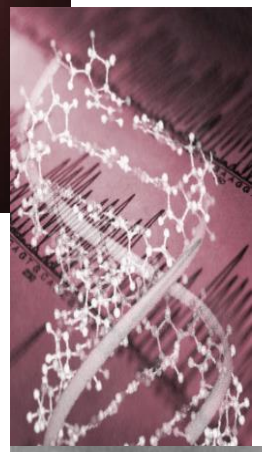
ICHQ13: Questions and Concerns



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CASSS Strategy Forum

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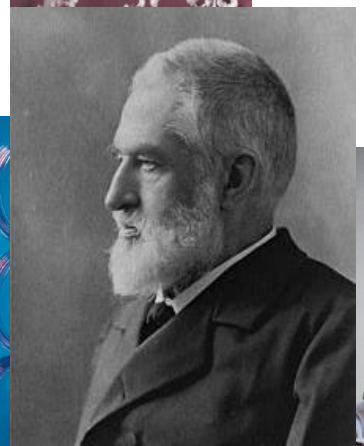


Dating the ICH…

ICH Q1
Stability of New Drug Substances and Products 1993

ICH Q5A-D
Quality of Biotech Products ‘99, ‘95 ‘95 ‘97

ICH Q5E
Comparability of Biotech Products 2004

ICH Q6B
Specs for Biotech ‘99

ICH Q7
GMPs for API, 2000

ICH Q8 (2009)
Development

ICH Q9 (2005) QRM

ICH Q10 (2008) PQS

Control Strategy: "A planned set of controls, derived from current product and process understanding, that assures process performance and product quality" (ICH Q10)

ICH Q13 Continuous Manufacturing of Drug Substances and Drug Products

Endorsed by the Assembly in June 2018 this new Guideline is proposed to:

- Capture key technical and regulatory considerations that promote harmonisation, including certain Current Good Manufacturing Practices (CGMP) elements specific to Continuous Manufacturing (CM),
- Allow drug manufacturers to employ flexible approaches to develop, implement, or integrate CM for the manufacture – drug substances and drug products – of small molecules and therapeutic proteins for new and existing products,
- Provide guidance to industry and regulatory agencies regarding regulatory expectations on the development, implementation, and assessment of CM technologies used in the manufacture of drug substances and drug products.

The US cGMPs require “batches” and “lots” but don’t require batch manufacturing and, in fact, are silent on mode of manufacture…

Laboratory determination of final specifications for release

21 CFR 211.165(a): For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product….. prior to release

Extended investigations of unexplained discrepancies

21 CFR 211.192: The investigation shall extend to other batches… that may have been associated with the specific failure of discrepancy.

Documentation of Manufacturing

21 CFR 211.188 Batch product and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch

Recall situation

21 CFR 211.150(b): Distribution procedures shall include… a system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary

Definition of a 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
(21 CFR 210.3)

Definition of a 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. (21 CFR 210.3)

Definition of Lagging Regulatory Modernization:

Current language in 21CFR 600.3(x) : *Lot means that quantity of uniform material identified by the manufacturer as having been thoroughly mixed in a single vessel.*

