The details are not the details. They make the design.

Charles Eames
Introduction – Examples of Pharmaceutical Continuous Processes

- **Continuous separation of optical isomers** *(levo enantiomers of α-methyldopa from the dextro species)*
  - Fluidized bed continuous crystallizer
  - Operates in the non-equilibrium conditions
  - Close control of supersaturation to prevent nucleation
  - Population balance maintained by crystal fracture (sonication)
  - Batch process could not be scaled up

- **Selective oxidation** *(Convert 4-methyl-thiazole to corresponding nitrile)*
  - Adiabatic packed-bed reactor
  - Obtained desired conversion/selectivity/quality
  - Previous process was shown to work at 1–2% yield

- Commercialized these process in the 1960s

*Edward Paul and Carlos Rosas, Challenges for Chemical Engineers in the Pharmaceutical Industry, Chemical Engineering Progress, December 1990*
Introduction

Traditionally the Pharmaceutical Industry has focused on batch processing

Perhaps due to:
- Flexibility of multipurpose plants
- Large number of products
- Increased regulation (ICH guidelines begin implementation in 1996)

Continuous process
- Cultural change
- Lack of experience
- Perceived regulatory barriers
- Not the way it has always been done

Graph data reference: www.fda.gov (Home> About FDA> What We Do> History)
Introduction

Continuous Process
Material continuous flows into and out of the equipment

Batch Process
Material flows into the equipment, processing occurs and material is emptied from the equipment

Semi Continuous Process
Material flows into the equipment, material enters or leaving during the processing and material is emptied from the equipment
Are the regulatory definitions applicable to continuous processing?

- ICH Q7: Good Manufacturing Practice for Active Pharmaceutical Ingredients a **batch (or lot)** is a specific quantity of material produced in a processes or series of processes so that it is expected to be homogeneous within specified limits. In the case of *continuous or semi-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.

- 21 CFR 210.3 (2): **Batch** means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.
Are the regulatory definitions applicable to continuous processing?

- **Batch** - A quantity of drug in dosage form, a raw material, or a packaging material, homogeneous within specified limits, produced according to a single production order and as attested by the signatories to the order.

In the case of *continuous manufacture*, a batch corresponds to a defined fraction of the production, that is characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. *(Health Canada Good Manufacturing Practices (GMP) Guidelines - 2009 Edition (GUI-0001))*

- A **batch** is considered homogeneous when equivalent parts or materials are manufactured and/or tested in the same manner, without interruption, typically *on the same day or in the same time period*, and produced by the same person, or with the same machine/equipment set-up and fulfill the same specifications. *(EMA MEDDEV 2.5/6 Rev. 1 February 1998)*
Are the regulatory definitions applicable to continuous processes?

- 21 CFR 210.3 (10) **Lot** means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by *continuous process*, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.

- **Lot** - A quantity of any drug in dosage form, a raw material, or a packaging material, homogeneous within specified limits, constituting all or part of a single batch and identified by a distinctive lot number that appears on the label of the finished product. (*Health Canada Good Manufacturing Practices (GMP) Guidelines - 2009 Edition (GUI-0001)*)

→ The regulatory definitions are applicable to continuous processing

- Appears to be no major hurdles in guidelines/laws (ICH, CFR, EMA for clinical trial or commercial applications)
How is steady state defined?

Steady state not in current regulations. *Proposed definitions*

- **Steady state** is obtained when all flows and concentrations do not change with time.
- **Steady state** is when the processing conditions (i.e. material flow rates, temperatures, and/or pressures) are within normal processing variations.
- **Steady state** is when the process controls are at the pre-determined, desired set points (for example, a reactor temperature set point) and there are only normal process variations.
- **Steady state** is when the critical process parameters are within a specified range.
Continuous Processing – Perceived Regulatory Hurdles

- Steady State → *On going discussions*

  - When is steady state obtained?

  - How are start up and shut down handled?

  - How are perturbations handled?

  - Steady state and perturbations can be mathematically modeled

  - First order reaction in a continuous stirred tank reactor can be calculated *

    \[ t_{\text{ steadystate }} = \ln \left( \frac{\tau}{1 + \tau} \right) \frac{k}{1 + \tau} \]

    - Fast reactions \( t_{\text{ steadystate }} = 4.6/k \)
    - Slow reactions \( t_{\text{ steadystate }} = 4.6 \tau \)

* Elements of Chemical Reaction Engineering, H Scott Fogler, 1992
ICH Q8, 9, 10 and 11

Are the current regulatory guidelines applicable to continuous processes?

