cGMPs for Active Pharmaceutical Ingredient (API) and Excipient Production

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For many years the only Food and Drug Administration (FDA) document specifically related to current good manufacturing practice (cGMP) requirements for active pharmaceutical ingredient (API) manufacturers was a guidance for FDA investigators that covered all Bulk Pharmaceutical Chemicals (BPCs). Over the past few years, two iterations of a DRAFT guidance for industry specifically addressing API manufacture were published. On September 25, 2001, the lack of specific, official cGMP guidance for API manufacturers came to an end when “FDA's Guidance for Industry: Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (“Q7A”)”, was formally made available by FDA [1]. This contemporary statement of cGMP obligations not only directly speaks to manufacturers of APIs, but also provides excipient producers with an alternative compliance paradigm to that offered by the cGMP regulations for finished pharmaceuticals at 21 C.F.R. Parts 210 and 211. In addition, Q7A serves as a reference point for drug product manufacturers who conduct audits of their API suppliers. Therefore, understanding the provisions of Q7A is essential to any drug substance manufacturer who wishes to adequately address customer assurance and regulatory compliance expectations. The clear intent of the guidance is to recognize the uniqueness of API manufacturing processes as distinguished from manufacture of finished drug products and to provide recommendations that reach all aspects of API production operations.

Q7A does not apply, however, to manufacturing steps that precede the introduction of the API starting material into the production process [3]. Therefore, the guidance does not contain recommendations concerning the production of API starting materials, and the collection, cutting, mixing, initial processing or extraction of biological material (i.e., for APIs derived from plant or animal sources). According to the guidance, a company should specifically designate the point at which API manufacturing begins and document the rationale behind that designation [4]. Further, Q7A does not cover sterilization and aseptic processing of sterile APIs, vaccines, whole cells, whole blood and plasma (and their derivatives), gene therapy APIs, medical gases, bulk packaged drug products, radiopharmaceuticals, or veterinary drug products. Registration and filing requirements for APIs also are not addressed in the guidance.

Scope of the Q7A Guidance

The final Q7A guidance, developed with the support of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, reflects FDA's strong interest in ensuring the quality and safety of finished pharmaceuticals through cGMP compliance by API manufacturers [2]. In Q7A, FDA outlines requirements for quality review programs, personnel, manufacturing facilities and equipment, record keeping, material storage and sampling, process and laboratory controls, validation, packaging and labeling, and warehousing and distribution procedures. The guidance also includes requirements for APIs intended for use in clinical trials, and those manufactured by cell culture/fermentation processes.

Specific Q7A Provisions

As mentioned above, there are many aspects of cGMP compliance covered in the Q7A guidance. For purposes of economy, we are not highlighting aspects of those provisions that may hinge on particular contractual relationships, or that cover only a narrow class of substances. Therefore, in this article, Q7A recommendations relating to company agents such as contract manufacturers and distributors (Sections 16 and 17) are not discussed, although suffice it to say, these parties are generally expected to conform to the requirements...
applicable to the original API manufacturer. Similarly, the Q7A recommendations for APIs manufactured by cell culture and fermentation (Section 18), and for APIs used in clinical trials (Section 19) also are not addressed in this article. FDA has identified special controls for these circumstances.

**Quality Management (Section 2)**

In Q7A, FDA encourages the establishment of a quality management system with designated quality assurance and quality control responsibilities. While the exact form of the quality units will depend on the size and structure of the company, their functions must be maintained independently from production operations. For a very small manufacturer, for example, it may be reasonable that a quality unit may be composed of only one individual. The quality units are the final authority for approving all written quality assurance procedures. That said, it may not be necessary for the quality units to be the clearinghouse for all housekeeping and maintenance documents relating to manufacture of the API, provided the tasks at issue are ministerial in nature (e.g., how to re-fill fluids in a piece of equipment). It is up to the company to use its judgment in these matters. The guidance also defines those responsibilities that can be delegated by the quality units, and those that cannot. Regularly scheduled internal audits and product reviews are recommended to verify process consistency and the effectiveness of quality controls, and all processes and process deviations should be properly documented.

