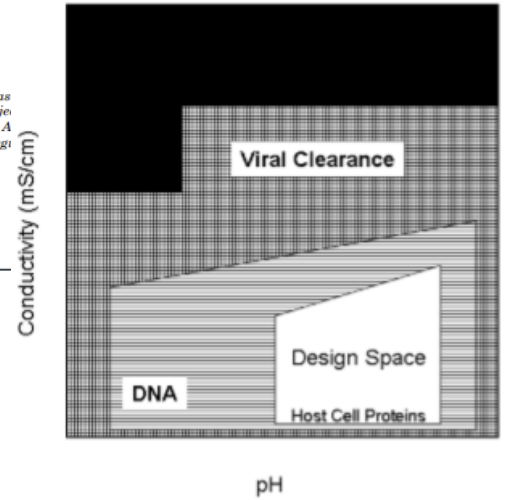
ICH HARMONISED TRIPARTITE GUIDELINE

DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES (CHEMICAL ENTITIES AND BIOTECHNOLOGICAL/BIOLOGICAL ENTITIES)
Q11

Current *Step 4* version

dated 1 May 2012

This Guideline has and has been subje the ICH Process. A adoption to the regu



ICH INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

2009 & 2010

Quality Implementation Working Group on Q8, Q9 and Q10 Questions & Answers (R4)

Current version dated November 11, 2010

ICH harmonisation for better health

2011

ICH QUALITY IMPLEMENTATION WORKING GROUP POINTS TO CONSIDER (R2)

ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation

Document date: 6 December 2011

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Existing Regulatory Tools – ICH Q12 (ECs & PACMPs)

ICH
harmonisation for better health

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

ICH HARMONISED GUIDELINE

TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT

Q12

Final version

Adopted on 20 November 2019

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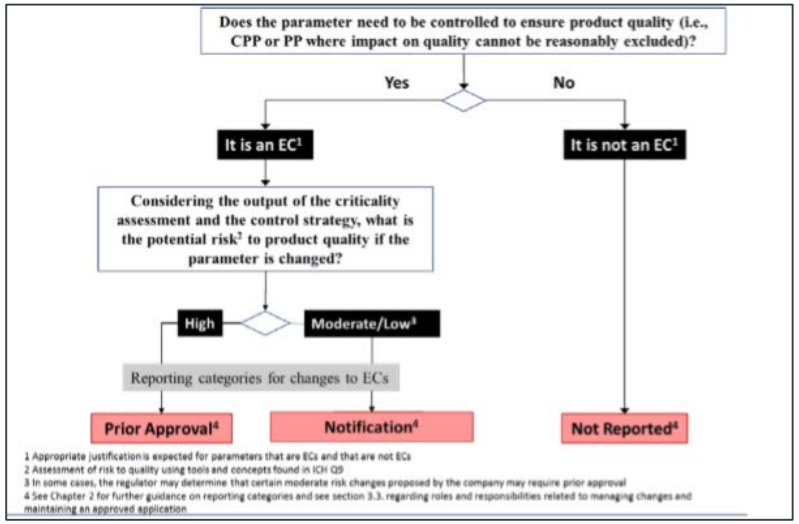
Q12 Annexes

Final version

Adopted on 20 November 2019

Established Conditions



Post Approval Change Management Protocols (PACMPs)

PACMP Component	PACMP Step 1 Contents (registration/approval of protocol)	PACMP Step 2 Contents (change implementation)
Overall Strategy (Scope and Limitations of proposed change)	Defined scope and limitations	Demonstrate requirements of scope are met
QRM	Description of QRM activities and summary of risk assessment	Confirmation that previously conducted risk assessment has not changed; or, if new information is available that impacts the risk assessment, an updated risk assessment is provided
Acceptance criteria	Tests and studies to be performed; description of any other criteria to be met, including plans to report outcomes from ongoing stability testing	Data demonstrating that acceptance criteria are met. Confirmation that other criteria are met. Updated CTD sections for S.2.1 Manufacturer(s) of Drug Substance and S.4.4 Batch Analyses for Drug Substance.

