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COMPLIANCE REPORT

Your Guide to Recent Recommendations and Insights from FDA and EU Officials

Modern Quality Systems with Quality by Design

from the FDA/PDA Joint Conference

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Topics:

- Regulatory trends
- Inspection expectations
- Process and policy recommendations



Introduction

The US Food and Drug Administration (FDA) and the Parenteral Drug Association (PDA) co-sponsored a two day conference in November 2007 to update attendees on the status of the FDA's *cGMP's for the 21st Century* as it applies to biotechnology and pharmaceutical companies.

Three themes emerged from the conference:

1. Biopharmaceutical companies need examine lessons from the implementation of modern quality systems in the device industry.
2. Key enablers for successful modern quality systems are also auditor and investigator expectations.
3. FDA is shifting to a more principle and standards approach to compliance in line with the International Conference on Harmonization (ICH) guidelines.

This report is summarized from presentations and discussions by:

- Helen Winkle, Director, Office of Pharmaceutical Science, FDA
- Kimberly Trautman, GMP Expert of CDER, FDA
- Dr. Douglas Throckmorton, Deputy Director of CDER, FDA
- Rebecca Rodriguez, National Expert Investigator, FDA
- Monica Caphart, Senior Compliance Officer, FDA
- Ian Thrussel, Senior Field Inspector, MHRA and EU

Further supplemental information comes from attending biotechnology and pharmaceutical industry speakers and facilitators during the two day conference in Bethesda, Maryland.

Regulatory Trends

Increasing collaboration with their counterparts abroad has forced the FDA to re-examine their approach to compliance. The result: an increasingly consistent global view that ICH compliance is the gold standard.

ICH Impact

The FDA is moving toward an ICH-like philosophy of principles and standards.

Investigators are being trained to assess a company based on the company's risk-based justifications and actions, and not on prescriptive checklists drawn from specific, line-by-line regulation. This is due in large part to the FDA's work with the ICH and the EU.

Complete your quality system and SOP overhaul based on risk management by 2012. Within the next 4-6 years, the FDA will have undergone significant personnel turnover from retirement. Expect the last stalwarts of line-by-line, phrase-by-phrase checklist compliance to have left the agency.

The FDA is orienting itself to align with both the ICH and the EU to foster international cooperation and industry innovation. The end objective is for the FDA to establish the core minimum requirements that will level the playing field expectations.

Review your quality system and compliance program in light of the ICH Q7-Q10 guidance documents. The ICH Q10 guideline, *Pharmaceutical Quality System*, is seen by regulators as consistent with 21 Code of Federal Regulations (CFR) Parts 210 and 211.

Quality Systems Integration

The modern quality systems approach sees Quality Control, Quality Assurance and Quality Management all under one big umbrella, the Quality Unit. This allows a quality system to be the integration across a company. The expectation

is that a good quality systems will help eliminate organization silos, invigorate innovation and enhance product development.

In this context, FDA officials recommended that companies look at ICH guidelines Q7, *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*, Q8, *Pharmaceutical Development*, Q9, *Quality Risk Management*, and Q10, *Pharmaceutical Quality System*, as an integrated whole. These four guidelines are designed to be used together.

Knowledge Management

Modern quality systems have, at their core, a means to manage knowledge that allows continuous, positive impact to product quality, safety and efficacy.

The increase in quality science and data leads to the question of relevance. FDA officials noted that being able to measure everything does not equate to safer, more efficacious products.

“Data is meaningless if it cannot be used to improve product quality, safety and efficacy.” - Helen Winkle, FDA

Create a knowledge repository usable by company personnel to improve science- and risk-based decision-making. Documenting failures and lessons learned is just as important as capturing successes. Executives need to play a leading role in breaking down fiefdoms of knowledge across the organization to allow greater capacity for information to be put to use.

Examples of knowledge management include process details, batch record results and trending, equipment support documentation (such as repair and maintenance records), and project summaries.

GMP Compliance

Compliance with Good Manufacturing Practices (GMPs) will only give a company a start on compliance with the modern, lifecycle-oriented quality system.