**Personnel, Facilities, and Equipment (Sections 3, 4, and 5)**

These provisions in Q7A focus on appropriately qualifying the personnel, building facilities, and equipment that are associated with the manufacturing processes for APIs and their intermediate substances. For example, there are specific recommendations for process water quality. Generally, water used in API manufacturing must be suitable for its intended use. As a baseline this means potable (drinking) water, although the use of purified water may be required to achieve certain chemical or microbiological specifications.

**Documentation and Records (Section 6)**

Section 6 of Q7A outlines the expectations for establishing a documentation system for records relating to API manufacturing. Such records may be in paper or electronic form, and FDA recommends that certain types of records (e.g., records for APIs with retest dates) be maintained for minimum periods of time. The documentation provisions of the guidance are intended to ensure that manufacturing records are reliable, properly maintained, and in the case of electronic signatures, authenticated. These are the same endpoints that are accomplished by FDA’s very detailed electronic record and electronic signature requirements at 21 C.F.R. Part 11 that are mandatory for finished dosage form manufacturers and other. The extent to which elements of the Part 11 requirements will come to be seen as essential to meet the reliability and authentication requirements of Q7A is yet to be determined.

**Materials Management (Section 7)**

This section of the guidance concerns the maintenance of written intake, handling, testing, sampling, quarantine, and acceptance and rejection procedures for API materials. Special systems are expected to be in place for “critical materials.” The term “critical” is defined in the glossary at the end of the guidance document to mean “a process, step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.” (Section 20). It is conceivable that ‘critical’ parameters can change over time with increased knowledge about manufacturing processes. Therefore, manufacturers should have procedures in place to routinely review and update the list of critical parameters.

**Production and In-Process Controls (Section 8)**

As with other facets of cGMP compliance, production and in-process controls (including deviations) should be appropriately documented and approved by the quality units. The guidance acknowledges that less stringent in-process controls may be appropriate in early processing stages, but that such controls may need to be tightened subsequently, such as for isolation and purification steps. The company is given deference in determining the type of acceptance criteria and testing that a particular substance or process might require. In-process control test procedures must be validated in accordance with the principles set forth in Section 12.

This section also outlines permissible blending processes, which are intended to ensure the quality of substances used in the blend. The perspective taken in this guidance is different than that applied to blending operations for finished drug products, where the focus is on uniformity rather than quality.

**Packaging, Labeling, Storage, and Distribution (Sections 9 and 10)**

The Q7A document advises that packaging and labeling materials should conform to established specifications that ensure their suitability for holding APIs and their intermediates. Procedures used in these operations should be designed to prevent labeling errors. The guidance also recommends that API containers transported outside of the manufacturers control should be sealed in a tamper-resistant manner. This particular cGMP is increasingly important in light of FDA’s recent focus on counter-bioterrorism initiatives for regulated products [5].

**Laboratory Controls, Validation, Change Control, and Reprocessing (Sections 11, 12, 13, and 14)**

Laboratory controls, which should be documented at the time of performance, require the establishment of specifications for APIs and investigation of out-of-specification results. Analytical testing to determine conformance to specifications, stability characteristics, or microbiological quality should be validated according to a written protocol and pursuant to an established company validation policy. Unlike
the case for finished pharmaceuticals, where all manufacturing steps need to be validated, only critical steps in API manufacturing must be validated [6]. Included in the validation recommendations are GMP-related computerized systems (Section 5.4). These provisions indicate that the extent of the validation should correspond to the significance of the computerized application to the manufacturing process, and its complexity.

Quality units should review any changes relevant to GMPs and their impact on the quality of the API or intermediate, pursuant to written procedures. Change controls should be in place for both critical and non-critical raw material changes. If process changes will affect the quality of the finished API, drug product customers should be informed before the change is made.

APIs or intermediates that do not conform to established specifications may be re-introduced into the established manufacturing process and subject to a repeated processing step. FDA acknowledges in the guidance that unlike in finished drug manufacturing operations, reprocessing often improves API quality. However, should the need for reprocessing occur for a majority of product batches, then it will need to be integrated into the standard manufacturing process. Choosing to rework non-conforming batches with different manufacturing processes should be done only after investigation into the reason for non-conformance. Reworked batches should be evaluated for quality; concurrent validation is appropriate.

