Combination Products: QS & Design Controls Requirements

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Presentation Goals

- Introduction to combination product CGMP requirements
- Present combination products
- Summarize combination product QSR requirements
- Explain key QSR provisions related to Design Controls
- Provide references for additional information

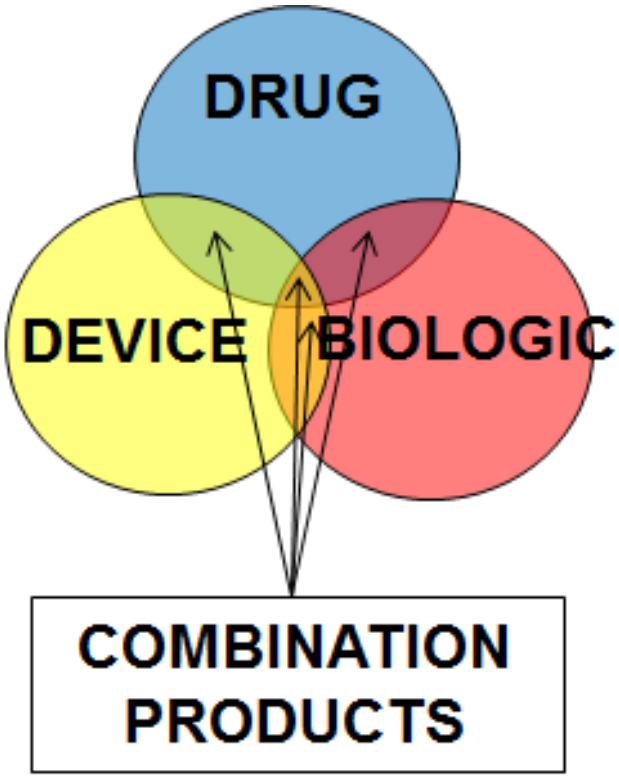
Definitions

Combination Product

- A product comprised of two or more types of medical products (e.g., drug and device, drug and biological product, or all three together).
- Not a product comprised of only two or more of the same type of medical product (e.g., drug and drug, device and device, or biologic and biologic).
- Not a medical product combined only with a non-medical product (e.g., drug and food, drug and cosmetic). *See* 21 USC 353(g).

Constituent part: A drug, device, or biological product that is part of a combination product. *See* 21 CFR 4.1.

At a glance


DRUG
DEVICE
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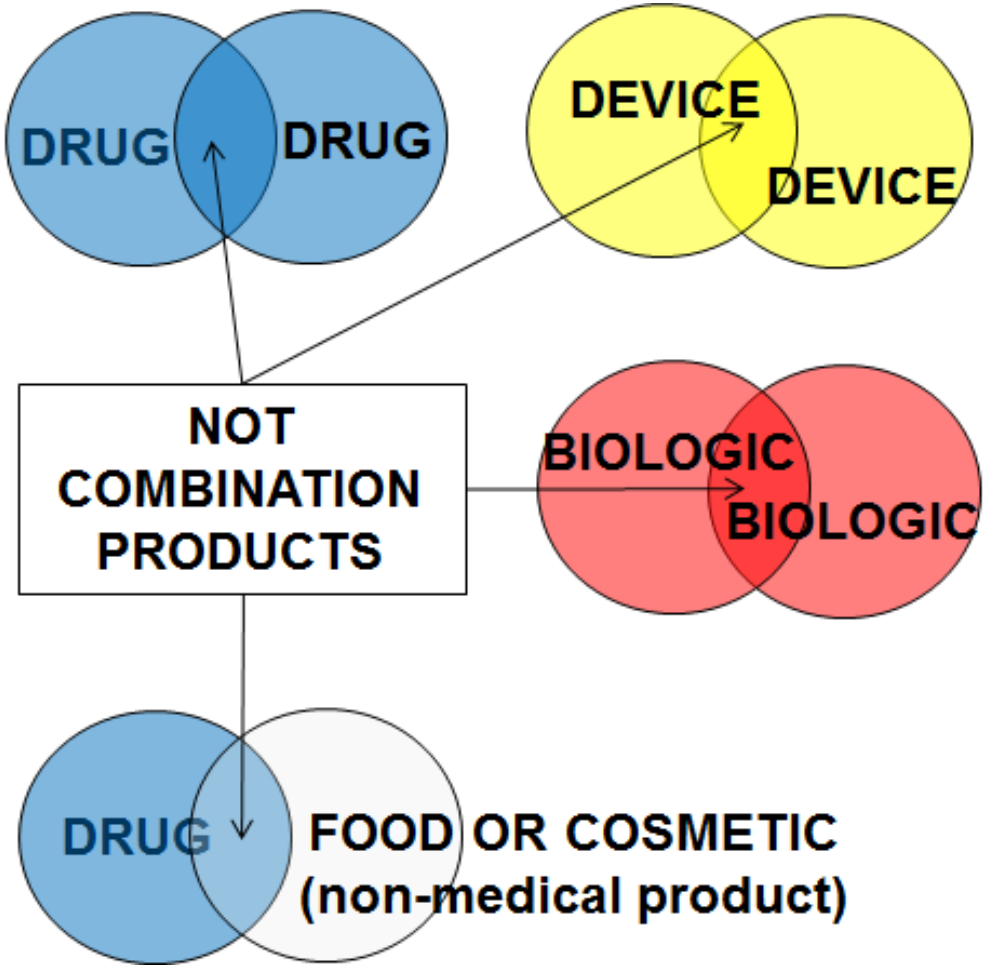
COMBINATION PRODUCTS


