ThermoFisher SCIENTIFIC

DEVELOPMENT AND SCALE UP

OF CONTINUOUS FLOW PROCESSES FOR THE MANUFACTURE OF API

S. Steinhofer, M. Vasiloiu, P. Poechlauer

patheon

fisher clinical services

DRIVE / MOTIVATION

Why go "continuous"?

Get the efficiency, flexibility and scalability of microreactor flow chemistry

1. **Safe Use of Extreme Reaction Conditions**
   - Efficient mixing
   - Excellent thermal control
   - Process intensification of hazardous reactions
2. **Reduced Development Time**
   - Small hold-up volume
   - Rapid reaction optimisation
   - Minimal scale-up steps
3. **Improved Process Control**
   - High level of reaction control
   - Process reproducibility
   - Quality by Design (QbD)
4. **Reduced Manufacturing Costs**
   - Increased product quality
   - Reduced safety investments
   - Higher unit productivity

METHOD

Time: the best time to decide on a continuous process…

Start as early as possible

Phase 0 Pre-clinical / tox	Phase 1 FIH/SRD	Phase 2A/B POC	Phase 3 Pivotal	Commercial
Rapid salt & polymorph screen: basic character-ization	Extensive polymorph screen to confirm most stable form/single crystal growth; Full characterization		Typically around phase 2 **process and formulation are fixed.** Most stable polymorph is selected	
Process selection / scouting		**Process development / scale-up**		**Process validation / conti. verification**
XRPD DSC/TGA PSD; DVS Log P; pKa Solubility Forced degradation	XRPD; Flow properties PSD; SEM; BET; DSC/TGA Intrinsic dissolution rate			

Data created here should not change during development

UNDERSTAND THE PRODUCT AND YOUR PROCESS!

QUALITY REGULATIONS

Define a batch

Ways to define a batch:

1. By a **specific time slot** during which a certain volume of uniform product is manufactured (6:00 a.m.– 6:00 p.m.)
2. By a time slot during which a **specific batch of raw material** is consumed

Both ways allow **tracing the product batches back to raw material batches**

Regulatory Definition of "Batch"
21 CFR 210.3

Batch: 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.

Batch refers to the quantity of material and does not specify the **mode of manufacture**

Regulatory Definition of "Lot"
21 CFR 210.3

Lot: 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.

Definitions for both "batch" and "lot" are applicable to continuous processes

RESULTS & CAVEATS

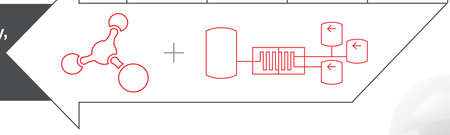
As simple as hoped?

No!

Detailed mutual understanding of disciplines is key

Discipline	Topics / tasks	Considerations on	Language / competency
Chemistry	Route definition; reagents; stoichiometry; chemical yield	Molecules; atoms; electrons; by-products	Chemistry; chemical formulae; reactions
Process technology	Energy balance; mass balance; kinetics; ther-modynamics	Mass flow; heat flow; Turbulence; viscosity	Differential equations; dimensionless figures
Reactor layout	Dimensioning; mixing time; heat removal;	Layout; reactor features; capacity; safety integrity level	Dimensions; key figures; Computational fluid dynamics
Plant engineering	Build reactor / plant that meets the requirements	Material of construction; corrosion; pumping principles	Mechanical engineering Machining; joining: welding, sintering

A close collaboration between the key disciplines of chemistry, process development and plant engineering working in parallel, delivers a robust and efficient continuous process



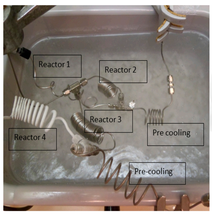
CASE STUDY

LOW TEMPERATURE METALATION: Activity Timeline

Lab development and Kg scale production 2013

Goals:

- Quick and simple lab setup
- Fast production start up



Advance development 2014

Goals for this development:

- Reactor design optimized
- Optimum set points
- PAR studies
- Production time runs

Commercial production 2014–2017

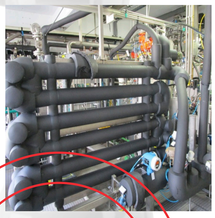
cGMP production:

- Several hundred Kg registration campaign → One flow reactor line
- Several tonnes validation campaign numbering up: Reactor lines in parallel
- Demonstration of fully continuous production at pilot scale

Implementation of fully continuous process 2018–2019

Implementation:

- Validation of fully continuous process at commercial scale



Validated and FDA Inspected

thermofisher.com/patheon • pharmaservices@thermofisher.com

Published 6/19 PATH0555R

Find out more at **thermofisher.com/patheon**