Supply Chain
Supplier Quality Management

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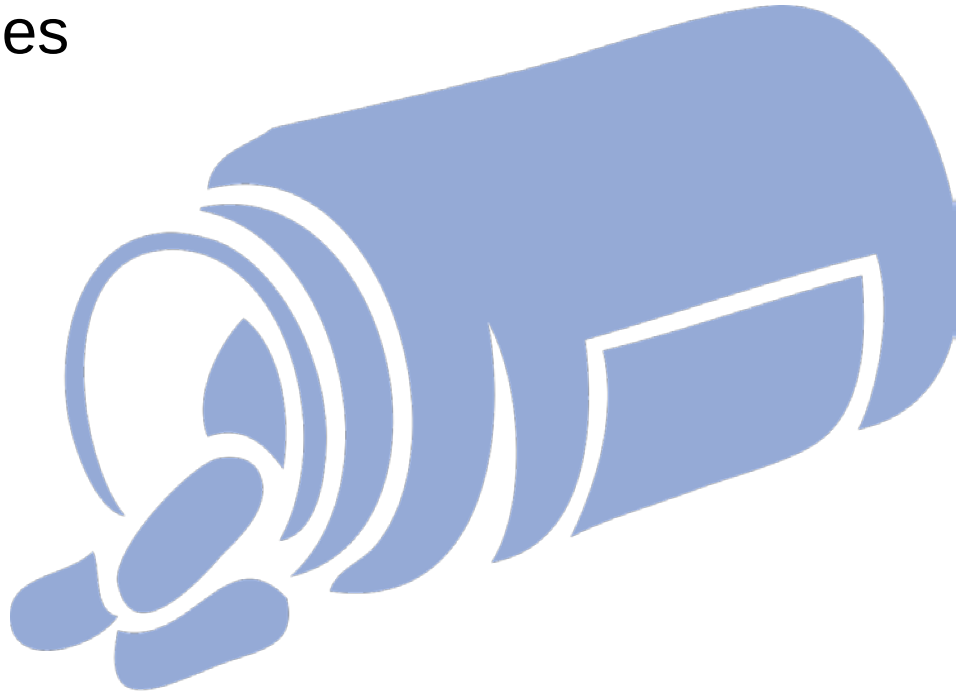
Overview

- Product Life Cycle
- Maintaining Quality in Supply Chain
- FDA and ICH Guidances
- Case Studies
- 483s/Warning Letters



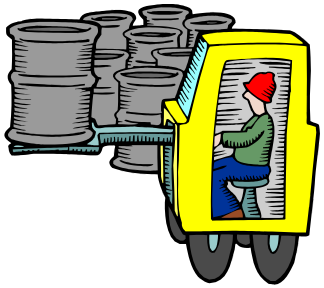
Product Life Cycle

Customers

Packaging / Labeling

Materials

Suppliers



QUALITY

Laboratory

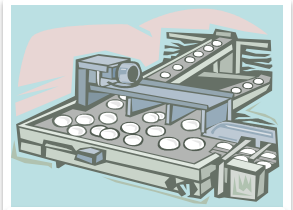
Production

Equipment

Drug Supply Chain: Life Cycle Model

Manufacture

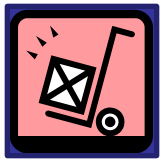
Contract Manufacturer/Labs; API/ Excipient Sources



Manufacturer

Distribution

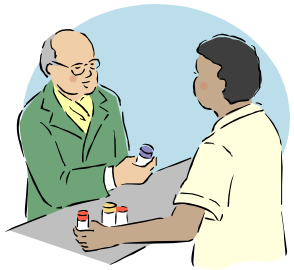
Pharmacy/Dispenser



Wholesaler(s)

Repackager(s)