Twenty years ago ICH concurred…

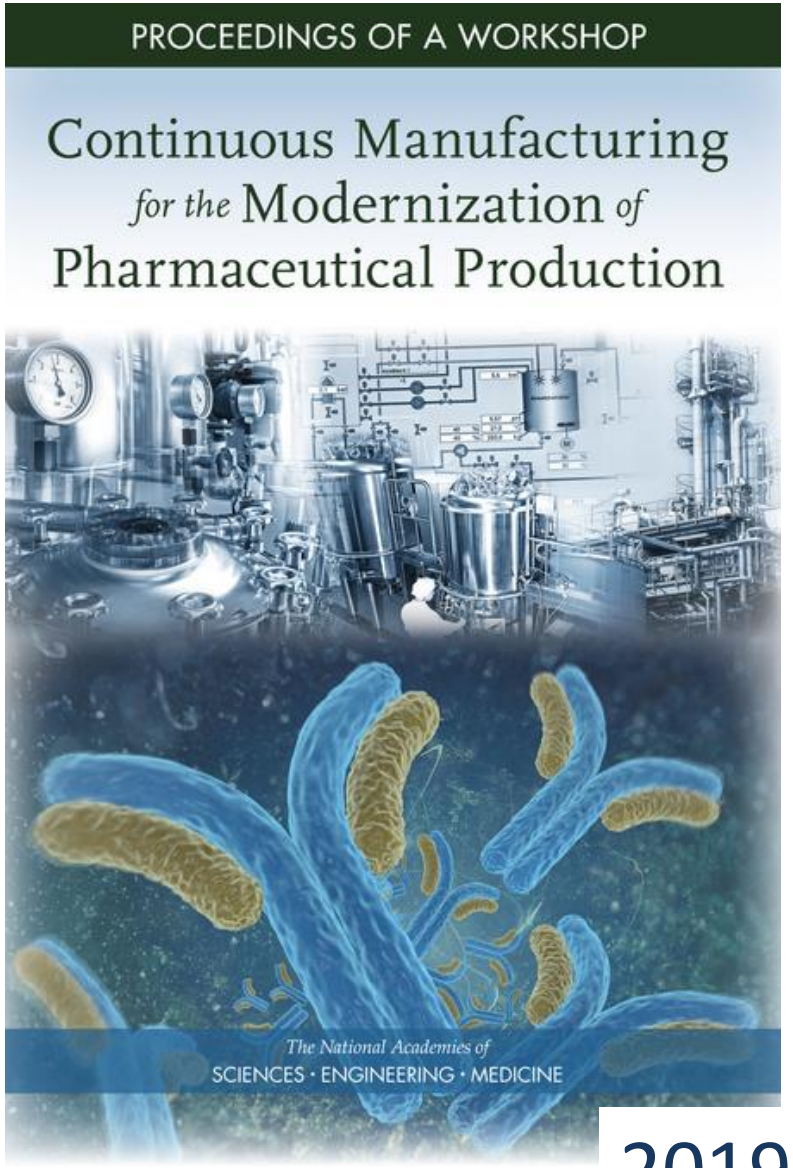
Batch (or Lot)

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. **(ICH Q7)**

"Jeffrey, always look before you sit. You might sit on nothin' or you might sit on a snake. You might sit on some bob-wire or you might sit on a cow flop. You might sit in some cactus and you might sit on your hat. Of all those possibilities only one will not have a very unfortunate result and fair amount of cleanup. Always look before you sit." --Marion "Choc" Wetzel