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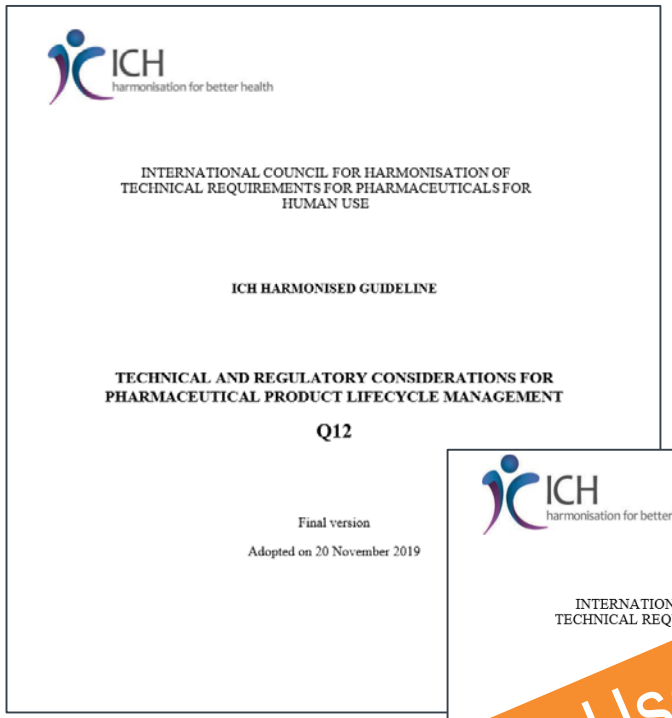
Existing Regulatory Tools – ICH Q12 (ECs & PACMPs)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Q12

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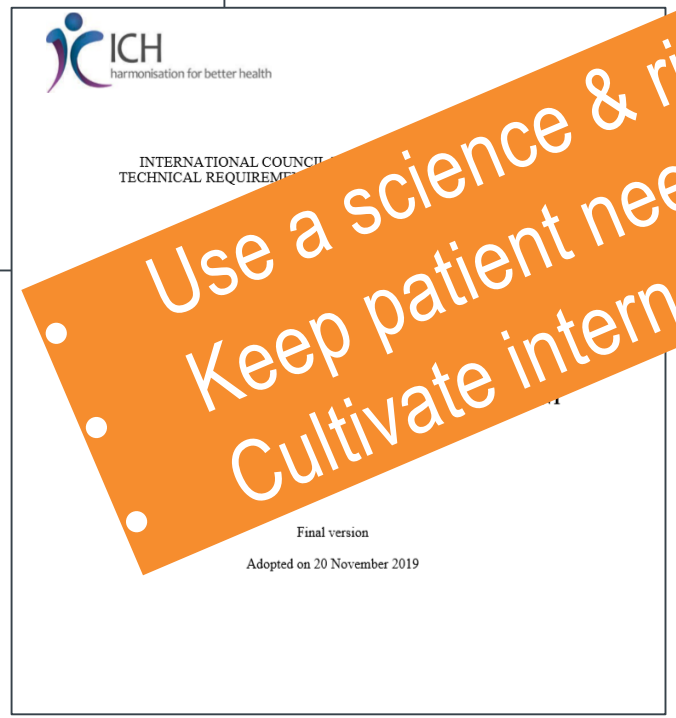
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harmonisation for better health

Final version

Adopted on 20 November 2019

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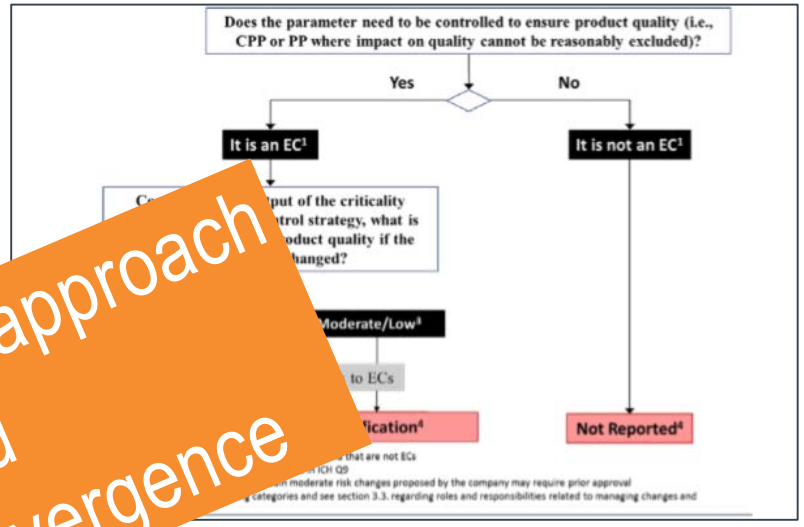

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Flexible Manufacturing – Regulatory Opportunities