Use



HCP and Patient

Lifecycle, According to Q10

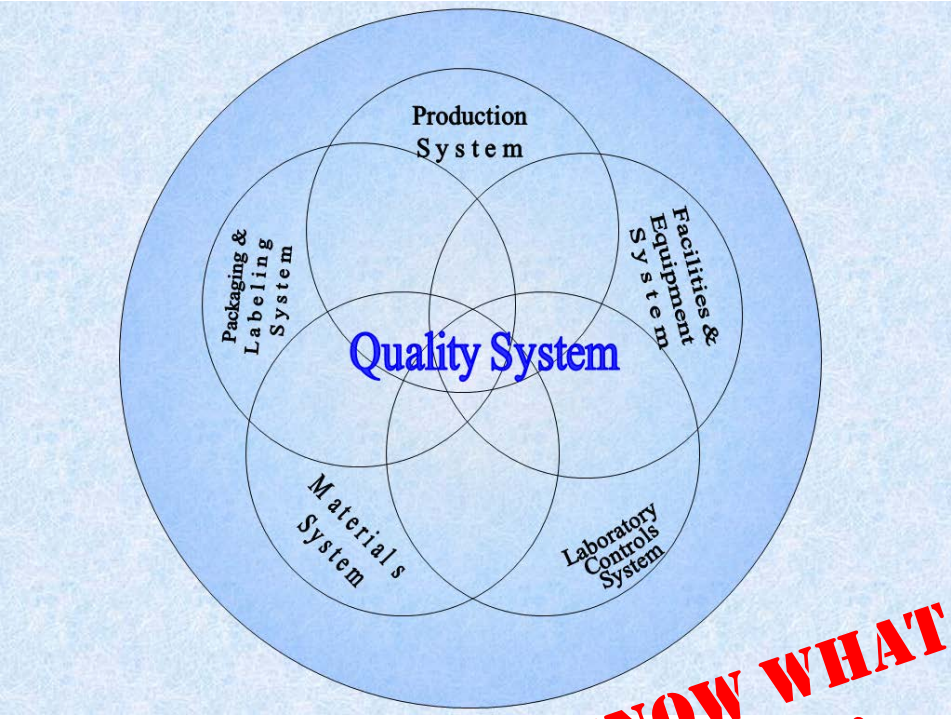
Quality is best maintained when monitored throughout the Product Lifecycle, as described in ICH Q10, Pharmaceutical Quality System. Building an appropriate Quality System that follows a product from development, transfer, and through to commercial manufacture and eventual product discontinuation ensures a robust product and process.

Life Cycle, According to Q10

By planning and executing a system for monitoring process performance and product quality, a state of control can be maintained. Such a system provides assurance of continued process and control capability, allowing a product of desired quality to be produced, while identifying areas for continuous improvement.

In simpler terms…

The more known about a product, its manufacturing processes and equipment, materials, components, personnel, and testing methods, the greater the opportunity to maintain and improve quality and robustness.



"YOU DON'T KNOW WHAT YOU DON'T KNOW"

Maintaining Quality in Supply Chain

Evaluating Suppliers of Materials and Services

- Supplier Qualifications
- Quality Agreements
- Site Audits
- Impact Assessment
- Maintenance / Monitoring

Maintaining Quality in Supply Chain

Relevant Supplier Operations That Might Be Contracted

- Manufacturers
- Control Testing Laboratories
- Packaging and Labeling Facilities
- Sterilizers

Maintaining Quality in Supply Chain

Goals

- Ensure consistency and control throughout (all of) your processes
- Expect reliability in materials or services provided
- Reduce time lost due to deviations
- Maintain accountability (but can't contract out all responsibility)
- Prevent recalls, drug shortages, Regulatory Actions

2012 FDASIA Revision to FD&C Act

Enhancing the Safety and Quality of the Drug Supply, Section 501 (21 USC 351):

"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**."

"Section 711: Enhancing the safety and quality of the drug supply" requires specific **management oversight from raw materials, through intermediates, to finished product**

Risks Associated With Contracting Out Parts of Process

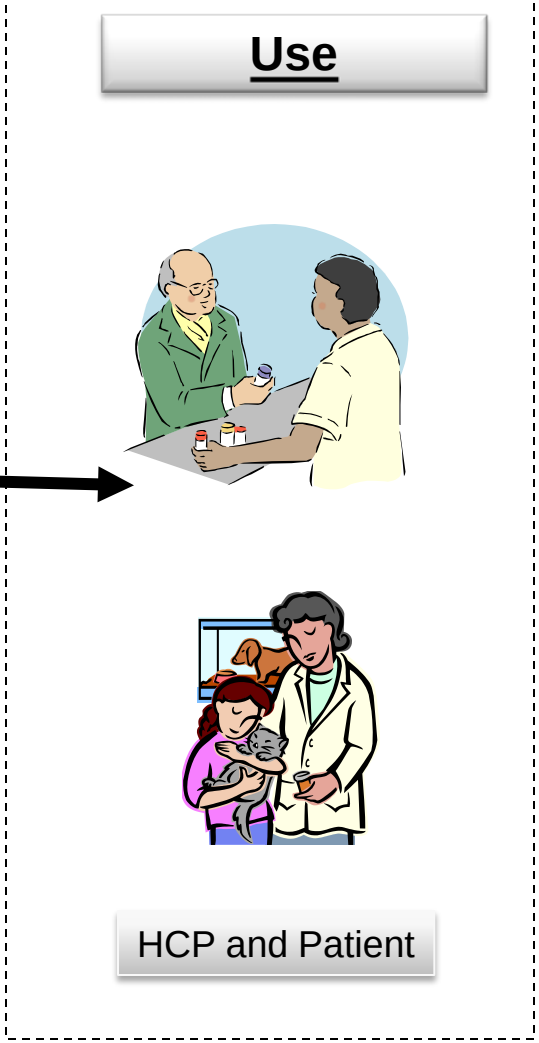
"Not only are buyers unable to observe manufacturing quality, but **firms that contract out manufacturing of their product often do not have the same level of insight into or oversight of the contract manufacturer's quality systems as they would have into their own**. Over-commitment on manufacturing capacity by a contract manufacturer can lead to an unsustainably high number of products on each line and substandard oversight of the process."