DRUG
DRUG
DEVICE
DEVICE
NOT COMBINATION PRODUCTS
BIOLOGIC
BIOLOGIC
DRUG
FOOD OR COSMETIC
(non-medical product)

Types

	"Cross-labeled"	"Co-packaged"	"Single-entity"
Description	Constituent parts sold separately	Constituent parts packaged together	Chemically or physically combined constituent parts
Examples	• Certain light-emitting devices and light-activated drugs • Certain imaging devices and imaging agents	• First-aid or surgical kit • Syringe packaged with vial of drug • Toothbrush packaged with fluoride toothpaste	• Drug-eluting stent • Prefilled syringe • Transdermal patch • Bone void fillers with drugs
Reference	21 CFR 3.2(e)(3), (4)	21 CFR 3.2(e)(2)	21 CFR 3.2(e)(1)

cGMP Regulatory framework

- The articles in combination products retain their regulatory status as drugs, devices, biological products, and human cellular and tissue-based products (HCT/Ps).
- Finished combination products are subject to the CGMP requirements applicable to each constituent part (drug, device, biologic, and/or HCT/P) in the product.
- Combination products were subject to these requirements before 21 CFR part 4 came into effect.
- 21 CFR part 4 clarifies CGMP duties and how to demonstrate compliance with them.

Applicable cGMPs

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Reference	21 CFR 3.2(e)(3), (4)	21 CFR 3.2(e)(2)	21 CFR 3.2(e)(1)

Constituent parts are subject to all CGMP requirements applicable to ***that type*** of article (e.g., drug CGMPs if article is a drug).

Applicable cGMPs

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Must comply with both **drug** and **device** cGMPs. **Streamlined approach** is available to show compliance with drug and device CGMP requirements.

Co-packaged and single-entity

cGMP OPTIONS

Non-streamlined approach	OR	Streamlined approach
Demonstrate compliance with both drug CGMPs (21 CFR 210 and 211) and device QS regulations (21 CFR 820) **in their entirety.**		Demonstrate compliance with both regulations by demonstrating compliance with **ONE** complete set of CGMP provisions and demonstrating compliance with only **provisions specified in 21 CFR 4** from the other.

Convenience kits

- Manufacturers of "convenience kits" are only obligated to implement cGMP requirements for the assembly, packaging, labeling, sterilization, or other processing they perform for the kit.

- A convenience kit (see 78 FR 4310, comment 5) ONLY contains products that are:
  - Also legally marketed independently, AND
  - Included in the kit as already packaged for independent marketing and with the same labeling as required for independent marketing.