The emphasis is on risk management and the implementation of a system that starts in product design and development, and flows all the way through product retirement. Quality systems are no longer confined to manufacturing.

Look to elements of Quality by Design to get you ready in preclinical and nonclinical to transfer product into pilot production, and then into scale-up for final manufacturing. Do not bring your manufacturing-based, rigid quality system into product development without some level of translation and balance. (See Cerulean's *An Executive's Guide to the FDA's Quality by Design* for more information.)

FDA officials noted that compliance with the GMPs is required from Phase I clinical trials onward, so this emphasis on quality starting in product design should not be unexpected. Any pilot product made for clinical trials must be made under GMP compliance.

EU GMPs Revised

As a result of the FDA and ICH initiatives, the EU has revised its GMPs to emphasize risk management and lifecycle quality systems.

While the new EU GMPs do not mandate the concept of “design space”, the EU now strongly encourages its adoption by biopharmaceutical companies.

EU Compliance Letter

The EU is shifting toward an annual compliance letter signed off on by the CEO of a company.

Based on those required by blood banks in the United Kingdom, and somewhat similar to certifications under Sarbanes-Oxley in the US, the intent is to weed out those firms that really need inspection and public warnings versus those companies that have their act together.

Create a simple, one-page cover letter to be signed by your CEO following your annual quality systems review. FDA officials suggested that those companies who currently submit an annual report to the agency might want to consider adopting such a “do and tell” cover letter for their report.

Inspection Expectations

The FDA is training its inspectors to focus on the adequacy and efficacy of a company’s quality system. The more effective and adequate the quality system, the better it will be able to handle the complexities of new biologic development and manufacturing.

Intent to Comply

Investigators expect to see a company’s intent to comply by examining three areas:

1. Documented risk assessments
2. Incorporation of Quality by Design principles
3. Review (and resulting actions) of metrics and trending analyses.

Record Integrity

Record integrity and risk management were identified by regulators and inspectors as crucial.

Regulators expressed frustration over how the consulting industry is pushing risk management to be a separate system in and of itself. Officials noted the similarities to how computer system validation (21 CFR Part 11) was turned away from product quality and patient safety data integrity to a separate focus on technology specifics and security configurations.

“The way the consulting industry misinterpreted and ran with Part 11 added very little to patient value.” - Dr. Neil Wilkinson, AstraZeneca

Today's slow shift toward data quality and long-term electronic data integrity is viewed as the start of getting Part 11 back on the right track.

Work with your computer department to verify the acceptability of data integrity checking and security access. Remember to focus not just on backup integrity, but also “live” data quality. Consider conducting an audit of backup data, particularly if your backup data is stored offsite at vendor.

Risk Management

Start with the risk to patients and then work backward to drive priorities and funding.

Risk assessments need to be science and fact-based, not structured to produce the answer a company wants. Risk assessments are iterative as knowledge grows. Without information, risk analyses and decisions should not be taken until the necessary information is gathered. Risk management should be incorporated across the board into any process.

“Risk management should be prospective, not reactive, to allow for new risk factor identification and control.” - Monica Caphart, FDA

Each SOP in which decisions are expected as part of the process should have risk evaluation as one of the core decision-making bases. Depending on your company, this may mean a much broader scale of risk management training. In this case, you will need to simplify and streamline your risk management processes to ensure everyone required to make decisions is able to make them based on sound risk management principles.

Internal Audits

Companies should consider giving FDA auditors summaries of their internal audits.

While EU inspectors have always been authorized to request a company's internal audit summary documents, FDA inspectors have recently been encouraged to use the summaries as proof of a company's intent to tackle issues proactively and not to play “gotcha.” FDA auditors are being trained to see “continuous improvement” as “continuous learning.”

Make sure to audit your own nonconformance, deviation and CAPA files. A small deviation log or file is a red flag to FDA auditors and will dramatically increase your chance of receiving a 483 observation. To test, auditors will look at the documents and procedures, then talk to people and observe, and then go back to the documents to capture gaps and inconsistencies.

In line with this, FDA inspectors are increasingly examining annual quality system reviews and corrective and preventative actions (CAPAs).

