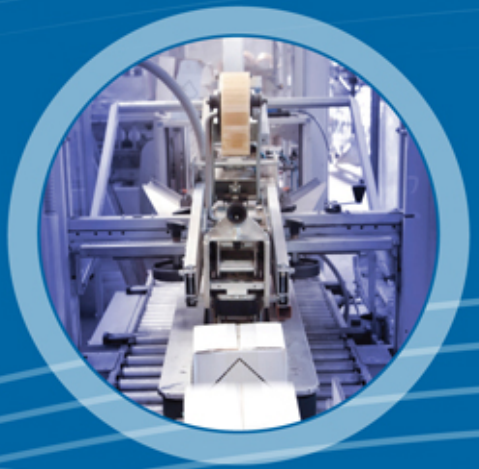
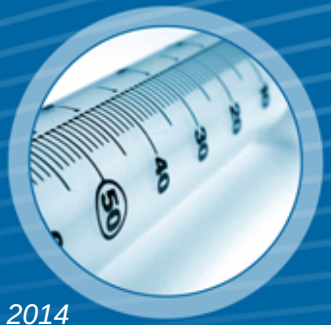
Connecting People, Science and Regulation®

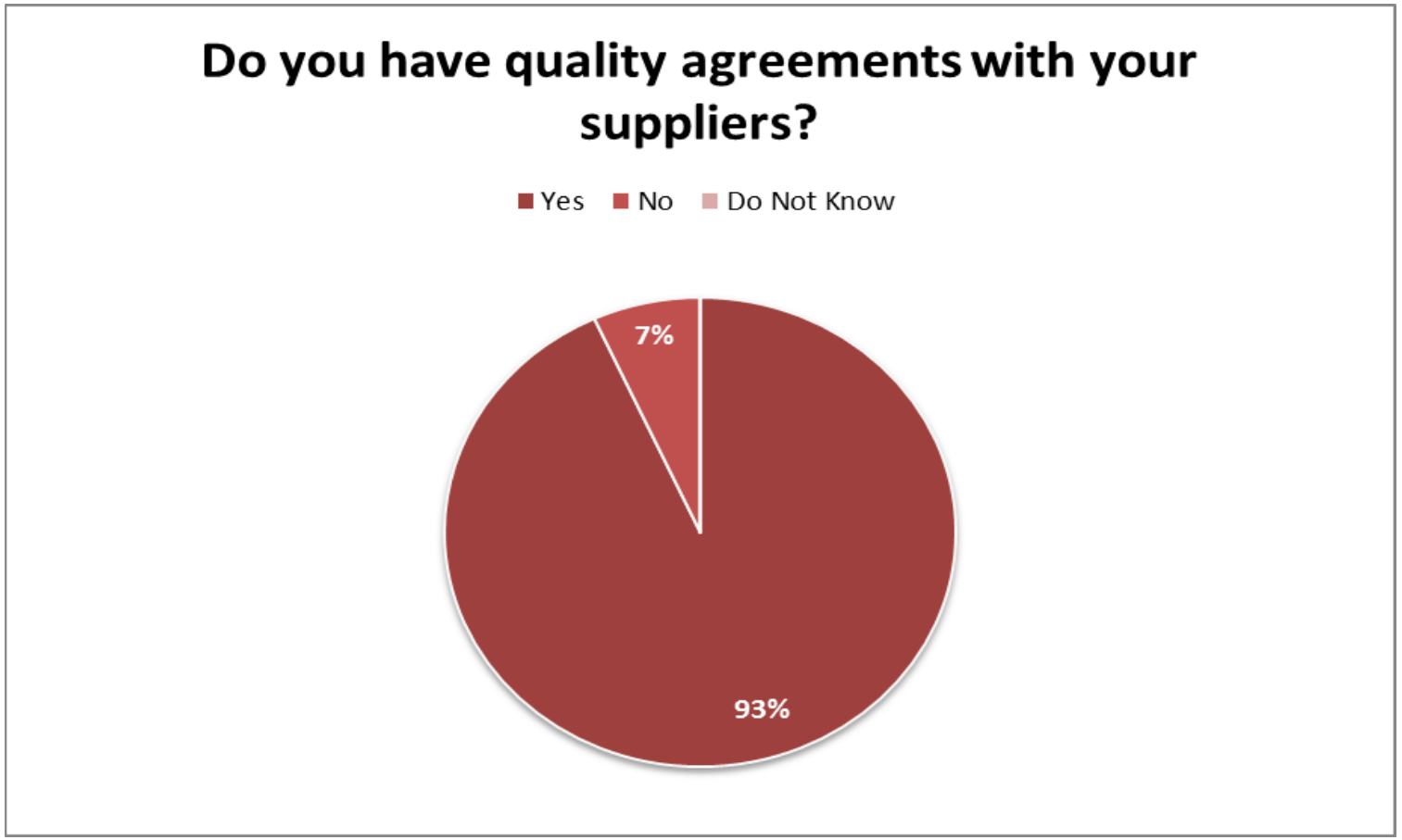
ICH Q7 Chapter 16:
Contract Manufacture





PDA - PIC/S ICH Q7 Training

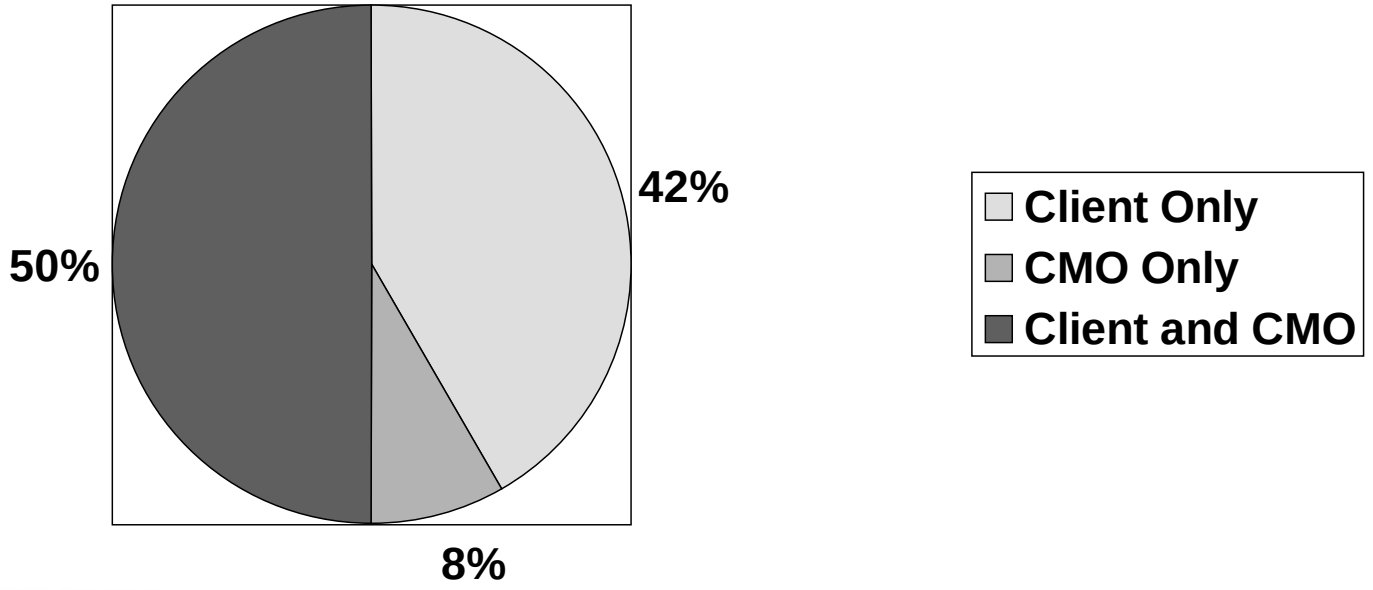
Quality Agreements



PDA Cost of Poor Quality Survey (20

CMO Responsibility

In cases where a Contract Manufacturing Organization (CMO) manufacturers product for you, where your company owns the drug application and/or application license, who is ultimately responsible for the quality of the product?



Special Note

Contractors

Data integrity is not only about ensuring your data is accurate and reliable, but also ensuring that your contractors' data is accurate and reliable.

Key Points FDA's CMO Guidance

1. Agency considers contractors an extension of the manufacturers own facility.

2. Both owners and contracted facilities are responsible for ensuring that their products are not adulterated or misbranded.

3. Both, the owner and CMO must work together to maintain quality oversight.

4. Contractors should be evaluated for cGMP compliance

5. Quality agreement should clearly describe the service, quality related activities responsibilities and communication mechanism

Key Points FDA's Guidance for CMOs

6. Competency of the site
7. Define who is responsible for what
8. Review of performance of the contracted site
9. All parties performing mfg. should monitor incoming materials and ingredients (approved sources)
10. Risk Assessment
11. Extent of Controls
12. Even if a contractor performs all or part of the mfg., processing, holding or testing, the owner's QU is ultimately responsible for approving and rejecting the drug product manufactured by the contract manufacturer.