Primary mode of action

- The primary effect of the combination product:
  - Chemical – drug
  - Non-chemical effect – device
- The FDA assigns primary mode of action

21 CFR Part 3, Definition of Primary Mode of Action of a Combination Product

Streamlined approach to cGMPs

- Can you use 21 CFR part 820, medical devices cGMPs, if your combination product's primary mode of action is as a drug?

- What about using the drug cGMPs if the primary mode of action is as a device?

Other applicable regulations

Biologic constituent part—

- Applicable requirements in 21 CFR parts 600 through 680.
  - Drug or device cGMPs will apply depending on product type regardless whether is a combination product.

HCT/P constituent part—

- Applicable Current Good Tissue Practices (CGTPs) for HCT/Ps under part 1271 must be met.
  - Additional considerations: see FDA issued guidance documents: https://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/tissue/default.htm

21 CFR Part 820 cGMP call outs 21 CFR 4.4(b)(1)

DRUG CGMP-BASED STREAMLINED APPROACH

Overview- called out regulations

- 820.20 – Management Controls
  - Top-level corporate commitment to product quality.
- 820.30 – Design Controls
  - Proactive consideration of product intended uses, user needs, and associated requirements:
    - "designing-in" quality
    - allows earlier recognition of problems and appropriate time to implement corrections.
  - Incorporation of relevant expertise at various preproduction phases.

Overview- called out regulations

- 820.50 – Purchasing Controls
  - Manage products and components supplied as well as services provided by contractors and consultants.
  - Incorporates supplier and component qualification.
- 820.100 – CAPA
  - Tracking sources of quality data and responding when needed to correct existing and/or prevent potential problems.
  - Ensure the solution is effective and doesn't create a new problem.
- 820.170 – Installation and 820.200 – Servicing
  - Applicable to products which must be installed and/or serviced.

820.20 Management Responsibility

- Helps insure executive commitment to quality.

	Applicability to Combination Product Manufacturer
Drug Constituent Part	**Yes**, only when used in the combination product
Device Constituent Part	**Yes**
Combination Product as a Whole	**Yes**

- Compare with 21 CFR 211.122 (Quality Control Unit) requirements, which incorporates some quality oversight responsibilities, and address the missing ones.

820.20 Management Responsibility

- Quality policy – implemented at all levels of the organization.
- Quality plan – how the requirements for quality of the product will be met.
- Quality system procedures
- Organizational structure:
  - Responsibility (higher organizational level than required by 211), authority, and resources.
  - Management representative – appointed by management with executive responsibility. Responsible for establishment, maintenance and report of quality system requirements.
- Management reviews

820.30 Design Controls

- Design controls help insure a focus on “designing-in” quality and incorporation of relevant expertise during the development process.

	Applicability of 820.30 to a Combination Product Manufacturer
Drug Constituent Part	**Yes**, drug product development activities related to its use in the combination product
Device Constituent Part	**Yes**, device product development activities related to its use in the combination product
Combination Product as a Whole	**Yes**

- Drug cGMPs don’t have provisions specific to product development. However, consider requirements for production and process controls at 211.110 and Laboratory controls at 211.160.

820.30 Design Controls

- Design and development plan.
- Design input. Requirements that address the intended use of the device, including the needs of the user and patient.
- Design output. Defined in terms that allow adequate evaluation of conformance to design input requirements. Includes acceptance criteria and identify design outputs essential for the proper functioning of the product.
- Design reviews. Includes an individual(s) who does not have direct responsibility for the design stage being reviewed.
- Design verification. Design output meets the design input requirements.
- Design validation. Devices conform to defined user needs and intended uses and includes testing of production units under actual or simulated use conditions. Includes software validation and risk analysis.
- Design transfer.
- Design Changes.
- Design History File.

Combination Products Considerations

When do design controls **"start"** for combination products?

- At the point that a company commits to pursue a commercial product (Reference QS Reg Preamble, Comment 62).
- Initiation of design controls varies depending on the combination product development process:

  Novel combination product, including those with novel constituent parts, will typically result in earlier initiation of design controls during the combination product development process. The complexity of the resulting design history documentation is also likely to increase for novel combination products.