[Woodcock, J. and M. Wosinsksa, Clinical Pharmacolgy & Therapeutics, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortage," Jan. 2013]

We Need Consistency

"We rely upon the **manufacturing controls and standards** to ensure that **time and time again, lot after lot, year after year the same clinical profile will be delivered because the product will be the same in its quality**… We have to think of the primary customers as people consuming that medicine and we have to think of the statute and what we are guaranteeing in there, that the drug will continue to be safe and effective and perform as described in the label."

[Janet Woodcock, M.D.]

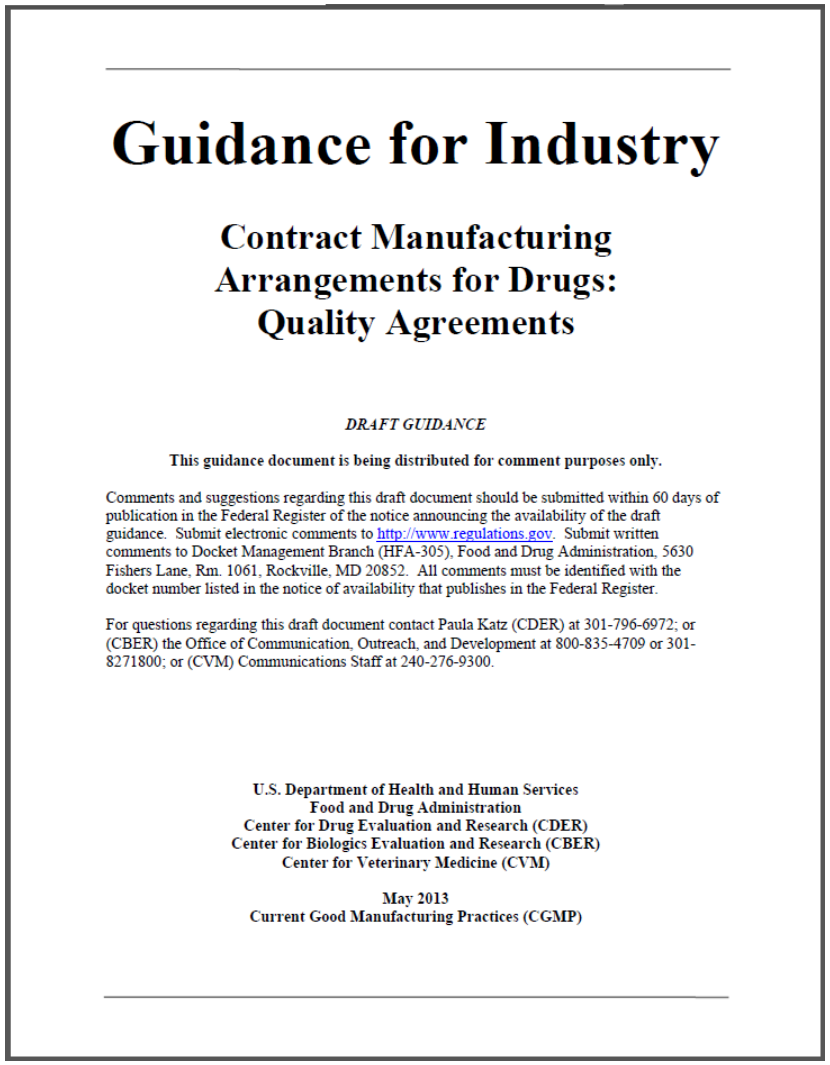


Key Components

Supplier Qualification Program

- Quality Agreements: a document agreed to by both parties that establishes responsibilities
- Assessment of Supplier: site audits
- Periodic Reassessment/Monitoring: ability to provide material or service of consistent quality; if issues arise, how are they addressed?

FDA Draft Guidance, May 2013



Guidance for Industry

Contract Manufacturing Arrangements for Drugs: Quality Agreements

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to Docket Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments must be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact Paula Katz (CDER) at 301-796-6972; or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 301-8271800; or (CVM) Communications Staff at 240-276-9300.

