FDA expectations

Role of the quality agreement

Helpful clarification resources

Suppliers that register with FDA

UNDERSTANDING OUTSOURCED ACCOUNTABILITY v. RESPONSIBILITY

"What can be outsourced?

Everything **except accountability**"

- Janet Woodcock, FDA,
testifying to US Senate on Heparin scandal
July 2009

Accountability

"The finished device manufacturer bears overall responsibility for the safety and effectiveness of the finished device and must control all contractors under 21 CFR 820.50 Purchasing Controls and 21 CFR 820.80 Receiving, In-Process, and Finished Device Acceptance…."

- FDA, CPG 7382.845

Implications

- device makers are legally accountable for overall safety, efficacy and quality of their finished device (including distribution to customer)
- responsibility for each individual work task can be delegated
- accountability for compliance, safety, and efficacy cannot be delegated

Accountability

"Since FDA is not regulating component suppliers, it believes…specifications for the finished device cannot be met unless the individual parts of the finished device meet specifications. Each manufacturer must establish procedures to ensure that received products and services conform to specified requirements."

- FDA, Preamble 21 CFR 820

Implications

- device makers are legally accountable for compliance of provided parts, outsourced services, etc. (including "regulated" data/records, etc.)
- responsibility for the actions of carrying out compliance can be delegated
- accountability under the law/regulation cannot be delegated

21 CFR 820.50

“Each manufacturer shall establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements.”

Translation for FDA investigators

“The objective of auditing the purchasing control subsystem is to verify that the manufacturer’s processes ensure that products, components, materials and services provided by suppliers are in conformity. This is particularly important when the product or service cannot be verified by inspection.”

- contract sterility services
- component manufacturers
- IT hosting services
- etc.

21 CFR 820.70

"(a) Where process controls are needed they shall include: (2) Monitoring and control of process parameters and component and device characteristics during product; (3) Compliance with specified reference standards or codes [CFRs] … (i) Automated processes. When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use…."

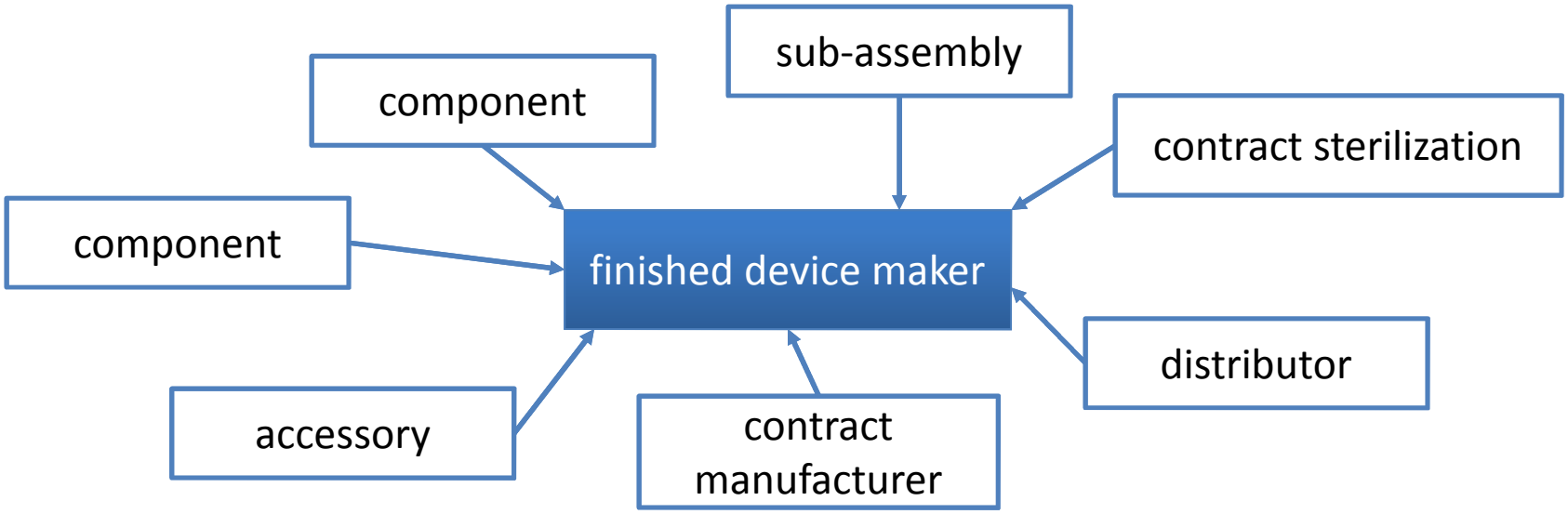
Translation for FDA investigators

"The Purchasing Controls subsystem should be considered a main subsystem for those manufacturers who outsource essential activities such as design and development and/or production to one or more suppliers:

- verify that the manufacturer evaluates and maintains effective controls over suppliers
- determine that the verification of purchased products and services is adequate"

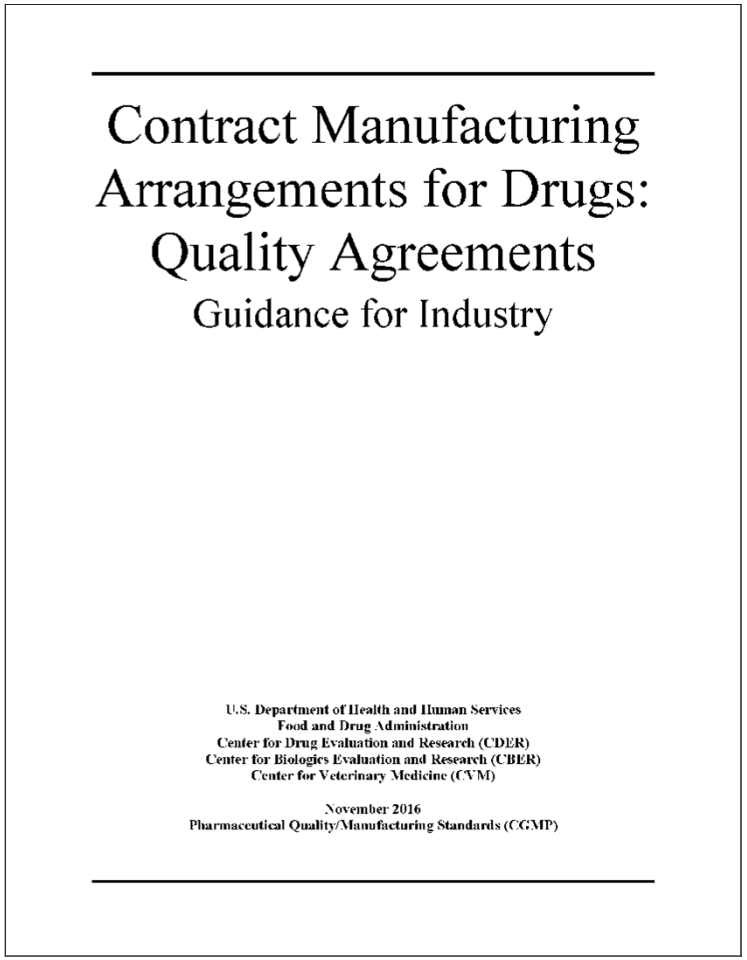
Gatekeeper Concept

Finished device manufacturer serves as the gatekeeper over all components, materials, and services brought into or used by the finished device – keys to the gate are compliance with your **contract/quality agreements**



Role of Quality Agreement

- review cGMP guidance
- used in FDA investigator training
- identify elements in quality agreement that FDA expects to see