Combination Products Considerations

- Each combination product (or product family) requires a Design History File (DHF). The DHF should reference all necessary design control elements, and be readily accessible.
- Actual DHF information may reside in various locations (e.g., for constituent parts developed by a specification developer, design controls information related to that constituent part may reside at that entity).
- Design changes for the combination product:
  - Consider the impact on the combination product as a whole of design changes to any constituent part.
  - Document the changes and change process.
- Leverage drug development processes and practices during the design process.
- Using existing drug terminology is acceptable.

Combination Products Considerations

The finished combination product manufacturer and product owner are responsible for design and development planning

To use existing or off-the-shelf finished product as a constituent part:

- Ensure that it meets appropriate design requirements for the combination product to be *safe and effective.*
- Understand the constituent part's existing design specifications to recognize need to modify the existing product for use as part of the combination product.
  - Manufacturer must assess what design control activities must be performed to ensure safety and effectiveness of the combination product.
  - DHF must address all design issues resulting from the *combination* of the constituent parts.

Risk Analysis

- "Risk Analysis" in 21 CFR 820.30 is consistent with "risk identification/risk assessment/risk control" as described in the Risk Management documents ISO 14971 Standard for devices and ICH Q9 Guidance for drugs.
- Should begin early in development process for the combination product and be evaluated/revised throughout product life-cycle.

Risk analysis

Start **early** in the design process continue **throughout the lifecycle** for the product

- Some risks are identifiable during initial design development
- Some risks become apparent later in product development, during premarket review, or based on postmarked experience

Identify unacceptable risks so that they can be mitigated

- Influences design control and purchasing controls

Risk analysis should include considerations for the combination product **as a whole**.

- Existing risk analysis for products used as constituent parts may be relevant.

Combination Products Considerations

Remediation of Design History Files

- Design controls apply to all combination products developed (or modified) after 1996; FDA has seen inconsistent application for products developed prior to promulgation of 21 CFR Part 4.
- Perform gap analysis and collect (and generate, if necessary) information for their DHFs.
- If remediation is necessary, use a risk-based approach – identify gaps and focus on remediation activities that are necessary to ensure continued product safety and effectiveness and support future design changes to the product.
- No necessary to re-create design and development plans and design reviews for already marketed products. Expected that such information will be generated on a going-forward basis as product designs are modified.

820.50 Purchasing Controls

- Helps control products and services procured from suppliers for use in the combination product.

	Applicability of 820.50 to a Combination Product Manufacturer
Drug Constituent Part	**Yes**, for the drug and components used in a combination product
Device Constituent Part	**Yes**
Combination Product as a Whole	**Yes**

820.50 Purchasing Controls

Establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements.

- *Evaluation of suppliers, contractors, and consultants*
  - Evaluate potential suppliers and define the type and extent of control to be exercised over them based on the evaluation results. May design and conduct evaluations based on factors such as the risks associated with the supplied product or service and complexity of the specifications for it.

- *Purchasing data*
  - Establish and maintain records of acceptable suppliers for purchased products and services, and establish and maintain data that clearly describe or reference the specified requirements for products and services received (e.g., contracts with relevant terms).