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)
Center for Veterinary Medicine (CVM)

May 2013
Current Good Manufacturing Practices (CGMP)

Statutory and regulatory framework

Suggested elements of a quality agreement

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm353925.pdf

FDA Draft Guidance, Contract Manufacturing Agreements for Drugs: Quality Agreements, May 2013

Illustrative example describes "**A Quality Agreement Does Not Exempt Contracted Facilities From CGMP Requirements Related to the Operations they Perform**, Regardless of Whether Such CGMP Requirements are Specifically Discussed in the Quality Agreement"

[Following examples…]

Case 1: Responsibility for Facilities and Equipment Maintenance and Upkeep at Contracted Facility

FDA inspection of a **Contracted Facility that manufactures injectable product for the product Owner** reveals **significant objectionable conditions at the Contracted Facility**. A **Warning Letter** is issued to the Contracted Facility; most of the conditions observed are **related to deficient maintenance of the facilities and equipment** used to manufacture the injectable product, such as defective or partially broken equipment, visibly tarnished piping, leaking seals, etc. In addition, **facility design is inadequate to prevent contamination**. This Contracted Facility has a **Quality Agreement specifying the product Owner's responsibility for upgrades and maintenance of the facilities and equipment.** The Owner fails to provide the requisite resources or carry out the necessary upgrades and maintenance, but and the Contracted Facility continues to manufacture the product under non-CGMP conditions that could result in product contamination.

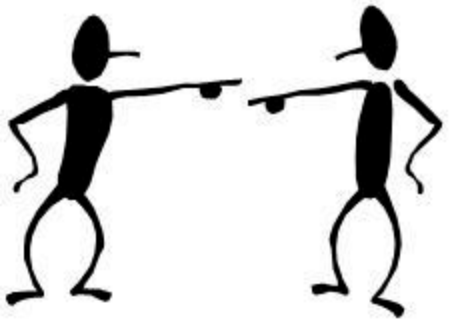
Case 2: Responsibility for Documenting Steps in the Manufacturing Process

The **Contracted Facility is responsible for contract manufacturing of a prescription product subject to the product Owner's ANDA**. On inspection, it is observed that the Contracted Facility's **batch records do not accurately reflect the actual manufacturing process** because the batch records do not document the addition of reclaimed powder. The Contracted Facility **claims that this practice of incomplete batch records was in accordance with the wishes of the product Owner**.

A Quality Agreement does not exempt Contracted Facilities from CGMP requirements related to the operations they perform, regardless of whether the Quality Agreement specifically discusses those CGMP requirements.

In either of the two cases described above, the Contracted Facility could be responsible for CGMP failures, because, regardless of the allocation of responsibilities in the Quality Agreement, the Contracted Facility cannot essentially agree to manufacture under non-CGMP conditions.

The Quality Agreement is not a substitute for compliance with CGMP requirements by either party. The lesson from cases like these is that Contracted Facilities should insist on greater clarity regarding how Owners will carry out specific obligations under the Quality Agreement, because the Quality Agreement will not serve as an excuse for manufacturing drugs in a non-compliant environment.



When the terms of the Quality Agreement prove inadequate during the lifetime of the contractual relationship, the Contracted Facility could **refuse to continue to manufacture the product under non-CGMP conditions** (e.g., in Case 2, the Contracted Facility could refuse to carry out the additional manufacturing step without including it in the batch record). Another option would be for the **Contracted Facility to bear the costs for modifying operations in order to maintain CGMP compliance, and then seek redress from the Owner later** (in Case 1, for example, the Contracted Facility might purchase necessary equipment, carry out cleaning, upgrades, validation, and repairs, etc., and then charge the costs to the Owner). In any case, stipulations in the Quality Agreement do not relieve the Contracted Facility of its obligations to meet CGMPs relevant to the operations it performs.

At the same time, the Owner is not relieved of its responsibility to ensure the quality and safety of the products it introduces or causes to be introduced to the marketplace because a Quality Agreement allocates a particular activity to the Contracted Facility. For example, after finding the types of problems at Contracted Facilities in the two cases above, FDA could inspect the Owner. Depending on the evidence gathered, **FDA could also hold the Owner liable responsible for CGMP failures, or for oversight failures in monitoring the activities of the Contracted Facility in order to ensure that its products are manufactured under CGMP conditions**. Depending on the significance, such failures on the part of a product Owner could be grounds for a **product recall, or for a seizure, injunction, or other action**. Additionally, for foreign sites, the Agency could consider refusing the Owner's products entry into the United States.