**Complaints and Recalls (Section 15)**

Quality-related complaints should be handled and recorded through a documented procedure. Complaint records should be reviewed so that trend data can inform the need for process improvements. Recall procedures should be established so that recipients of defective product can be identified. Rapid notification to customers of product defects may permit a quarantine to be instituted before the API is formulated into a high value finished drug product. The adoption of a recall procedure is further indicated to thwart bioterrorism risks.

**Implementing Q7A Guidance**

Q7A is considered the definitive guidance for API cGMPs. The expectation, therefore, is that the consolidation of all API guidance into this document will improve industry compliance. In fact, the introductory “Objective” section of the Q7A guidance (Section 1.1) uses the term “should” to identify “recommendations that, when followed, will ensure compliance with cGMPs.” Importantly, the recommendations in the Q7A document are not mandatory. If a recommendation in Q7A is inappropriate, or sound scientific data document that alternative measures provide an equivalent level of quality assurance, no violation of cGMP arises [7].

**Recent Developments in Enforcement of cGMPs for APIs**

As stated in its August 21, 2002 announcement, FDA has launched its new program to improve cGMPs relating to the manufacture of human and veterinary drugs, including biologics. Through the “Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach” initiative, FDA intends to (1) focus regulatory resources on those parts of the manufacturing process that pose the greatest risks; (2) ensure that its program does not restrict the development of new pharmaceutical manufacturing methods and technologies; and (3) unify the approach to quality control and safety among the Agency’s centers and field operations [8]. Toward this end, the Agency has indicated it will merge cGMP oversight responsibilities at the Center level, removing some of the autonomy that has been present in the field offices in recent years. That said, FDA does intend to focus improvement efforts on field inspectional activities, including the possibility of developing a cadre of specialized inspectional personnel for pharmaceutical products. Therefore, while all the Centers will be the final arbiters on technical and scientific issues, the field offices will remain on the front lines.

From a global perspective, the Q7A document reflects the intent of the ICH regions to foster mutual recognition of cGMPs in API production. Q7A has been formally adopted in several countries (e.g., Australia, Japan, the European Union) and has provoked interest on the part of other international regulatory bodies to inspect API manufacturers and enforce cGMPs. In fact, the World Health Organization is currently evaluating Q7A for possible adoption as an international standard.

**Conclusion**

In conclusion, the recommendations in Q7A serve to clarify, for both drug ingredient manufacturers, its pharmaceutical industry customers and Agency personnel, FDA’s expectations with regard to cGMPs for APIs. The intent behind Q7A, therefore, is not to necessarily heighten quality assurance requirements, but rather to more specifically define those quality control measures that will ensure a company is properly manufacturing APIs. Q7A will likely become the touchstone for harmonizing international quality assurance regulation of drug substances even beyond the countries that participated in the ICH process.

**Footnotes**

2. An API is defined in Q7A as, “any substance of mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. 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.” (Section 20).
3. Starting materials are defined in Q7A as “a raw material, an intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API.” (Section 1.3). This is a less restrictive definition than FDA has applied in the past; commercial availability of the substance is no longer an element of the definition. Unlike an API starting material, API intermediates are covered by Q7A. Intermediates are defined in the guidance as “material produced during the steps of processing an API that undergoes further molecular change or purification before it becomes an API.” (Section 20).

4. If a manufacturing procedure has been incorporated into an FDA approval of a new drug, typically by reference to a Drug Master File established by the API manufacturer, a change to take advantage of the flexibility allowed by Q7A in designation a starting material will typically require coordination with the holder of the approval; prior approval of a supplemental application may be required.

5. See e.g., Guidance for Industry - Food Producers, Processors, Transporters, and Retailers: Food Security Preventive Measures Guidance (January 2002) (identifying preventive measures that food producing establishments can take to reduce the risk that food under their control will be subject to tampering or criminal or terrorist actions).

6. Specifically, Section 12.2 states that, “Validation should extend to those operations determined to be critical to the quality and purity of the API.”


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