Combo Product Considerations

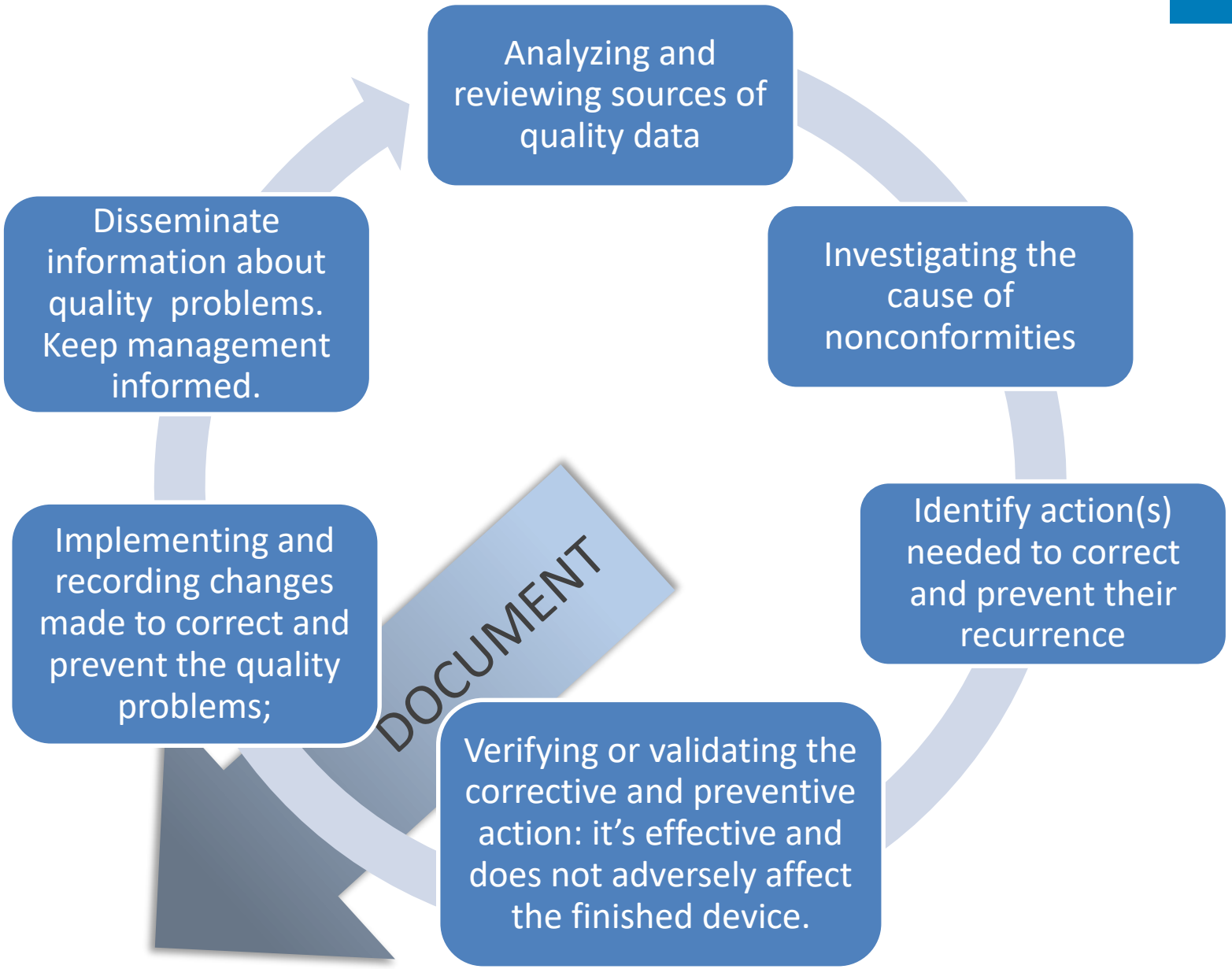
Ensure Supplier Agreement Includes a 'Notification of Changes to the Supply'

- Contracts/agreements with suppliers and contract manufacturers
- Confirmation that suppliers have adequate agreements between themselves or sub-suppliers
- When supplier won't notify of changes, have controls in place to identify them, and take action.

21 CFR 211.84 Testing Requirements

- Drug components
- Container closure systems (may include the device constituent parts or subparts)
- Qualifications of Consultants at 21 CFR 211.84

820.100 CAPA


Analyzing and reviewing sources of quality data
Investigating the cause of nonconformities
Identify action(s) needed to correct and prevent their recurrence
Verifying or validating the corrective and preventive action: it's effective and does not adversely affect the finished device.
DOCUMENT
Implementing and recording changes made to correct and prevent the quality problems;
Disseminate information about quality problems. Keep management informed.

CAPA Considerations

Product owner CAPA duties are comprehensive, applying to all relevant facilities and all appropriate measures for the product.

For products with *multiple* manufacturers, the scope of the duties for each manufacturer parallels and depends upon the scope of the activity undertaken at that manufacturer's facility.

The applicant and any other manufacturer(s) must ensure an comprehensive review of activities is undertaken at facilities that are relevant to determining the root cause of manufacturing problems, deviations, or nonconformities.