Case 3: Responsibility for Data Integrity in Laboratory Records and Test Results

In this scenario, a **Contracted Facility providing contract analytical laboratory services repeatedly reports passing results in its CGMP records when failures were obtained in actual analysis**. The Contracted Facility also **fails to report accurate results to its client**, the product Owner. When FDA inspects the Owner, it is revealed that the **Owner did not audit** the contract laboratory prior to FDA's inspection of the Owner, despite the fact that the Owner has a **written procedure in place requiring a site audit** of contracted facilities every two years.

Case 4: Responsibilities for Method Validation

Routine inspection of this Contract Laboratory discloses its **failure to conduct complete investigations of out-of-specification results and sample duplication failures reported for stability samples of an injectable product**, and for the failure to implement adequate corrective actions. Some of the investigations suggest that sample duplication failures were related to analytical techniques in sample preparation, but the specific problematic techniques are not clearly identified in the investigations and in the analytical method. The **Contract Laboratory's management claims that, since the method they used for testing belonged to the NDA holder, the Contract Facility is not responsible for investigating and implementing corrections related to the analytical method**. Despite the Contracted Facility's knowledge that the method is not suitable, and is therefore not compliant with CGMP, the **laboratory continues to use the questionable method to test the product**.

Contract Laboratories are Contracted Facilities like any others, and they are **responsible for complying with CGMPs** that relate to the operations they perform, regardless of the specific terms of any Quality Agreement they have reached with the product Owner.

As a part of those responsibilities, they **must employ controls to assure the integrity and reliability of the data they generate, and, in addition, they must provide data and test results that the Owner can use in final disposition decisions**.

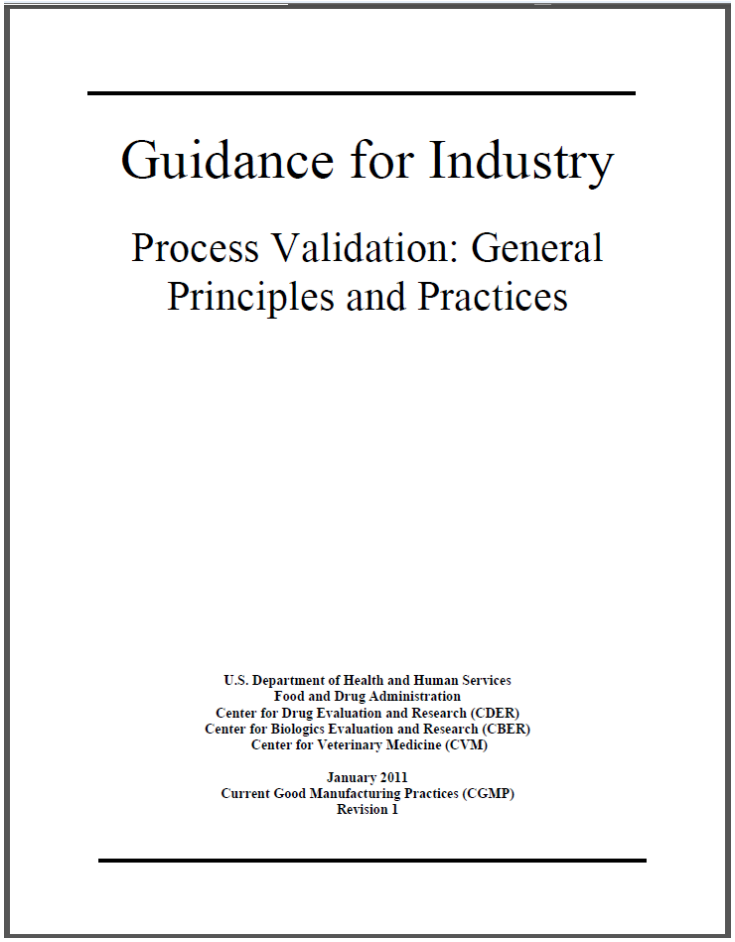
In either of the cases above, the **Contracted Facilities could be held responsible for clear CGMP violations** related to the laboratory activities they conduct.

Additionally, the **Owners could be responsible for CGMP violations because, regardless of who tests the products or the agreements in place regarding the manufacturing and testing of those products, the Owner is ultimately required to ensure that the products are manufactured in accordance with the Act, assuring the identity, strength, quality, purity, and safety of the products**. The Owners might further be cited for failure to follow their own procedures for evaluating, qualifying, auditing, and monitoring contractors/suppliers.

FDA Draft Guidance, January 2011

"After establishing and confirming the process, **manufacturers must maintain the process in a state of control over the life of the process**, even as materials, equipment, production environment, personnel, and manufacturing procedures change."

(ICH Q10, Pharmaceutical Quality System, defines "State of Control" as "A condition in which the set of controls consistently provides assurance of continued process performance and product quality.")