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Portable Manufacturing

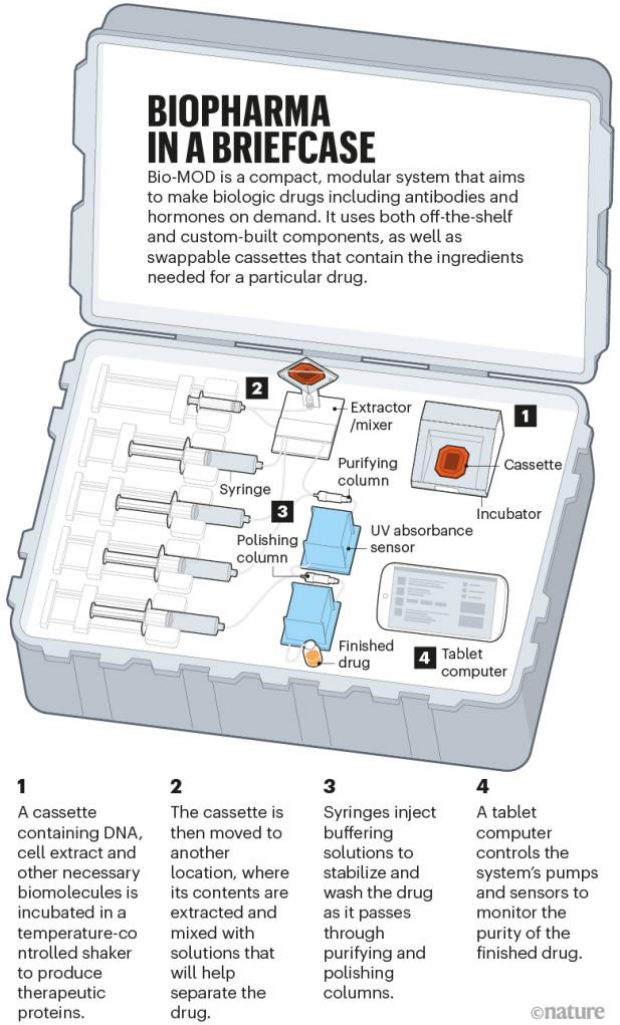
Portable On-Demand (POD) Manufacturing

Constructed at factory

Transported to manufacturing site

Current: Multiple units assembled in a host structure

Future???
Fully contained, mobile, stand alone unit



https://www.natureasia.com/en/nindia/article/10.1038/nindia.2019.147

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Questions Related to Portable Manufacturing

Can an establishment have a flexible location?

- FDA defines establishment as *a place of business under one management at one general physical location*

How are the support functions provided to the portable manufacturing (e.g., utilities, warehousing, training)?

- Consistency of POD/host site interface and quality system elements

•How is product quality assured when changing locations?

- Expectations related to process validation, stability and bioequivalence

Would an inspection be required when moving the location?

- Lowered risks related to a change in location of the POD

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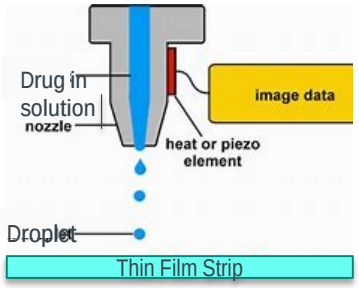
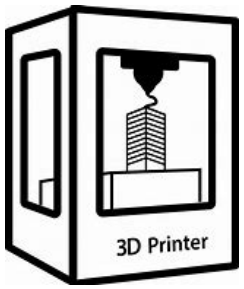
Individualized Medicine

What if medicines were manufactured in your pharmacy or in your home?

Solid Oral Drug Products





Autologous Cell Therapies

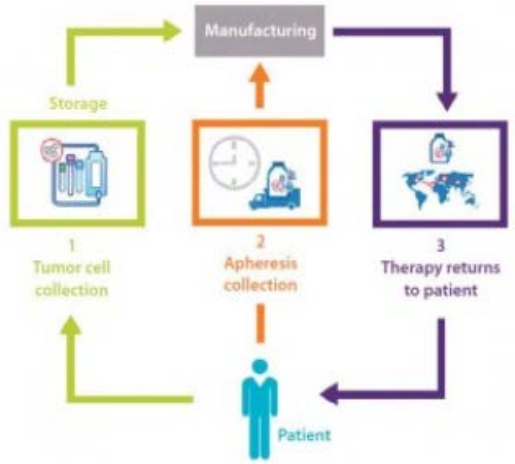


Figure 2: Typical process chain for autologous cell therapies

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

Is this compounding or pharmaceutical manufacturing?

How do you meet regulatory requirements for batch release?

How to regulate variable dose combinations?

Concluding Thoughts

Regulation for Innovative Technology

Technology is advancing at a rapid pace:

- Manufacturing flexibility is needed to rapidly adapt to changing needs
- Goal is availability of quality medicines to patients

Regulatory Recommendations:

- Use a science & risk based approach
- Keep patient needs in mind
- Cultivate international convergence

https://www.packagingdigest.com/pharmaceutical-packaging/pmp-we-have-many-innovative-opportunities-as-packaging-professionals-160721

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THANK YOU!

Questions, comments, copies:
christine.moore@merck.com

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