Combination Product Considerations

- CAPAs can be triggered based on problems identified in constituent parts and/or the combination product as a whole.
- The CAPA process for combination products should consider implications of corrective and preventive actions to all constituent parts and the combination product as a whole, including during effectiveness checks.
- Manufacturers should consider whether corrective and preventive actions have broader implications.
  - For example, if root cause of an issue is associated with quality of a particular supplied product, it may be appropriate to assess whether any other materials from that supplier should also be evaluated.

820.170 Installation, 820.200 Servicing

Insures that, where applicable, installation and servicing activities, which often occur at a customer site, are adequately controlled and documented.

	Applicability of 820.170 & 820.200 to a Combination Product Manufacturer
Drug Constituent Part	**No**
Device Constituent Part	**Yes**, when the device constituent part needs installation and servicing requirements.
Combination Product as a Whole	**Yes**, only when requirements are applicable to the combination product as a whole.

Combination Product Considerations

- Generally applicable only to large, durable medical devices, typically part of cross-labeled combination products (e.g., multi-use contrast agent delivery systems, tissue targeted drug delivery systems, etc.).
- In most cases the medical device will be manufactured at a separate facility and the manufacturer will be subject only to 21 CFR 820.

Re-Cap

- Definition of a combination product and types.
- CGMP regulatory environment – 21 CFR part 4.
- Individual 21 CFR part 820 call outs in part 4 streamlined approach:
  - 820.20 – management controls
  - 820.30 – design controls
  - 820.50 – purchasing controls
  - 820.100 – CAPA
  - 820.170 and 200 – Installation and Servicing

Last words …

Consider that cGPM requirements may also be:

- Product specific requirements:
  - Could be shared by several facilities.
  - Design controls, Corrective and Preventive Action (CAPA), Management responsibility.
- Facility specific:
  - Requirements for testing of the product by a specific facility.
  - Controls over the supplies brought into the facility (Purchasing Controls).

THANK YOU

Questions?

ELECTRONIC RESOURCES

Regulations

- **Regulations**:
  - "Current Good Manufacturing Practice Requirements for Combination Products," Final Rule
    https://www.federalregister.gov/documents/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products
  - 21 CFR Part 3, Definition of Primary Mode of Action of a Combination Product
    https://www.gpo.gov/fdsys/pkg/FR-2005-08-25/pdf/05-16527.pdf

- **Companion Guidance**:
  - Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (January 2017)
    http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

Other guidance documents 1

- Preamble to the Quality System Regulation
  (http://www.gpo.gov/fdsys/pkg/FR-1996-10-07/pdf/96-25720.pdf)
- GHTF Final Document: Quality Management System – Medical Devices – Guidance on the Control of Products and Services Obtained from Suppliers, Dec 2008
  (http://imdrf.org/docs/ghtf/final/sg3/technical-docs/ghtf-sg3-n17-guidance-on-quality-management-system-081211.pdf)
- Global Harmonization Task Force (GHTF) Final Document Quality management system – Medical Devices – Guidance on corrective and preventive action and related QMS processes, Nov 2010
  (http://imdrf.org/docs/ghtf/final/sg3/technical-docs/ghtf-sg3-n18-2010-qms-guidance-on-corrective-preventative-action-101104.pdf)
- FDA Guidance for Industry, Q10 Pharmaceutical Quality System, April 2009
  (http://www.fda.gov/downloads/Drugs/Guidances/ucm073517.pdf)
- Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations
  (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070337.pdf)

Other guidance documents 2

- Implementation of risk management principles and activities within a Quality Management System, May 2005

  (http://www.imdrf.org/docs/ghtf/final/sg3/technical-docs/ghtf-sg3-n15r8-risk-management-principles-qms-050520.pdf)
- ICH Q8(R2) Pharmaceutical Development, Nov 2009 (http://www.fda.gov/downloads/Drugs/Guidances/ucm073507.pdf)
- ICH Q9 Quality Risk Management, Jun 2006 (http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073511.pdf)
- Guidance, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production

  (http://www.fda.gov/downloads/Drugs/Guidances/ucm070287.pdf)
- FDA Guidance Contract Manufacturing Arrangements for Drugs: Quality Agreements, May 2013 (https://www.fda.gov/downloads/drugs/guidances/ucm353925.pdf)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