How a company reacts to findings in Annual Reviews and CAPAs is increasingly viewed by FDA officials as indicative of the executive team's integrity.

EU investigators are committed to helping US companies who need help and guidance, in large part because EU inspectors have the liberty – because of US companies' compliance with FDA – to just focus on equipment that directly touches the product. For the rest of the company's quality system, the EU inspector can rely upon FDA compliance. This leaves the EU investigator free to offer quality systems advice without unduly worrying about a conflict of interest.

Process Recommendations

In addition to CAPA and Annual Review discussions, FDA officials made it clear that purchasing controls are no longer narrowly confined. Controls should be integrated across the product spectrum in tandem with risk management and Quality by Design.

Corrective and Preventative Action (CAPA)

Corrective and preventative action is evolving to be proof of continual improvement.

Investigators expect CAPAs prioritized in three ways:

1. Patient safety
2. Product efficacy
3. Sustainability

Confine CAPAs to what your firm did to solve significant, systemic problem, not one-off deviations or short-term issues.

“Every nonconformance should not open a CAPA. Maybe 1 out of every 100 deviations should be a CAPA.” - Kim Trautman, FDA

From attendee discussion, two consensus suggestions emerged:

- Only allow CAPAs to be opened if senior management approves

- CAPAs should be limited to only those impacting patient safety

Consider revising your CAPA standard operating procedure to focus only on systematic and/or finished product issues. Create a separate process that handles typical, more day-to-day nonconformances and deviations. Make sure that separate process is broad enough to handle a wide array of issues without being so broad that it encompasses non-quality system related activities. Use a risk-based approach to avoid overwhelming the new nonconformance approach.

Timelines to resolve findings need to be realistic. Consider setting a 30-day timeline for nonconformances that automatically escalates into a more systemic CAPA if more than 180 days have expired without a root cause identification and solution.

To further help companies focus on continual improvement and root cause sleuthing, the FDA is drafting validation guidance on “real-time” quality assessments and checks. This is also part of the furthering of Quality by Design and process analytical technology.

Contract Organization Oversight

The best relationships with contract organizations treat the contract organization as an internal division.

Review and monitor who in each organization has what specific responsibility for the various touch points and overlaps of each organization’s quality system. Define ahead of time what processes and decisions require the sponsor’s involvement, what requires the sponsor’s agreement and what only requires the sponsor to be informed of after the fact.

For areas of little or no overlap, audit to ensure compliance. Examples include:

- Computer systems
- Records management
- Training
- Maintenance
- Environmental controls

Annual Quality System Review

Inspectors are inspecting a company's annual reviews in two ways:

1. Trending and analyses
2. Determination of problem areas (and what the company did about them)

Companies need to incorporate business planning into their annual reviews so the quality system is not isolated from business realities.

Incorporate a summary of the next year's business plans, even if in draft form, to be reviewed in tandem with the annual quality systems review.

Make sure to mark this "confidential" and to include it within the supporting documents and data of the annual review. This will also help avoid a potentially awkward situation when a quality systems professional may ask to serve in a more senior business planning capacity.

Limit the areas to improve to no more than ten in one year. Several FDA officials expressed serious skepticism at most companies even being able to accomplish that many. Prioritize these improvement activities based on risk to the end patient and product quality, safety and efficacy, not on internal corporate risks. Make sure to document the logic behind the prioritization.

Conclusion

The modern quality system as envisioned by the FDA (and the EU) is increasingly consistent with the ICH's product lifecycle philosophy, tracing science and risk management from product conception to retirement.

Biopharmaceutical companies that intend to wait it out will find themselves significantly behind the curve. During the conference, FDA officials repeatedly alluded to major alignment changes coming by 2012.

“The real challenge in the industry is to change the culture to allow modern quality systems with Quality by Design and risk management.”

- Helen Winkle, FDA

Are you ready?

If you would like a complimentary copy of *An Executive's Guide to the FDA's Quality by Design* referenced in this report, email reports@ceruleanllc.com or visit the “Resource Library” on the Cerulean website (www.ceruleanllc.com).

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