Align and Understand FDA’s GMPs and ICH Q10 Pharmaceutical Quality System Guidance

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Agenda

- Status of guidelines versus regulations in US GMP
- Origin and purpose of ICH Q10
- Overview of Q10 concepts and how they align to GMP requirements (using selected key areas of Q10)
- Keys to successful implementation of Q10 in your organization
- Enforcement implications during FDA inspections
Hierarchy of Regulatory Documents

- **Federal Laws**
  - Passed by Congress, signed by the President; compliance mandatory

- **FDA Regulations**
  - Written by the FDA, finalized after public comment; most have the force and effect of law

- **FDA and Industry Guidelines**
  - Written or adopted by the FDA; advisory, not mandatory, but most follow closely
Guidance for Industry
Q10 Pharmaceutical Quality System

Additional copies are available from:
Office of Communication Division of Drug Information Center for Drug Evaluation and Research Food and Drug Administration 10903 New Hampshire Ave., Bldg. 51, Room 2201 Silver Spring, MD 20993-0002 (Tel) 301-796-3400
http://www.fda.gov/cder/guidance/index.htm


U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER)
April 2009 ICH

Advisory – “Represents current thinking”
The GMP Regulations

- 21 CFR 210/211
- Legally binding for finished pharmaceuticals, including clinical trial materials
- No binding regulation for Active Pharmaceutical Ingredients
  - ICH Guideline Q7 provides additional detailed guidance for APIs
- GMP regulations are broadly worded; context-specific interpretation is necessary to maintain a state of compliance
International Conference on Harmonization (ICH)

- Core members are the US, the EU and Japan
- Other interested parties who participate include Canada, Australia and others
- Industry members also participate
- Guidelines are issued in many areas; the “Q” guidelines are the key ones for GMP, among them:
  - Q7 – API GMP
  - Q8 (and annex) – Pharmaceutical Development (aka “Quality by Design”)
  - Q9 – Risk Management
  - Q10 – Pharmaceutical Quality System
  - Several others in the Q series also
Purpose of Q10

“This internationally harmonized guidance is intended to assist pharmaceutical manufacturers by describing a model for an effective quality management system for the pharmaceutical industry, referred to as the pharmaceutical quality system. Throughout this guidance, the term pharmaceutical quality system refers to the ICH Q10 model.”

- Recommended for adoption in June, 2008
- Converted to a final Guideline by FDA in April, 2009
- As a Guideline, its status is advisory, not mandatory, but the industry should take it seriously and follow it to the extent feasible
- Application of Q10 will differ between companies based on a variety of variables, size, nature of operations, diversity of product line, etc.
Key Elements of Q10

- Q10 is based on a set of *stated Objectives*, supported by specified *Enablers* which support *continual improvement* of product quality and the Quality System itself.
- It relies heavily on the concept of *Management Responsibility* for the Quality System.
- It advocates quality planning, scheduled periodic management review of the quality system, and the creation of a unifying Quality Manual to serve as the fundamental governing document for the Quality System.
- This approach mirrors FDA’s Quality System Regulation (21 CFR Part 820), the “GMP” for the medical device industry much more closely than it does the pharmaceutical GMP.
- The approach is very consistent with basic ISO principles (by design and intent).
The Three Q10 Objectives

“Achieve Product Realization”
- “To establish, implement and maintain a system that allows the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with approved regulatory filings) and other internal and external customers.”

“Establish and Maintain a State of Control”
- “To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes. Quality risk management can be useful in identifying the monitoring and control systems.”

“Facilitate Continual Improvement”
- “To identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfil quality needs consistently. Quality risk management can be useful for identifying and prioritizing areas for continual improvement.”
The Two “Enablers”

Knowledge Management

“Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation. …Knowledge management is a systematic approach to acquiring, analyzing, storing and disseminating information related to products, manufacturing processes and components. Sources of knowledge include, but are not limited to prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and change management activities.”

