A Graded or Risk Based Approach to cGMP Compliance for API Manufacturing

Paul A. Steiner

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Elements of cGMP

- Adequate documentation / records
- Environmental monitoring
- Equipment qualification / calibration
- Facility design/operations compatible
- Personnel training / certification
- Production and process controls
- Quality control
- Quality Assurance / change control
- Validation
What is an Active Pharmaceutical Ingredient?

- The *intended use* clause:
  
  “Any substance or mixture of substances intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient of the drug product.”

* ref. ICH Q7A
What is an Active Pharmaceutical Ingredient?

- The *pharmacological activity* clause:
  
  “Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.”*

* ref. ICH Q7A
Regulatory Status of APIs in the US

- Definition of a “Drug” in the FD&C Act encompasses APIs

- Section 501(A)(2)(b) of the Act requires that all drugs be manufactured, processed, packed, and held in accordance with cGMPs

- No distinction is made between APIs and finished pharmaceuticals in the Act
API’s Regulatory Status

- FD&C Act – 21 CFR 210 & 211 apply to drugs and finished pharmaceuticals
- No “specific” GMP Regulation
- Drug cGMP regulations can be used as a general guide for API processing
- FD&C Act requires compliance with cGMPs without benefit of a regulation specific to APIs
Status of Q7A with Respect to other Documents

Q7A is the definitive GMP guidance for APIs!
What is ICH?

- Established in 1990 between EU, US and Japan
- Committed to reducing duplication during R&D for new drugs while safeguarding quality, safety, and efficacy
- Developed over 40 guidance documents mostly addressing technical (quality, safety, efficacy, etc.), clinical, and regulatory requirements for new human drug products
Caution! Status of Q7A with Respect to FDA

- “The Commissioner maintains that these regulations can serve as useful guidelines in the manufacture of chemicals. The agency plans to develop specific regulations on production of bulk drugs (APIs).”*

* Ref: Response to comment in the Preamble to the Sept. 29, 1978 revisions to cGMP Regulations

- Q7A: It is not yet codified! It’s not a regulation!
  - It’s not the law!

- Never reference sections of Q7A in response to FDA observations
Importance of Q7A: Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients

- First internationally harmonized tripartite GMP guidance developed jointly by industry and regulators under ICH
- Establishes one global GMP standard for APIs
- Intended to facilitate API inspection
- Impacts any manufacturer that markets APIs in ICH regions
- Addresses the uniqueness of API processes
“This guidance represents the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.”*

*FDA preamble to Q7A
Process Characteristics: API vs. Drug Product

- **API**
  - Chemical & Biological Processing
    - (synthesis, fermentation, extraction, purification)

- **Drug Product**
  - Physical Processing
    - (granulating, dissolving, mixing, compressing)

Different Facilities, Equipment and Processes
Characteristics of API Processes

- APIs produced by chemical or enzymatic reactions, recombinant DNA, fermentation, recovery of natural materials, or a combination of these processes

- Usually involves synthesis, extraction, or crystallization resulting in significant changes to starting materials/intermediates

- Typically includes purification steps
Uniqueness of API Processes Accounts for Differences in:

- Process water quality
- Blending of Intermediates and APIs
- In process controls
- Process validation
- Reprocessing/Reworks
- Recovery of materials and solvents
Section 1.1: Meaning of “Should”

FDA Version:

“In this guide the term *should* identifies recommendations that, when followed, will ensure compliance with cGMPs.

An alternative approach may be used if such approach satisfies the requirements of the applicable statutes.”

* ref. ICH Q7A
## Application of Q7A to Manufacturing

### Process Steps (Shown in Grey)

<table>
<thead>
<tr>
<th>Manufacturing</th>
<th>Production of the API starting material</th>
<th>Introduction of the API starting material into process</th>
<th>Production of Intermediate(s)</th>
<th>Isolation and purification</th>
<th>Physical processing, and packaging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical Manufacturing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>API derived from animal sources</td>
<td>Collection of organ, fluid, or tissue</td>
<td>Cutting, mixing, and/or initial processing</td>
<td>Introduction of the API starting material into process</td>
<td>Isolation and purification</td>
<td>Physical processing, and packaging</td>
</tr>
<tr>
<td>API extracted from plant sources</td>
<td>Collection of plant</td>
<td>Cutting and initial extraction(s)</td>
<td>Introduction of the API starting material into process</td>
<td>Isolation and purification</td>
<td>Physical processing, and packaging</td>
</tr>
<tr>
<td>Herbal extracts used as API</td>
<td>Collection of plants</td>
<td>Cutting and initial extraction</td>
<td></td>
<td>Further extraction</td>
<td>Physical processing, and packaging</td>
</tr>
<tr>
<td>API consisting of comminuted or powdered herbs</td>
<td>Collection of plants and/or cultivation and harvesting</td>
<td>Cutting/comminuting</td>
<td></td>
<td></td>
<td>Physical processing, and packaging</td>
</tr>
<tr>
<td>Biotechnology: fermentation/cell culture</td>
<td>Establishment of master cell bank &amp; working cell bank</td>
<td>Maintenance of working cell bank</td>
<td>Cell culture and/or fermentation</td>
<td>Isolation and purification</td>
<td>Physical processing, and packaging</td>
</tr>
<tr>
<td>&quot;Classical&quot; Fermentation to produce an API</td>
<td>Establishment of cell bank</td>
<td>Maintenance of the cell bank</td>
<td>Introduction of the cells into fermentation</td>
<td>Isolation and purification</td>
<td>Physical processing, and packaging</td>
</tr>
</tbody>
</table>

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**Increasing GMP Expectations**
Applying Q7A

Chemical Manufacturing

Outside Scope

Covered by Q7A

Production of API Starting Material

Introduction of API Starting Material → Production of Intermediates → Isolation & Purification → Physical Processing & Packaging

Increasing GMP Expectations
Where Does API Production Begin?