Contract Manufacturing Arrangements for Drugs: Quality Agreements

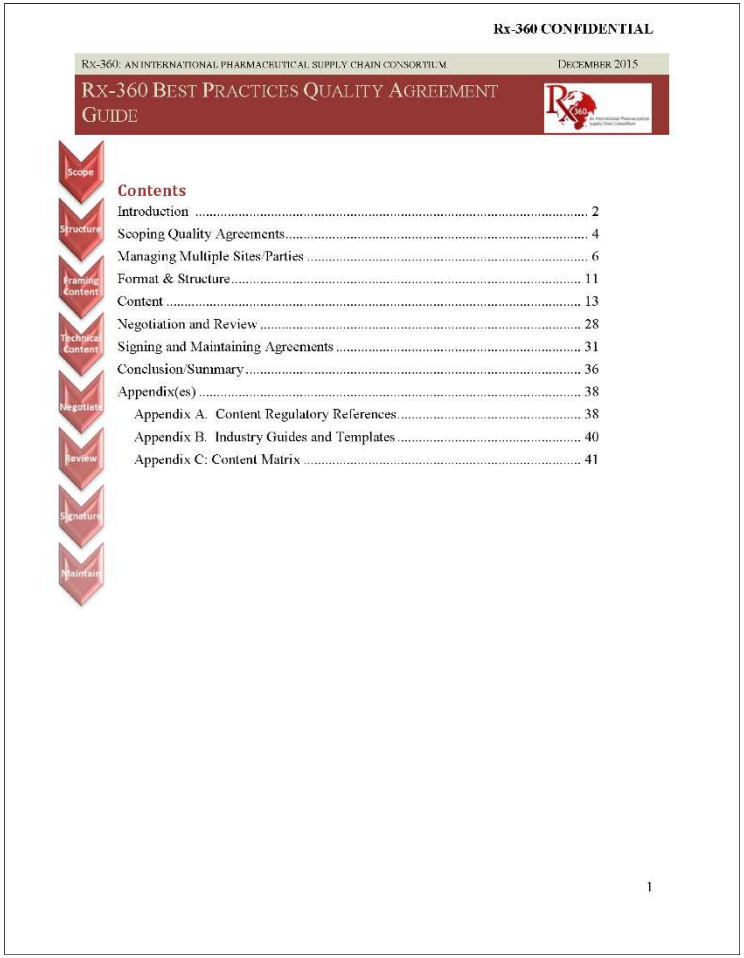
Guidance for Industry

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)

November 2016
Pharmaceutical Quality/Manufacturing Standards (CGMP)

Role of Quality Agreement

- Set of best practices that 100's of companies have had success with for quality agreements
- Largely pharma firms; some combo device firms
- Download (free) at http://rx-360.org/en-us/Resources/Documents-Guidelines-PTC-White-Papers



Rx-360 CONFIDENTIAL

Rx-360: AN INTERNATIONAL PHARMACEUTICAL SUPPLY CHAIN CONSORTIUM DECEMBER 2015

RX-360 BEST PRACTICES QUALITY AGREEMENT GUIDE

Scope
Structure
Framing Content
Technical Content
Negotiate
Review
Signature
Maintain

Contents

Introduction 2
Scoping Quality Agreements 4
Managing Multiple Sites/Parties 6
Format & Structure 11
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Negotiation and Review 28
Signing and Maintaining Agreements 31
Conclusion/Summary 36
Appendix(es) 38
Appendix A. Content Regulatory References 38
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Appendix C: Content Matrix 41

1

Document Records Responsibility and Transfer

Create records-location-transfer matrix

Clarify *if/when* transfers of records

- CMOs often don't like to hold onto records more than 4 years
- FDA may be expecting you to hold onto records for decades
- Make sure supplier cannot delete/destroy without your approval!

Record Type	Our Company	CMO	Transfer to Our Company?
DMR		XX	No
DHF	XX		N/A
Lot production QC records		XX	Yes – 2 years after lot distribution
Sterilization records		XX	Yes – 2 years after lot distribution

Document Activity and Workflow Responsibilities

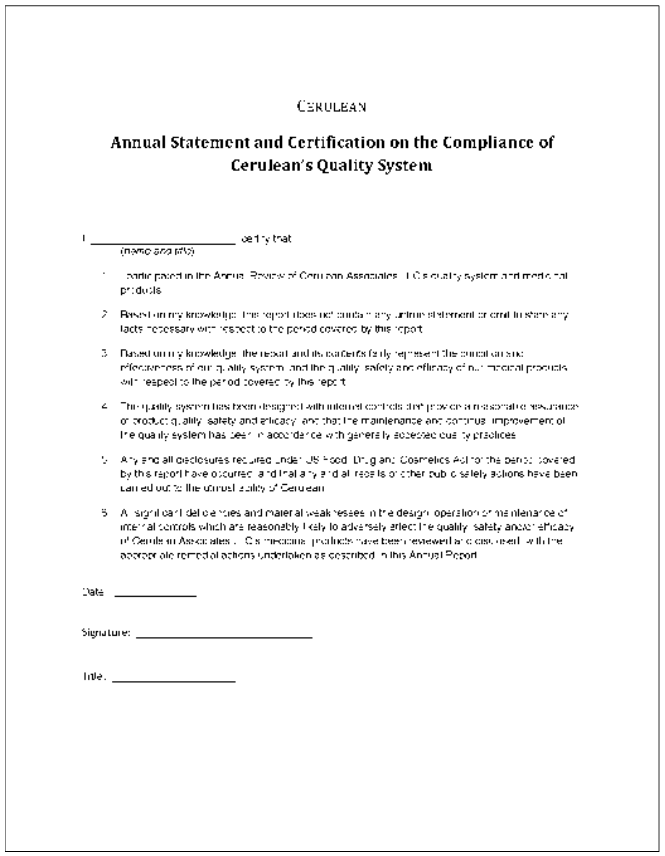
Create clear workflow of responsibilities