Quality Risk Management

“Quality risk management is integral to an effective pharmaceutical quality system. It can provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality. It facilitates continual improvement of process performance and product quality throughout the product lifecycle. ICH Q9 provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality.”
The Quality Manual – Purpose and Elements

“A Quality Manual or equivalent documentation approach should be established and should contain the description of the pharmaceutical quality system. The description should include:

(a) The quality policy;
(b) The scope of the pharmaceutical quality system;
(c) Identification of the pharmaceutical quality system processes, as well as their sequences, linkages and interdependencies. Process maps and flow charts can be useful tools to facilitate depicting pharmaceutical quality system processes in a visual manner;
(d) Management responsibilities within the pharmaceutical quality system”
Alignment of these Elements to GMP

- So far, ICH Q10 is completely in line with the stated objectives of the GMP regulations.
- Q10 simply prescribes a particular approach and pathway to achieve GMP compliance and objectives, while the regulation is not prescriptive on the means as much as the ends.
- The GMP regulations self-define that they are a minimum standard*; ICH Q10 reaches higher than that standard, but certainly includes everything in it.

* 21 CFR 211.1(a): “The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products (excluding positron emission tomography drugs) for administration to humans or animals.”
Management Responsibility

- ICH Q10 states “Senior management has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the quality objectives, and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the company.”

- Two major Supreme Court cases in the US* establish that the so-called “doctrine of strict liability” applies to the Federal Food, Drug and Cosmetic Act. This is otherwise known as the “Responsible Corporate Officer” doctrine, or simply the Park doctrine (named for one of the two precedent setting cases)

- This doctrine holds those who “stand in a responsible relationship” to the acts of a company can be held personally criminally liable for those acts, even if they knew nothing about them and did not intend for them to occur.

- Following ICH Q10 management practices is consistent with the intent of the Supreme Court rulings. Applying these principles helps protect the company and executive managers from potential legal exposure under this doctrine.

*U.S. v. Dotterweich (1943) and U.S. v. Park (1975)
Management Responsibility

ICH Q10 establishes that Management should:

(1) Participate in the design, implementation, monitoring and maintenance of an effective pharmaceutical quality system;

(2) Demonstrate strong and visible support for the pharmaceutical quality system and ensure its implementation throughout their organization;

(3) Ensure a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management;

(4) Define individual and collective roles, responsibilities, authorities and inter-relationships of all organizational units related to the pharmaceutical quality system. Ensure these interactions are communicated and understood at all levels of the organization. An independent quality unit/structure with authority to fulfil certain pharmaceutical quality system responsibilities is required by regional regulations;

(continued…)
Management Responsibility

(5) Conduct management reviews of process performance and product quality and of the pharmaceutical quality system;

(6) Advocate continual improvement;

(7) Commit appropriate resources.

Alignment to GMP:

- The first three activities align to the expectation established under strict liability doctrine
- The fourth is aligns to 21 CFR 211.22 (Responsibilities of the Quality Unit) and other sections, in particular 211.28 and 211.100
- The fifth and sixth are also supportive of meeting strict liability expectations
- The seventh aligns to the GMP requirement for an adequate number of appropriately trained personnel to conduct GMP governed activities [21 CFR 211.25(c)]
Quality Policy

- Q10 recommends the establishment of a quality policy; specifically:

  Quality Policy

(a) Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality.

(b) The quality policy should include an expectation to comply with applicable regulatory requirements and should facilitate continual improvement of the pharmaceutical quality system.

(c) The quality policy should be communicated to and understood by personnel at all levels in the company.

(d) The quality policy should be reviewed periodically for continuing effectiveness

Alignment to GMP: While not a literal requirement, this approach is very consistent with the overall intent of GMP and also consistent with prevailing industry practice in most parts of the industrialized world
Quality Planning

Quality Planning

(a) Senior management should ensure the quality objectives needed to implement the quality policy are defined and communicated.
(b) Quality objectives should be supported by all relevant levels of the company.
(c) Quality objectives should align with the company’s strategies and be consistent with the quality policy.
(d) Management should provide the appropriate resources and training to achieve the quality objectives.
(e) Performance indicators that measure progress against quality objectives should be established, monitored, communicated regularly and acted upon as appropriate …

Alignment to GMP: Not required, but a prudent approach that ensures consistency and management oversight. FDA is currently driving significant efforts to mandate the submission of specified quality metrics under new authority resulting from the FDASIA amendments to the FDCA, passed in July of 2012.
Management Review

- Senior management should be responsible for pharmaceutical quality system governance through management review to ensure its continuing suitability and effectiveness.

- Management should assess the conclusions of periodic reviews of process performance and product quality and of the pharmaceutical quality system...