Key Points FDA's Guidance for CMOs

13. Change controls and revisions
14. The Quality Agreement should describe how deviations will be investigated, documented and resolved.
15. Any and all cGMP responsibilities relevant to the agreement should be described
16. The Quality Agreement should be clear with respect to product release

Key Points FDA's Guidance for CMOs

"Although the Quality Unit of each Contracted Facility is responsible for release of the product of the operations it performs, final product release of finished goods for distribution must be carried out by the Owner and cannot be delegated to a Contracted Facility under the CGMP regulations or any terms of the Quality Agreement (21 CFR 211.22(a)).

Suggested Questions to Ask:

1. How does the existing quality structure assure open and full communication of unexpected events?
2. Who will be the liaison?
3. What information will be communicated, and how ?
4. Specific timeframes to communicate quality related information.

FDA Added

Suggested Questions to Ask:

5. How often are Quality System Management Reviews conducted?
6. Are site and corporate level reviews conducted?
7. What areas are included in the quality review?

   * deviations * CAPAs * change management

   *innovation/continuous improvements

   * results of audits or previous EI findings

FDA added Points to Considered when Outsourcing:

1. Sponsor or application holder should confirm that CMO is cGMP compliant.
2. Well designed audits by competent auditors have been conducted.
3. Verification of compliance status is not delegated and should be a continual.
4. Supply chain must be known, documented, verified and maintained.

FDA added Points to Considered when Outsourcing:

5. After selection of a CMO or supplier, companies may have to consider the need for onsite oversight of manufacturing and testing of their products, using their own highly trained quality and operations people, fluent in the language used at the CMO facility.

6. Quality oversight is not the responsibility of the local regulatory authority.

FDA added: Contracting Risks and Complexity

(ADDED)

"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 Pharmacology & Therapeutics, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortage," Jan 2013]

Warning Letter - Basic Flaws in Quality System

Please note that a CGMP-compliant quality system supports a sustainable state of control. This includes but is not limited to systems to ensure proper raw materials, vigilant quality monitoring, and appropriate corrective and preventive (CAPA) actions. FDA expects your firm to perform a comprehensive assessment of manufacturing operations to ensure that drug products conform to FDA requirements.

FDA Warning Letter
(ADDED)CMO (Manufacturing Reliability)

Your responsibility as a contract manufacturer is to inform all of your customers of a significant production problem or possible product hazard immediately. In fact, your Quality Agreements with customers require that your firm notify the other party within two business days… Please explain how and when you identified and informed all customers affected by your IV bag manufacturing problems. Also include your SOP describing how you keep customers promptly informed of significant occurrences (e.g., complaints, OOS, rejections, major deviations or discrepancies, any potential product hazard), concerning the products you manufacture for them.

Quality Systems: The Framework for Industrial Quality Assurance

A drug manufacturer is responsible for implementing dependable daily operations that assure consistent drug quality. Management's daily decisions on myriad issues involving equipment, materials, maintenance, staff qualifications, supervision, process control, and investigations will ultimately determine the quality of the drugs that are shipped from a given facility. [Woodcock, J and M. Wosinska, Clinical Pharmacology & Therapeutics, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortage," Jan 2013]

Reliable Manufacturing

- **…Clearly the responsibility for maintaining quality rests squarely with the manufacturers themselves...the widespread and successful adoption of six sigma and related quality management techniques in other manufacturing sectors would imply that reliable, high-quality manufacturing is also attainable in the pharmaceutical sector.**

- **We must ask ourselves, in an area where the stakes are so high, why is this not being achieved?**

Dr. Janet Woodcock

Commentary in May-June 2012 edition of PDA Journal

Some Corrective Action examples include:

- Correcting a manufacturing problem that led to a batch non-conformance
- Retraining staff because original training (and subsequent supervision) was inadequate
- Fixing an equipment problem (e.g., that could have been prevented by better monitoring of equipment performance or preventive maintenance program)
- Responding to a significant regulatory observation, instead of addressing earlier indications (e.g., internal audit) of an emerging issue
- Addressing CMO and contract laboratory issues only after rejects, lab issues, and supply problems

Thank You

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