- Concepts in ICH Q8, 9, 10 and 11 are applicable to continuous processes
  - A more systematic approach to development (Quality by Design: QbD)
  - Multivariate interactions emphasized
  - Incorporation of risk
  - Knowledge management
  - Product lifecycle
  - Increased assurances of quality
  - May reduce post-approval regulatory burden
  - Provides the flexibility to use modern manufacturing approaches
Real Time Release

• All quality tests are on-line/at-line

• Manufacturing flexibility
  o Increased efficiency
  o Control in real-time
  o Process adjustments in real-time

• Increased assurance of quality
  o More representative of the process
  o More information gained

• Adoption of PAT technologies
  o Continuous process monitoring
  o Feedback control
Continuous Processing – Perceived Regulatory Hurdles

Process Validation of Continuous Processes

• Traditional three batch approach

• Continuous Process Verification
  o An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated (ICH8)
  o “Continuous Quality Verification (CQV) is described as an approach to process validation where manufacturing processes (or supporting utility systems) performance is continuously monitored, evaluated and adjusted as necessary.” *

*ASTM E2537
The holy grail

Continuous Processing
Telescoped
Real Time Release
Continuous Quality Verification

Diagram:
- Raw Materials
- Recycle
- Excipients
- RTR API
- RTR DP
- Packaged Drug Product
Continuous Processing

- Potential hurdles for continuous processing
  - Tractability of raw material lots and intermediate batches
  - Regional regulatory differences and acceptance
    - Potential for additional queries and longer review period
    - Some regulatory agencies have additional requirements
  - Steady state
    - Definition of steady state
    - How to handle start up/shut down
    - How to handle perturbations and deviations
  - Inventory
    - Need more inventory? Need less inventory?
Benefits of Continuous and Batch Processing

**Continuous Processing**

- Increased control of flows, temperature and pressure
  - Higher temperatures/pressure possible
  - Short material contact time better controlled
    → better for fast kinetics (i.e. reactions & crystallizations)
    → better for exothermic operations
- Neat processing possible
  - Less waste, lower environmental impact
- Typically operated in dedicated equipment and non stop; often with less inventory

**Batch Processing**

- More flexible operations
  - Slow material contact time
    → better for slow kinetics (i.e. reactions & crystallizations)
- Typically operated dilute
  - Often higher solvent load
- Typically operated in multipurpose equipment and in campaigns; often with large inventories of intermediates/finished products
Benefits of Continuous and Batch Processing

**Continuous Processing**

- Further processing options
- Most continuous operations would be new equipment
  - small scale skids possible
- Less product variability
  - No batch to bath variation
  - Process variations and upsets

**Batch Processing**

- Less processing alternatives
- Most existing pharmaceutical plants are multipurpose batch plants
Benefits of Continuous and Batch Processing

- **Continuous Processing**
  - Typically lower cost at high production rates *

  - However continuous operations typically have increased flow and temperature control → can operation processes that are not possible in batch processing

  - Can be a large advantage in early development

- **Batch Processing**
  - Typically lower cost at low production rates *

* Douglas, Conceptual Design of Chemical Processes, 1988
Cost Analysis is likely part of the Batch or Continuous decision

- Typically process cost analysis examines
  - Raw Material cost
  - Waste Cost
  - Processing (Overhead) Costs

- Other processes costs are hard to quantify
  - Cost of lot failures and investigations
  - Cost of recalls and stock outs
  - Cost of inventory (finished product, intermediate, raw materials)
  - Cost of analytical tests and release
Comments about Process Costs

- **Analytical Release Costs**
  - Analytical release time and costs can be high → examples below
  - Real time release has potential to decrease these costs

(Graph source: G. K. Raju, M.I.T. FDA Science Board Meeting, November 16, 2001)
Comments about Process Costs

- **Intermediate Storage**
  - Batch processes are typically operated in campaigns with large intermediate storage
  - Continuous process are typically operated non-stop with less intermediate storage → potential to decrease storage cost

![Inventory Holdings Chart](image_url)

Inventory holdings for 17 pharmaceutical companies based on inventories listed in each individual companies 2008 annual report.
Comments about Process Costs

- Cost impact of decreasing processing time with continuous processing
  → What is the cost contributors of typical Pharmaceutical processes in terms of raw material, waste and overhead costs

- **Case study:**
  - 8 drug substance development/commercial compounds
  - Commercial scale basis
    - equipment size
    - cost per hour
    - raw material costs
  - Comprehensive modeling of including mass balances, raw material amounts, unit operations, cycle time, number of batches, waste amount
  - Estimated commercial cost
**Comments about Process Costs**

- **Question**: Cost analysis of typical drug substance Pharmaceutical processes

- **Observations:**
  - Raw material costs range from 30 to 75%
  - Waste costs typically < 20%
  - Overhead costs range from 10 to 70%
  - Shows the potential for process improvements
    - Example 1 (yellow bar) was later optimized lowering the overhead time/cost and greatly decreasing the overall cost
    - Provides impact of decreasing processing time
      - Processes with low overhead costs might have limit benefit converting to continuous processing
Question: Cost analysis of typical drug substance Pharmaceutical processes

Observations:
- Average raw material costs 51%
- Average waste cost 11%
- Average overhead costs 38%
Conclusions

• Continuous Processes
  • Is established technology
  • Have been implemented in the Pharmaceutical Industry

• The current guidelines are applicable to continuous processes
  • There are no major regulatory hurdles
  • There are several unique regulatory aspects of continuous processing
    o Steady state, startup/down, perturbations

• Modern manufacturing operations (Continuous Processing, real time release) have potential to
  • Decrease process costs
  • Decrease intermediate storage and costs
  • Decrease release costs
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