“The company *should* designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which “API starting materials” are entered into the process.”*

* ref. ICH Q7A
“From this point on, appropriate GMPs, as defined in the guidance, should be applied to these intermediate and/or API manufacturing steps.”*
Definition: API Starting Material

“Material used in production of an API that is incorporated as a *significant structural fragment into the structure of the API*”

“May be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or may be produced in-house”

“Normally of defined chemical properties and/or structure”

* ref. ICH Q7A
Companies should designate/document rationale for point at which production of API begins: For synthetic processes, this is known as point at which starting materials are entered into process.

For other processes this rationale should be established on a case-by-case basis.

Raw Material: Any ingredient intended for use in the production of API’s. These include starting materials, intermediates, process aids, and solvents.
Spectrum of cGMP Controls in API Manufacturing

Controls increase as process proceeds to final isolation and purification steps.

- Apply GMP control beginning with the use of API starting materials.
- Degree of control depends on process and manufacturing stage.
Section 8.3: In-Process Sampling & Controls

- Type/extent of testing and acceptance criteria depends on:
  - Nature of intermediate or API
  - Reaction or process step
  - Degree of variability introduced by process
Section 8.3: In-Process Sampling & Controls

- Less stringent in-process controls may be appropriate in early processing steps.
- Tighter controls may be appropriate for later processing steps.
- Out of specification (OOS) investigations are not normally needed for in-process tests performed for the purpose of monitoring and/or adjusting the process.
## Process Water Quality

### Drug Products

- Potable water not acceptable for preparation of USP dosage forms
- Purified water generally used for non-sterile dosage production

### APIs

- Potable water acceptable for preparation of USP drug substances
- Purified water often used in later isolation and purification steps
Section 4.3: Process Water Quality

- “Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use”

- “Unless otherwise justified, water should at a minimum, meet WHO guidelines for potable water”

- If tighter chemical and/or microbiological specifications are necessary, these should be established

* ref. ICH Q7A
Water used in final isolation and purification steps of a non-sterile API intended for producing a sterile drug product should be monitored and controlled for:

- Total microbial counts
- Objectionable organisms
- Endotoxins
## Process Validation: Dosage Forms vs. APIs

<table>
<thead>
<tr>
<th>Drug Products</th>
<th>APIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validate cleaning procedures and significant mfg. steps, such as amount of water in granulation, spray rate, mixing/blending time, fill accuracy, and labeling</td>
<td>Validate critical processing steps determined to impact the quality and purity of the API</td>
</tr>
</tbody>
</table>
Definition of Critical

“A process step, process condition, test requirement, or any other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.”

* ref. ICH Q7A
Section 19.6: Validation of APIs Used in Clinical Trials

- Process validation normally inappropriate (*Phase I & II*) because:
  - Process changes during API development
  - Production of a single or limited number of API batches

- Clinical APIs should be manufactured in *qualified* facilities using appropriate production and control procedures to ensure safety, quality, and homogeneity of the API
## Reprocessing & Reworking

<table>
<thead>
<tr>
<th>Drug Products</th>
<th>APIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vague distinction</td>
<td>Clear distinction between activities</td>
</tr>
<tr>
<td>between activities</td>
<td>activities</td>
</tr>
<tr>
<td>Reprocessing is atypical</td>
<td>Reprocessing is typical</td>
</tr>
<tr>
<td>Reprocessing rarely improves drug quality</td>
<td>Reprocessing generally improves API quality</td>
</tr>
</tbody>
</table>
Definition of Reprocessing

“Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps that are part of the established manufacturing process.”

* ref. ICH Q7A
Definition of Reworking

“Subjecting an intermediate or API *that does not conform to standards or specifications* to one or more processing steps that are *different from the established manufacturing process* to obtain acceptable quality material.”

* ref. ICH Q7A
# Reprocessing vs. Reworking

<table>
<thead>
<tr>
<th>Reprocessing</th>
<th>Reworking</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intermediates and APIs</strong></td>
<td><strong>Intermediates and APIs</strong></td>
</tr>
<tr>
<td>Conforming or non-conforming batches</td>
<td>Only non-conforming batches</td>
</tr>
<tr>
<td>Subject batch to one or more steps that are part of established process</td>
<td>Subject batch to one or more steps different from established process</td>
</tr>
</tbody>
</table>
ICH Q7A Summary

- Pragmatic balance of “What” vs. “How”
- Clarifies cGMP expectations
- Not intended to ratchet up cGMPs
- Should provide enough guidance to address cGMP problems in API production
Think ICH Q7A!

Please wear your API hat!