Traceability in Continuous Manufacture

Lessons from 54 years of Continuous Manufacture of Avicel PH
Avicel® PH Grade Production

Process Summary

1. Reaction
2. Filtration
3. Drying
4. Packaging
Production & Process Control

Automated control system

- Honeywell TDC 30000 - highly automated control system
- Controlled to tight operating limits by TDC recipes
- Hydrolysis is batch operation
- Remainder of process is continuous
Spray Drying

Spray dryer process controls particle size, loss on drying & loose bulk density
Quality Control

Product Sampling & Testing

• In-line calibrated instrumentation monitors temperature, conductance, pH, etc.

• Microbiological monitoring of air, water and product

• In-process sampling & testing

• Packed product sampling & testing

<table>
<thead>
<tr>
<th>Test Parameter</th>
<th>Dryer In-process</th>
<th>Packed Product</th>
<th>Composite from Packed Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>*FMC + CoA</td>
<td>Samples every 2 hours</td>
<td>Samples every 2 tons &amp; testing frequency as per LIMS</td>
<td>Every batch tested – populates CoA</td>
</tr>
<tr>
<td>** Not on CoA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whiteness**</td>
<td>*</td>
<td>*</td>
<td>* Colour meter</td>
</tr>
<tr>
<td>Loss on Drying</td>
<td>*</td>
<td>*</td>
<td>* Oven</td>
</tr>
<tr>
<td>Loose Bulk Density*</td>
<td>*</td>
<td>*</td>
<td>* Scott</td>
</tr>
<tr>
<td>pH</td>
<td>*</td>
<td>*</td>
<td>* Meter</td>
</tr>
<tr>
<td>Conductance</td>
<td>*</td>
<td>*</td>
<td>* Meter</td>
</tr>
<tr>
<td>Particle Size Distribution*</td>
<td>*</td>
<td>*</td>
<td>* Malvern</td>
</tr>
<tr>
<td>Alpine Sieve Test*</td>
<td>*</td>
<td>*</td>
<td>* Sieve</td>
</tr>
<tr>
<td>Dark Speck Count*</td>
<td>*</td>
<td>*</td>
<td>* Visual</td>
</tr>
<tr>
<td>Lint Material**</td>
<td></td>
<td></td>
<td>* Visual</td>
</tr>
<tr>
<td>Degree of Polymerisation</td>
<td></td>
<td>*</td>
<td>* Viscometer</td>
</tr>
<tr>
<td>Yeast &amp; Mould</td>
<td></td>
<td></td>
<td>* Micro Lab</td>
</tr>
<tr>
<td>TPC</td>
<td></td>
<td></td>
<td>* Micro Lab</td>
</tr>
<tr>
<td>Pathogen</td>
<td></td>
<td></td>
<td>* Micro Lab</td>
</tr>
<tr>
<td>Heavy Metals</td>
<td></td>
<td></td>
<td>* Analytical Lab</td>
</tr>
<tr>
<td>Sulphated Ash</td>
<td></td>
<td></td>
<td>* Analytical Lab</td>
</tr>
<tr>
<td>Water Solubles</td>
<td></td>
<td></td>
<td>* Analytical Lab</td>
</tr>
<tr>
<td>Ether Solubles</td>
<td></td>
<td></td>
<td>* Analytical Lab</td>
</tr>
<tr>
<td>Identification</td>
<td></td>
<td></td>
<td>* Analytical Lab</td>
</tr>
<tr>
<td>Solubility</td>
<td></td>
<td></td>
<td>* Analytical Lab</td>
</tr>
<tr>
<td>Residue on Ignition</td>
<td></td>
<td></td>
<td>* Analytical Lab</td>
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</tbody>
</table>
Quality Control

Dryer In-Process Sampling and Testing

In-Process Sampling every 2 hours & testing for LOD/pH/Conductance/Speck count/APS

Target material
Pack-Out Silo

Out of specification material
Reprocess Silo

Screens & Magnet Banks

Pack-Out
Quality Control

Packed Product Sampling & Testing

Pack-out material sampled every approx. 2 TONS.

Chemical and Physical tests as per LIMS schedule.

Out of specification product is segregated electronically for disposition.

Full traceability and control by barcode scan.
Process capability

PH102NF Average Particle Size
Mean 108; Stdev 6.2; Cpk 1.23

Jan - Dec 2006

Cpk value indicates PH102 manufacturing process is well-controlled

Courtesy of FMC BioPolymer

Bruno C. Hancock

Quality Control

Composite Sampling & Testing for Certificate of Analysis

Full Compendial Analysis on every batch.
- Batch = pack-out of same grade in 1 week period.

Pathogen testing and Compendial Chemical test from composite of batch.

Out of specification product is segregated electronically for disposition.

Full traceability and control by barcode scan.
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
Avicel PH Lots

• Batch = $\sum$ orders vs Clean Down (weeks)
• Lot = Time period (days) or Packaging Run
• Each container serialized
Production & Process Control

Lot numbering and Labelling

**Batch 61545C**

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>6</td>
<td>Code for PH-101</td>
</tr>
<tr>
<td>15</td>
<td>Year 2015</td>
</tr>
<tr>
<td>45</td>
<td>Week 45 of calendar yr.</td>
</tr>
<tr>
<td>C</td>
<td>Cork</td>
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</table>

Batch includes all PH-101 packed out in week 45 of 2015 by FMC International Cork.
Sampling in Continuous Manufacturing

- Sample frequency capable of detecting process upsets
- Start-up frequency vs. steady state
Diversion of Non-Conforming Material

• The ability to isolate and reject material that is out of specification if the process is no longer in a state of control can be one of the key aspects of a continuous manufacturing control strategy
  - Planned process start-ups and shutdowns
  - Temporary process disturbances or upsets

• The evaluation of overall residence time distribution and the understanding of propagation of a disturbance between extraction points in the system are important to justify the amount of material at risk due to an unexpected even or disturbance

• Ideally, measurement (PAT) and material extraction points should be near where the event can occur, but downstream extraction is possible with understanding of process dynamics
High volume continuously manufactured excipient

What do Certificate of Analysis results mean?

The NIPTE-FDA Excipients Knowledge Base https://pharmahub.org/
In-process data behind CofA

2500 x 50kg drums = 125000kg

The NIPTE-FDA Excipients Knowledge Base https://pharmahub.org/
The risk of averages

Average depth of river is 3 feet.

From John Peterson, 2012

The Flaw of Averages: Why We Underestimate Risk in the Face of Uncertainty by Dr. Sam Savage
Traceability essential for Continuous Manufacturing

The ability to isolate material that is out of specification

The ability to provide relevant in-process data where variance in an excipient attribute is critical to finished product performance.