Alignment to GMP: Required under the medical device QSR but not the pharmaceutical GMP. Consistent with ISO management principles and currently widely adopted in the pharmaceutical industry
Management of Outsourced Operations and Purchased Materials

- See Section 2.7 of Q10 for specifics, it is fairly detailed

**Alignment to GMP:** Very consistent with the intent of a major change in the wording of the GMP section of the FDCA which happened with the passage of the FDASIA amendments in July of 2012; under this change, the wording of Section 501(a)(2)(B) of the FDCA, the GMP requirement, was modified by adding the following flush text to the end of the section:

  "For purposes of paragraph (a)(2)(B), the term 'current good manufacturing practice' includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products."

To date, FDA has not amended the GMP regulations to implement this change, but they have issued a Guideline on Quality Agreements, and further guidance or change to the GMP is expected in the future. Implementation of the controls outlined in Q10 is the best guidance we have currently to ensure compliance with the wording of this part of the FDCA.
Other Parts of Q10

- In the interest of time, you are referred to the Guideline for details of how it addresses other topics, importantly:
  - Management of Change in Product Ownership
  - Continual Improvement Of Process Performance And Product Quality
  - CAPA
  - Change Management
  - Lifecycle Management
  - Continuous Improvement of the Quality System

Each of these areas either aligns directly with existing GMP requirements or is supportive of their intent.

The bottom line is Q10 is a modern, well crafted approach to GMP compliance which is above the “minimum standard” GMP states it embodies, but which is both prudent and widely prevalent in the industry today.
Key Challenges in Q10 Implementation

- Management support is the most important factor since it is the major driving force behind Q10.

- Senior management must be persuaded of the value of adoption of this approach.

- It is suggested that it be presented as simply a proven, effective system to manage a critical aspect of the company’s business, like other areas already under executive managerial oversight (e.g., financial management, strategic planning, succession planning, organizational development and other areas; we are just adding quality and compliance to that list since they impact business success).

- Management review may be hard to “sell” to the leadership team. It must be sold as a good business practice, not a regulatory mandate.
Process for management review

- **SOP-driven**

- Establish agenda; include only items that require the attention of the participants; avoid inclusion of inconsequential information that does not require the attention or action of the management review team

- Review minutes and action items from prior meeting; hold action item owners responsible and accountable for completion of tasks assigned, and for verification of the effectiveness of steps taken

- Consider any roadblocks that have developed that impede progress; determine cause (priorities, resources, lack of clear communication, etc.) and plan steps to overcome roadblocks

- Reach formal conclusion as to whether or not the Quality Management System is functioning as determined; document the conclusion and rationale in the meeting minutes
Process for management review (continued)

- Assign action items and owners
- Prepare minutes of meeting in draft form, circulate to participants for edits or agreement, finalize minutes for review at next meeting
Management Review: Pitfalls to avoid

- True decision makers not present or not supportive of the meeting
- Lack of clear purpose for the meeting
- Lack of understanding of each participant as to why he/she is there and what is expected of him/her
- Lengthy, complicated presentations (keep presentations short and crisp; have background data available if participants want to hear it; consider making pre-reads available as opposed to taking up meeting time; consider a consolidated “dashboard” slide for QS status reporting)
- Failure to assign action items and require accountability for progress from action item owners
- Failure to document the discussion and decisions made
- Failure to accomplish the primary purpose, to determine if the Quality System is performing as required
Best practices for effective management review - summary

- Clearly stated purpose of review, understood and agreed to by all
- Frequent enough to catch issues before they become crises
- Metrics that matter, annual “rolling” trends for comparison of progress over time
- Efficient process, SOP-driven
- Right attendees present (decision makers)
- Focus on policy/priority setting, overcoming roadblocks to success, resource allocation, messaging, task delegation, and accountability for progress against plan
- Documented discussion and final conclusion
Concluding Thoughts – Enforcement Implications of Q10

- As a Guideline, FDA Investigators cannot cite the failure to implement Q10 itself on a 483.

- However, as we have seen, there are many places where Q10 aligns directly to a GMP requirement, and failure to comply with those can and will be cited on a 483.

- During an inspection, the lack of adherence to the principles established in Q10 (rather than the Guideline itself) may be seen by an Investigator as a predictor that the Quality System will not be under good control, and may therefore prompt closer scrutiny than would otherwise occur.

- Implementation of the management controls aspects demonstrates diligence on the part of the leadership team to prevent, detect and correct issues and mitigates the impact of strict liability doctrine under the FDCA.

- Companies are urged to use Q10 to its fullest advantage in management of quality and continuous improvement.