Think through actual workflow

- Make this easy for future review of contract and supplier re-evaluation
- Try to keep activity steps in order of real-world

Work Task	Our Company	Contract Sterilizer
Define sterilization specifications	XX	
Conduct test runs and verify sterility		XX
Sterilize product shipments (pallet-level)		XX
Validate sterilization process		XX
Verify and approve sterilization validation	XX	

Request Annual Statement of Compliance



CERULEAN

Annual Statement and Certification on the Compliance of Cerulean's Quality System

I _____ certify that
(name and title)

1. I am employed in the Annual Review of Cerulean Associates' US quality system and medical products
2. Based on my knowledge, this report does not contain any untrue statement of material fact or omit any facts necessary with respect to the period covered by this report
3. Based on my knowledge, the report and its contents fully represent the annual assessment of our quality system and the quality, safety and efficacy of our medical products with respect to the period covered by this report
4. The quality system has been designed with internal controls that provide a reasonable assurance of product quality, safety and efficacy, and that the maintenance and continual improvement of the quality system has been in accordance with generally accepted quality practices
5. Any and all disclosures required under US Food, Drug and Cosmetics Act for the period covered by this report have occurred, and that any and all recalls or other public safety actions have been carried out at the utmost quality of Cerulean
6. All significant deficiencies and material weaknesses in the design, operation or maintenance of internal controls which are reasonably likely to adversely affect the quality, safety and/or efficacy of Cerulean Associates' US medical products have been reviewed and discussed with the appropriate remedial actions undertaken as described in this Annual Report

Date: _____

Signature: _____

Title: _____

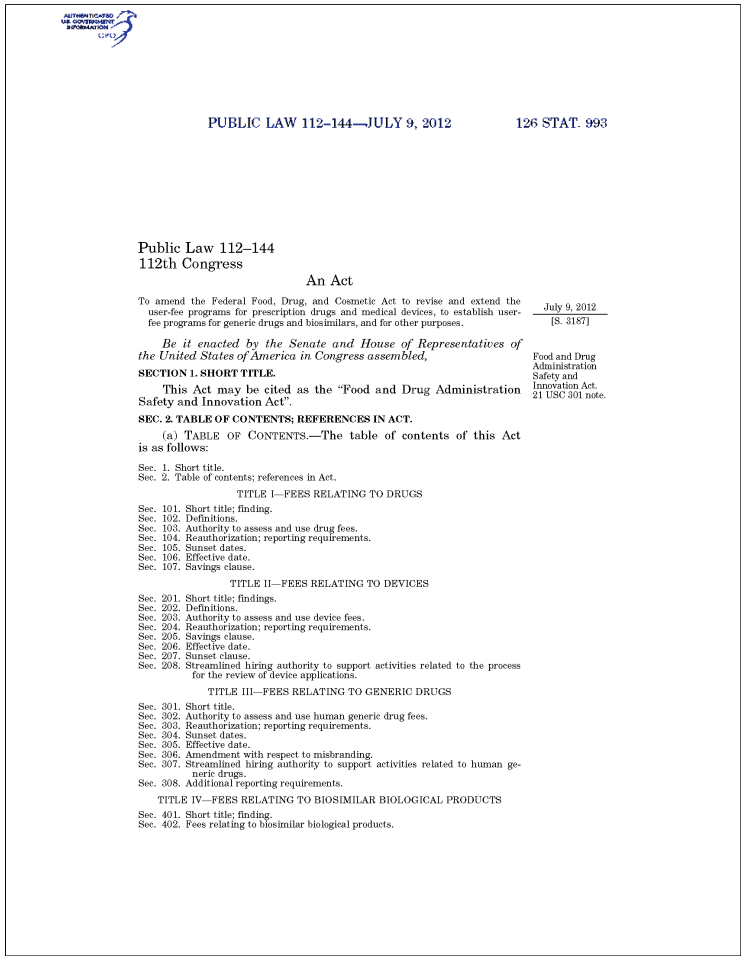
- Certifies critical supplier remains in compliance
- Signed by officer of their company
- States they are in compliance with QSR, cGMPs, ISO, etc. and/or your contractual terms
  - clarify no personnel debarred
- Summarizes what they looked at in order to make that statement
- Retain in supplier dossier