Guidance for Industry

Process Validation: General Principles and Practices

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)
Center for Veterinary Medicine (CVM)

January 2011
Current Good Manufacturing Practices (CGMP)
Revision 1

ICH Guidance

ICH Q10, Pharmaceutical Quality System

"The pharmaceutical quality system, including…**management responsibilities…extends to the control and review of any outsourced activities and quality of purchased materials**.

The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials."

ICH Q10, Pharmaceutical Quality System

Responsibilities include:

- "**Assessing** prior to outsourcing operations or selecting material suppliers, the **suitability and competence of the other party** to carry out the activity or provide the material using a defined supply chain (e.g., audits, material evaluations, qualificat[illegible])…"

- "**Defining the responsibilities and communication processes** for quality-related activities of the involved parties. For outsourced activities, this should be included in a written agreement between the contract giver and contract acceptor…"

ICH Q10, Pharmaceutical Quality System

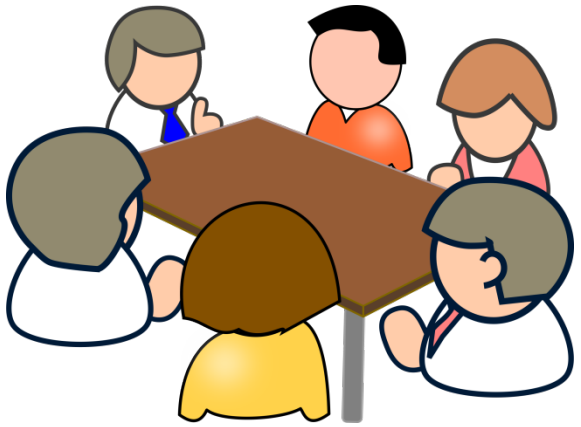
Responsibilities include:

- "**Monitoring and review of the performance** of the contract acceptor or the **quality of the material from the provider**, and the identification and implementation of any **needed improvements**…"

- "**Monitoring incoming ingredients and materials** to ensure they are from **approved sources using the agreed supply chain**…"

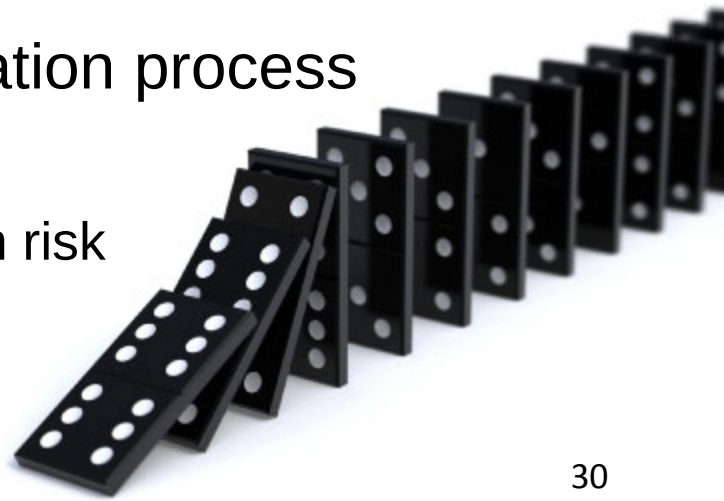
Periodic Reassessment/Monitoring

- Annual Product Reviews
- Quarterly Management Reviews
- Quality Metrics (monthly, weekly)



Periodic Reassessment/Monitoring

- Perform impact assessment
- Effective change management system
- Risk assessment
- Thorough and effective investigation process
- Audits or assessments
    - Frequency commensurate with risk
    - For cause



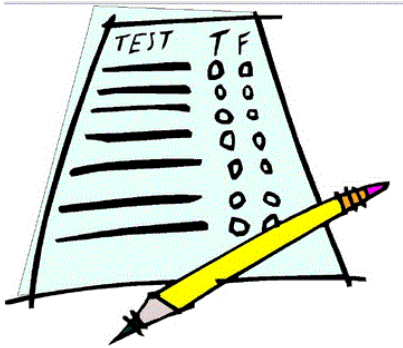
ICH Guidance

ICH Q9, Quality Risk Management

"**Risk management should be an ongoing part of the quality management process**. A mechanism to review or monitor events should be implemented…The output/results…should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that **process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned** (e.g., results of product review, inspections, audits, change control) **or unplanned** (e.g., root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk."

Case Studies

Incomplete paper audits went unaddressed



- Background:
  - Firm had numerous issues with foreign material in product and raw materials—many suppliers had not been evaluated

OBSERVATION 1

The quality control unit lacks the responsibility and authority to approve and reject all components, in process materials, and drug products.

