Continuous manufacturing: Challenges and opportunities. EMA perspective

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Overview

1. Potential advantages of CM
2. Scientific challenges
3. Regulatory environment
4. EMA support to innovation
5. Conclusions & recommendations
1. Potential advantages of CM

New chemical reactions

Fast development & screening
Scale-up*

Flexibility and agility

Smaller footprint

Shorter production times

Easier to accommodate supply needs

Enhanced process understanding & control

On line monitoring & control
Real time product quality info.

Benefits to patients, industry & regulators
2.1 Scientific challenges- Development considerations

Some traditional concepts might need to be further explored -

- **Additional considerations:**

  - Raw material properties (and lot to lot variability) - 
    specifications!
  - **Process dynamics:** feeders refill, RTD
  - Material traceability
  - **State of control,** Detection of disturbances
  - Segregation of material
  - **Design spaces** - potential interactions between steps
  - Scalability (equipment design)

- Process description may look different (descriptions in terms of material transformation kinetics, e.g.
  mass flow rates in kg/hour, flow rates per kg of material, mean residence time in sec with associated
  RTD,...)
2.2. Scientific challenges- manufacture & CS considerations

- The definition of a batch should be stated prior to manufacture

  *ICH Q7 (EU GMP Guide Part II)*

  "A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval."

- Systems and controls: automated valves, **feed-back and feed-forward controls**
- **Flow rate** of material
- Feeder controls
- IPCs and sampling considerations different than batch process
- Routine use of **PAT tools** (e.g. in-line NIR, at-line Raman) and non-spectroscopic (PSD, imaging)
- Use of **models (first principles, empirical)**: intention and relevance for routine production?
2.2. Scientific challenges- manufacture & CS considerations

- Procedures for start up/shut down and interruption
- Control strategy is product and process specific, may be different to that for batch mode!
- Procedures for handling deviations and non-conforming material (segregation points, how is segregation decided?)
- RTRT: Parallel testing and plan for end product testing when PAT data is not available (back-up/redundancy)?
- Process validation strategy: traditional process validation or Continuous Process Verification (CPV), based on data rich environment of PAT-enabled CM
2. Scientific challenges – Equipment

- Plans for maintenance?
- Strategy for cleaning validation?
- Indicators of equipment failure?
- Potential for microbial growth?
- Potential fouling?
- Location of PAT tools
- Location of diverting valves
- Design/ engineering: larger contact surface

Mainly discussed during pre-approval inspection
3. Regulatory environment

No specific EU guidance on CM currently available - case-by-case evaluation but supportive:

- ICH Q8, Q9, Q10 and Q11, and PtC: principles apply to enhanced development, manufacturing and control strategy approaches including CM

  EU Guideline on *Process Validation* (revised 2014): introduced CPV

- EU Guideline on *RTRT*: more flexibility in batch release (integrated product testing)

- EU Guideline on *Manufacture of drug product* (under revision): CM not specifically addressed, but not in contradiction

- EU guideline on *Chemistry of new active substances* (published Nov 2016): CM not specifically addressed, but not in contradiction

- EU Guideline on *Use of NIR* (revised 2014): principles applicable to other chemometric models

  PhEur: chapter on *Chemometrics* (5.21), *NIR* (2.2.40), *Raman* (2.2.48), *Large sample sizes* (UDU 2.9.47), ...

- Q&A on QbD: *Lessons learnt from the pilot, Level of details, DSp verification, NORs/PARs/DSp* (draft not published but shared with Industry), ...

- GMP Annex 15 & Annex 17
EMA guideline on PV finished product

Process Validation strategies

**Traditional approach**

Normally performed when pharmaceutical development and/or process development is concluded, after scale-up to production scale and prior to marketing of the finished product.

**Hybrid approach**

Combination of traditional process validation and continuous process verification approach for different steps within the manufacturing process.

**Continuous process verification**

An alternative approach to PV in which manufacturing process performance is continuously monitored and evaluated. (ICH Q8)

It can be used in addition to, or instead of, traditional process validation.

It is a science and risk-based real-time approach.

Extensive in-line, on-line or at-line controls and monitor process performance and product quality on each batch.

PAT tools, MSPC.

**Most appropriate method for validating continuous processes.**

3. EU experience to date

✓ Several discussions with companies at PAT team

✓ Several scientific advice requests

✓ Two applications in the centralised procedure (one under the EMA-FDA QbD pilot program)

✓ Still limited experience (both industry and regulators need to learn more) → EMA recommends establishing an early dialogue with regulators during CM development
3. Regulatory considerations-legacy products

Risk based approach to determine the type of bridging information to support the change.

An early discussion of the proposed change and bridging strategy (physicochemical equivalence and BE) with the regulators is encouraged.

a. Replacement of the manufacturing process
b. Addition of a new manufacturing process

Considerations- Impact on:

- appearance, visual description
- qualitative and quantitative composition
- specifications
- product information, e.g. sections 3, 6.1, excipients in the label & PL:
  
  

- Annex A
4. EMA support to innovation

Develop appropriate and accessible regulatory platforms, tools, incentives

- **CHMP Scientific Advice** - official advice from the CHMP on appropriate tests and studies
  

- **PAT team** - support of PAT and QbD activities in the EU
  

- **Innovation Task Force (ITF)** - platform for early dialogue scientific (Q, NC, clinical), regulatory and legal
  

- **EMA SME office** – dedicated support to small pharmaceutical companies.
  

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**Early dialogue**
5. Conclusions and recommendations

- Regulators are supportive of innovative pharmaceutical manufacturing.

- Current regulatory framework is adequate to allow CM. No specific guideline currently available, but existing GL are supportive.

- CM offers advantages over batch manufacture. Additional considerations may need to be explored.

- Complex dossiers.
  - Level of detail commensurate with impact on the commercial manufacturing process and control strategy.
  - Stick to ICH terminology. Provide clear definitions for in-house terms when unavoidable.

- Regulators need to understand the product and process development, manufacturing and process control strategy (and decision making).

- Early dialogue with regulators to ensure there is a mutual understanding.
Acknowledgements

EU PAT team
Thank you for your attention!

Further information

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