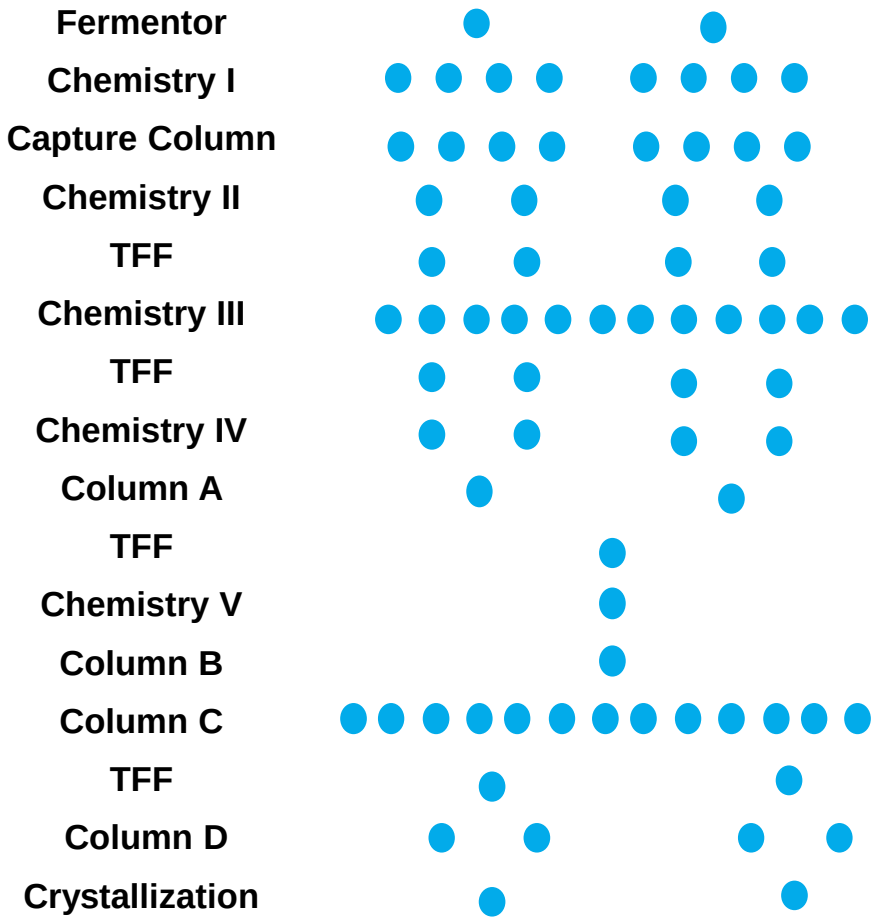


2019

In biotechnology continuous manufacture is evolution not revolution, less a question of "can we" than "should we".

- Induced bioreactors and perfusion bioreactors
- Continuous solid-liquid separations
- In line mixing of concentrated buffers or feeds
- PAT based feedback loops in the fermentor based upon biological parameters and off-gases
- Chromatography cutting, flow, and conductivity adjustments made based upon PAT
- Data historians directly linked to IO feeds and SPC packages.
- "Bleed and feed" TFF ops
- End point based lyophilization or crystal drying

Semi-continuous batch operations have long been used in biopharma manufacturing



This scheme shows a 24/7 plant running linked operation centers of varying throughputs and capacities with sophisticated monitoring and modeling. The plant had over 15,000 IO points, 7 control rooms, and archived 13,000 pieces of data per second to a data historian from the processing floor.

Intermediate and process attributes were managed within specified ranges by combinations of on-line, at-line, and off-line (process at risk) assays.

"Lots" and "Batches" were defined, forward processed, and dispositioned by the Quality Management System

CASSS Strategy Forum Knowledge Test: *This plant, that harvested a 40,000L fermenter approximately every 14 hours, was awarded "Automated Plant of the Year" by* Control Magazine *in what year?*

1995!

Figure is from "85 years of Large Scale Protein Purification: Insulin, Insulin Analogs and the Continuous Re-Invention of Biotechnology", University of Iowa Seminar, J.C. Baker 2008

DON'T BE NEGATIVE! BE HOPEFUL!

MAYBE THIS TIME THE FOCUS WILL BE ON UNMET NEEDS…

" Hope is the dream of the waking man."
-- Pliny the Elder

WHAT DO I NEED?

1. Affirmation

- Definitions of Lots and Batches in current practice: defined by the sponsor based upon uniformity of quality attributes.
- Commissioning and qualification as assurance of equipment's suitability for use at time of use, validation as assurances of assay and process capability, specifications as product attributes assuring suitability for use.

2. Clarification on Matters Unique to CM

- Dynamic Measures (cm/hr; liters/hr; dx/dt; d^2x/dt^2, P_x)
- Disposition of Process Transitions (leads, tails, starts/stops/slows)
- Representative sampling of process and data streams
- Conduct of maintenance

3. Commitment

- Commitment to Totality of the Evidence & Clinical Relevance as Decisional Principles
- Commitment to inspection as an extension of review
- Commitment to articulation of contemporary consensus (not aspirational or regional) practice

“Do not spoil what you have by desiring what you have not; remember that what you now have was once among the things you only hoped for." --- Epicurus

“The truth is that many people set rules to keep from making decisions.” --Mike Krzyzewski

Desperado, why don't you come to your senses?
You've been out ridin' fences for so long now
Oh, you're a hard one
I know that you got your reasons
These things that are pleasin' you
Can hurt you somehow

Don't you draw the queen of diamonds, boy
She'll beat you if she's able
You know the queen of hearts is always your best bet
Now it seems to me, some fine things
Have been laid upon your table
But you only want the ones that you can't get

Desperado, oh, you ain't gettin' no younger
Your pain and your hunger, they're drivin' you home
And freedom, oh freedom well, that's just some people talkin'
Your prison is walking through this world all alone

Don't your feet get cold in the winter time?
The sky won't snow and the sun won't shine
It's hard to tell the night time from the day
You're losin' all your highs and lows
Ain't it funny how the feeling goes away?

Desperado, why don't you come to your senses?
Come down from your fences, open the gate
It may be rainin', but there's a rainbow above you
You better let somebody love you before it's too late

-- Don Henley & Glenn Frey , 1972