[a. through d. discuss black particles, other contamination issues]

e. The Quality Unit has not evaluated all suppliers of raw materials and active pharmaceutical ingredients to assure their quality and suitability for intended use. Specifically, assessments of raw material suppliers have not been completed and limited testing is used to approve a new supplier. For example, no cGMP evaluations of suppliers of the APIs [A, B, and C] have been conducted.

Case Studies

Inappropriate supplier selected

- Background:
  - Particles found among several drums of raw material
  - Supplier never fully audited
  - Pharma customer only a small portion of business
    - Material mostly supplied for industrial applications, site claims to be non-GMP
    - Unable to supply material of appropriate level of quality, free of contamination

Outcome: discontinuation of product

Case Studies

Lack of sufficient process capability, inadequate oversight

- Background:
  - Drug/device combo final assembly at contract site; “right the first time” product
  - Internal components damaged during assembly process
  - Inability to deliver drug, only found when attempt to use, otherwise difficult to detect
  - Lack of true knowledge of extent of defect

Outcome: Recall of all marketed lots

More oversight of process to prevent/detect

Case Studies

Facility housekeeping issues

- Background:
  - Facility inspection found holes in roof of facility and open bay doors
    - Holes linked to “pest control” method

Outcome: no longer supplying pharmaceutical grade material

Case Studies

Heparin contamination

- Background:
  - Influx of adverse events, sensitivity reactions in dialysis patients, early 2008
  - OSCS in material from supplier → supplier → finished dosage manufacturer
  - Reported contamination in at least 10 other countries
  - Deemed to be economically motivated adulteration, to reduce cost of material

Outcome: require additional test methods to detect potential OSCS contamination

Guidance for Industry

Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality

for use (i.e., sufficiently validated for the degree of precision/accuracy required for its use) in screening crude heparin for the presence of OSCS.

3. Know the identity and role of the actual manufacturer of crude heparin and any repackers and distributors who handle crude heparin before receipt and use.

Manufacturers of APIs, finished drug products, and heparin components for use in medical devices should sufficiently audit[18] and qualify their crude heparin suppliers to ensure conformance to appropriate quality standards.

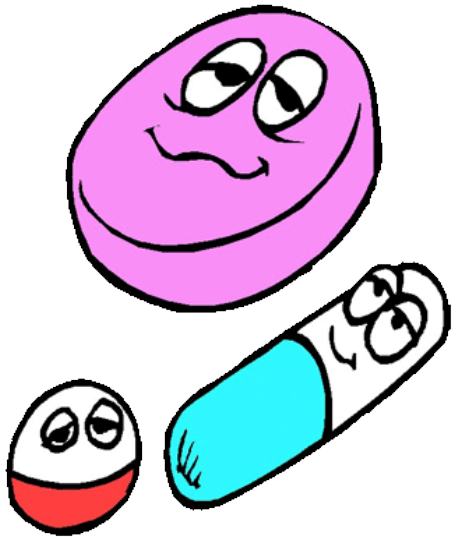
4. Employ the controls described in ICH Q7 to prevent the use of crude heparin containing OSCS or ruminant or unlabeled sources of crude heparin and to fully and promptly investigate and resolve deviations and failures of quality, especially identity and purity.

5. Reject for use any crude heparin found to contain any amount of OSCS, or to be derived from, in any amount, ruminant mucosa (unless approved in the drug application). If imported into the United States, control and properly dispose of any such crude heparin or heparin products in which it was used and notify the local FDA district office of the finding.[19]

Case Studies

High-risk opiate tablet mix-up

Product owner “aware of only three product mix-ups with respect to these products since 2009; all three were detected by pharmacists”



“FDA advises patients and healthcare professionals to examine opiate medicines made by [product owner] in their possession and ensure that all tablets are the same. FDA and [product owner] are providing instructions on how to identify an incorrect tablet in these medicines.”

Outcome: “[Contract manufacturer] has initiated a consumer level recall of the other non-opiate products made at their…manufacturing facility out of an abundance of caution for these other products.”

Case Studies

Sterile contract manufacturer

Particulate contamination found in various products. Example of many deficiencies found on inspection:

Observation 1

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

Specifically, Your firm has not validated the 100% vision light inspection testing with regard to personnel qualification, inspection speeds and technique…

- **There is no inversion of any vial, ampoule or cartridge to facilitate particulate inspection**
- **…24 units inspected at once…**
- **…[There is no] seeded qualification panel (known defects inserted into a sample lot of "good product" to assess the trainee's aptitude in finding defects)…**
- **…Visual inspection employees…verbally stated they do not inspect the top of the lyophilized cake…**

Outcome: contract manufacturer has initiated multiple recalls for various types of particulate contamination in injectable products

Relevant Regulations

- **21 CFR 210.1**: Failure to comply with cGMPs renders the drug adulterated under 501(a)(2)(B), and subject to regulatory action