Clarify Re-Evaluation Triggers

Go beyond metrics or time…

- Failure of an FDA, EMA, or other IMDRF-based regulatory inspection
- Loss of ISO certification
- Awareness of public investigation into supplier (financial, FDA-driven, etc.)
- FDA issues relevant new guidance (or regulation) applicable to supplier's services, products, etc.
- Supplier is purchased, undergoes a merger, or moves site supplying you

Some Helpful Resources



PUBLIC LAW 112–144—JULY 9, 2012 126 STAT. 993

Public Law 112–144
112th Congress

An Act

To amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and medical devices, to establish user-fee programs for generic drugs and biosimilars, and for other purposes.

July 9, 2012
[S. 3187]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Food and Drug Administration Safety and Innovation Act.
21 USC 301 note.

SECTION 1. SHORT TITLE.

This Act may be cited as the "Food and Drug Administration Safety and Innovation Act".

SEC. 2. TABLE OF CONTENTS; REFERENCES IN ACT.

(a) TABLE OF CONTENTS.—The table of contents of this Act is as follows:

Sec. 1. Short title.
Sec. 2. Table of contents; references in Act.

TITLE I—FEES RELATING TO DRUGS

Sec. 101. Short title; finding.
Sec. 102. Definitions.
Sec. 103. Authority to assess and use drug fees.
Sec. 104. Reauthorization; reporting requirements.
Sec. 105. Sunset dates.
Sec. 106. Effective date.
Sec. 107. Savings clause.

TITLE II—FEES RELATING TO DEVICES

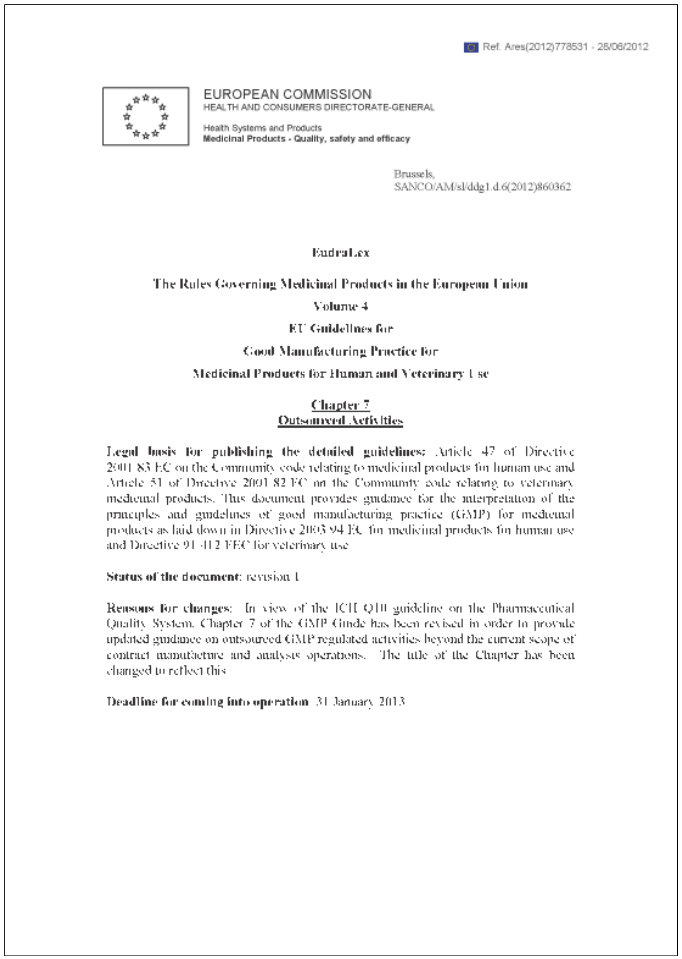
Sec. 201. Short title; findings.
Sec. 202. Definitions.
Sec. 203. Authority to assess and use device fees.
Sec. 204. Reauthorization; reporting requirements.
Sec. 205. Savings clause.
Sec. 206. Effective date.
Sec. 207. Sunset clause.
Sec. 208. Streamlined hiring authority to support activities related to the process for the review of device applications.