- **21 CFR 210.2(b)**: Must comply with cGMPs applicable to the operations you perform (can't "contract around" cGMP)

- **21 CFR 210.3(b)(12)**: manufacture, processing, packing, or holding of a drug product includes packaging and labeling operations, testing, and quality control of drug products

Relevant Regulations

The cGMP regulations do not explicitly require a written quality agreement, but…

- **21 CFR 211.22(a)**: Quality Unit responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company
- **21 CFR 211.22(d)**: Quality Unit procedures and responsibilities must be in writing and fully followed
- **21 CFR 200.10**: Contract manufacturers are an extension of the manufacturer's own facility

483s and Warning Letters

21 CFR 211.22(a)

- There is no quality control unit…
- The quality control unit **lacks authority to [review production records to assure that no errors have occurred] [fully investigate errors that have occurred]…**
- The quality control unit **lacks the responsibility and authority to [approve] [reject]** all [components] [drug product containers] [closures] [in process materials] [packaging material] [labeling] [drug products]….
- The quality control unit **lacks responsibility for approving or rejecting drug products [manufactured] [processed] [packed] [held] under contract by another company…**

Description	2015	2014	2013	2012
483 (FY)	52	51	54	68
Warning Letters (CY)	**6**	**--**	**4**	**12**

*** CDER may change the citation used in the Warning Letter**

483s and Warning Letters

21 CFR 211.160, General laboratory requirements
21 CFR 211.165, Testing and release for distribution
21 CFR 211.166, Stability testing

21 CFR Reference	2015	2014	2013	2012
211.160 – 483s (FY)	294	235	245	293
211.160 – WLs (CY)	**4**	**4**	**11**	**14**
211.165 – 483s (FY)	160	143	179	171
211.165 – WLs (CY)	**12**	**9**	**9**	**10**
211.166 – 483s (FY)	142	115	153	155
211.166 – WLs (CY)	**13**	**18**	**12**	**14**

*** CDER may change the citation used in the Warning Letter**

483s and Warning Letters

21 CFR 211.84(d)(2)

- **Reports of analysis** from component suppliers are **accepted** in lieu of testing each component for conformity with all appropriate written specifications, **without [performing at least one specific identity test** on each component] [**establishing the reliability of the supplier's analyses through appropriate validation** of the supplier's test results at appropriate intervals]…
- **Establishment of the reliability of the component supplier's report of analyses is deficient** in that the test results are not appropriately validated at appropriate intervals…
- Component testing is deficient in that **each component is not tested for conformity with all appropriate written specifications** for purity, strength, and quality…
- Specific **identification tests are not conducted** on components that have been accepted based on the supplier's report of analysis…

Description	2015	2014	2013	2012
483 (FY)	59	38	71	73
Warning Letters (CY)	**5**	**3**	**11**	**9**

*** CDER may change the citation used in the Warning Letter**

Report on the ISPE Drug Shortages Survey June, 2013

Common causes are quality problems, such as contamination or presence of foreign particles (estimated 46% of drug shortages in 2011), as well as raw material issues and packaging component problems (FDA)

“Globalization of drug manufacturing and complex supply chains [are] factors that increase the risk of drug shortages” (EMA)

Report on the ISPE Drug Shortages Survey June, 2013

Survey respondents described 19.5% (for sterile drugs) and 20.5% (for non-sterile drugs) of drug shortages or near misses at their facilities to be associated with material issues (second only to quality issues)

Circling Back

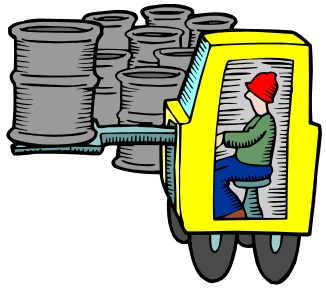
Contaminated Material

Lack of Control

Packaging / Labeling

Materials

Suppliers



Customers

QUALITY

Laboratory

Production

Adverse Events
Field Alerts
Recalls

Inadequate Testing

Equipment

Bad Process

Acknowledgements / References

Acknowledgement

- Richard L. Friedman, M.S., Deputy Director, Science and Regulatory Policy, Office of Manufacturing Quality, Office of Compliance, CDER, FDA

Outside References

- ICH Guidances Q8(R2), Pharmaceutical Development; Q9, Quality Risk Management; and Q10, Pharmaceutical Quality System (www.ICH.org)
- Report on the ISPE Drug Shortages Survey, June 2013 (www.ISPE.org)

FDA References

- http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm353925.pdf
- http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf
- http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm
- http://www.fda.gov/ICECI/Inspections/ucm250720.htm

Thank You / Questions