TITLE III—FEES RELATING TO GENERIC DRUGS

Sec. 301. Short title.
Sec. 302. Authority to assess and use human generic drug fees.
Sec. 303. Reauthorization; reporting requirements.
Sec. 304. Sunset dates.
Sec. 305. Effective date.
Sec. 306. Amendment with respect to misbranding.
Sec. 307. Streamlined hiring authority to support activities related to human generic drugs.
Sec. 308. Additional reporting requirements.

TITLE IV—FEES RELATING TO BIOSIMILAR BIOLOGICAL PRODUCTS

Sec. 401. Short title; finding.
Sec. 402. Fees relating to biosimilar biological products.



Ref. Ares(2012)778531 - 28/06/2012

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health Systems and Products
Medicinal Products - Quality, safety and efficacy

Brussels,
SANCO/AM/sl/ddg1.d.6(2012)860362

EudraLex

The Rules Governing Medicinal Products in the European Union

Volume 4

EU Guidelines for

Good Manufacturing Practice for

Medicinal Products for Human and Veterinary Use

Chapter 7
Outsourced Activities

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

Status of the document: revision 1

Reasons for changes: In view of the ICH Q10 guideline on the Pharmaceutical Quality System, Chapter 7 of the GMP Guide has been revised in order to provide updated guidance on outsourced GMP regulated activities beyond the current scope of contract manufacture and analysis operations. The title of the Chapter has been changed to reflect this.

Deadline for coming into operation: 31 January 2013

FDASIA 2012

Title VII – Drug Supply Chain

- Specifies types of suppliers that comprise the supply chain that FDA considers “regulated”
    - Contract manufacture organizations (CMO)
    - Contract research organizations (CRO)
    - Contract clinical sites
    - Contract laboratories
    - Contract sterilizers
    - Contract label and product insert designers
    - Contract distributors
    - Contract active pharmaceutical ingredient (API) makers

FDASIA 2012

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  - **Contract sterilizers**
  - **Contract label and product insert designers**
  - **Contract distributors**
  - Contract active pharmaceutical ingredient (API) makers

It will be almost impossible for you to argue that these supplier types are not "critical" suppliers

EMA cGMP

Updated **Chapter 7: GMP – Outsourced Activities**

http://ec.europa.eu/health/files/eudralex/vol-4/vol4-chap7_2012-06_en.pdf

For Non-Off-the-Shelf Materials/Services:

- Requires written contracts
- Contract must:
  - specify responsibilities AND communication
  - clearly define which party is responsible for each step of outsourced activity
- Contract ***should*** **allow Contract Giver to audit the supplier**
- Contract ***should*** **specify that records are to be kept (or otherwise given to) the Contract Giver** and not retained by the supplier

EMA cGMP

Updated **Chapter 7: GMP – Outsourced Activities**

http://ec.europa.eu/health/files/eudralex/vol-4/vol4-chap7_2012-06_en.pdf

Responsibility of Contract Giver

- Accountable for all supplied materials and services
  - includes any records required by regulation/law or to prove conformance
- *Prior to contract*, **Contract Giver must assess supplier**
- Throughout contract, Contract Giver must **monitor and continuously evaluate supplier performance**

EMA cGMP

Updated **Chapter 7: GMP – Outsourced Activities**

http://ec.europa.eu/health/files/eudralex/vol-4/vol4-chap7_2012-06_en.pdf

Responsibility of Supplier

- Responsible for carrying out terms of contract
- Not directly accountable for compliance with cGMPs unless part of normal operations (*e.g.*, Contract Giver cannot delegate accountability for cGMP compliance to supplier)

Key Points

- Sponsor (you) are always held legally accountable
- Sponsor may delegate individual work task responsibility
- Supplier is only accountable to your contractual terms
- EU cGMP chapter 7: Outsourcing is a helpful resource

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