FDA 21 CFR Part 4 Requirements – Impact on Drug Delivery Systems

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Presentation Overview

- Definitions
- Impact on Drug Delivery Systems
- Combination Product Regulatory Framework (US)
- 21 CFR Part 4 cGMP Requirements:
  - Applicability
  - Management Controls
  - Design Controls
  - Supplier Controls
  - Corrective and Preventive Actions (CAPA)
  - 21 CFR 210/211 (Drug) Requirements
  - Post Market Surveillance Reporting Requirements

Disclaimer

- Not a detailed training on
  - Device Quality System Requirements (QSR) – 21 CFR 820
  - Drug/Biologic Good Manufacturing Practices (cGMP) – 21 CFR 210/211
  - Combination Procduct cGMP – 21 CFR 4

- Opinions for consideration based on general observations
- From a device regulation perspective
- Impact on Combination Product manufatures
- Recommendations for Drug Delivery Systems

Definitions (simplified)

- Combination Product: (21 CFR Part 3) a combination product (CP) is a product composed of any combination of drug, device or biological product.
  - Device - Drug
  - Device - Biologic
  - Drug - Biologic
  - Device - Drug - Biologic
- Combination Product Types: (21 CFR 3.2 (e))
  - Single entity
  - Co-packaged
  - Cross-labeled
- Constituent Parts: Drug, device and biologic products in the combination products are referred to as “constituent parts”.
- Component: (21 CFR 820.3 and 210.3) ingredients, raw material, plastic components, sub-assemblies.

Impact on Drug Delivery Systems

- A product which consists of a drug delivery system (DDS) that is intended to be used with a specific drug/biologic to achieve a common purpose, is a combination product.
- The drug delivery system is the device constituent part.
- The drug/biologics is the drug/biologic constituent part.
- If the system contains a plunger, the plunger is a component of the whole combination product. Other components may include the packaging material, the syringe, the drug excipient, etc…

Combination Product Regulatory Framework

- Final rule: 21 CFR Part 4
  - cGMP Requirements for Combination Products (effective July 22, 2013)
- Draft guidance (January 2015)
- Final guidance (January 2017)
- Notes:
  - Part 4 does not introduce new requirements but aligns the existing requirement (21 CFR 210/211, 820).
  - Investigators with expertise in pharmaceuticals and medical devices are sent to combination product manufactures.

21 CFR Part 4 cGMP Requirements: Applicability

Type	Device Only	Drug Only	Combination Product
Examples	Manufactures only the auto injector	Manufactures only the epinephrine	Final Assembly/Final product owner/Sponsor
Regulations	QSR - 21 CFR 820	cGMP - 21 CFR 210/211	21 CFR Part 4
	MDR – 21 CFR 803	AER – 21 CFR 314	PMRS - Combination

Similarities:

- Focus on management, organization, and personnel
- Documentation and record keeping requirements
- Flexible in some aspects and prescriptive in others
- Objective is to ensure control and assure the quality of the manufactured products

21 CFR Part 4 cGMP Requirements: Applicability

- Facilities subject to 21 CFR Part 4, can chose to use a “streamlined approach” to comply with the cGMP requirements (21 CFR 4.4(b)(1)):
  - Option 1: Drug based operating system by complying with:
    - all drug cGMP requirements (21 CFR 210/211)
    - biological product - HCT/Ps requirements (21 CFR 600-680)
    - applicable device requirements
      - Management Controls (21 CFR 820.20)
      - Design Controls (21 CFR 820.30)
      - Supplier Controls (21 CFR 820.50)
      - Corrective and Preventive Action – CAPA (21 CFR 820.100)

21 CFR Part 4 cGMP Requirements: Applicability

- Option 2: Device based operating system by complying with:
  - all device QSR requirements (21 CFR 210/211)
  - applicable drug/biological product requirements
    - Testing and approval or rejection of components, drug product containers, and closures (21 CFR 211.84)
    - Calculation of yield (21 CFR 211.103)
    - Tamper-evident packaging for OTC drugs (21 CFR 211.132)
    - Expiration dating (21 CFR 211.137)
    - Testing and release for distribution (21 CFR 211.165)
    - Stability testing (21 CFR 211.166)
    - Special testing requirements (21 CFR 211.167)
    - Reserve Samples (21 CFR 211.170)
    - Applicable biological product - HCT/Ps requirements (21 CFR 600-680)
- Notes:
  - FDA expects the selected approach to be documented (i.e. quality manual)
  - Option chosen can be unrelated to the Primary Mode of Action (PMOA)
  - Human Cells, Tissues, and Cellular and Tissue-Based Products = HCT/Ps

21 CFR Part 4 cGMP Requirements: Management Controls (820.20)

- For CP manufactures (i.e. DDS which is also owner/performs final assembly)
  - Whole organization (combination product and constituent parts)
  - Organizational structure (diagram/table):
    - “virtual owners”
    - coordination and oversight of multiple sites
    - clear description of the functions and responsibilities
  - Quality policy/QMS requirements are understood, implemented, and maintained at all levels (quality manual)
    - Management reviews – all QS departments and sites
    - Audits (all part 4 requirements)
    - Training - Not explicit in drug cGMP regulations. Limited to job responsibilities (21 CFR 211.22).

21 CFR Part 4 cGMP Requirements: Management Controls (820.20)

- For DDS manufactures (independent/non-owner/suppliers)
  - Drug manufactures/Virtual owners often rely on device manufactures to assist in meeting device requirements.
  - Collaboration through Quality Agreements.
    - Responsibilities clearly defined.
  - If MC responsibility is deferred to the DDS
    - Coverage of all part 4 requirements.
    - Drug and Device requirements (management reviews, training, and audit programs).
  - Ultimate responsibility lies with the finished product owner.

21 CFR Part 4 cGMP Requirements: Design Controls (820.30)

- For CP manufactures
  - Overall finished combination product
  - All phases of development
  - New concept for pharmaceutical manufactures
  - Quality agreement with outsourced specification developers
    - Compliant DC requirements.
    - Control over drug-device interactions
    - Understanding of all user needs and device specification requirements
  - Design and Development Plan
    - Specify responsibilities of all involved parties.
    - Quality Agreements

21 CFR Part 4 cGMP Requirements: Design Controls (820.30)

- For CP manufactures
  - User needs, design inputs and outputs
    - Identification of critical specifications
    - Use of traceability matrix
    - Device:
      - Intended population user needs (complexity, legibility, human factors, etc…)
      - Dose accuracy, material, and biocompatibility, etc…
      - Force to activate, dispensing time, etc…
    - Drug
      - Formulation/viscosity to be compatible with device
      - Maintenance of potency, quality, efficacy, safety, stability, etc…

21 CFR Part 4 cGMP Requirements: Design Controls (820.30)

- For CP manufactures
  - Design Verification
    - stability and product retention programs (21 CFR 211 Subpart E).
      - Device with drug (finished combination product)
    - Packaging and labeling operation (21 CFR 211.130)
    - Laboratory controls (21 CFR 211 Subpart I) - drug product components meet specifications when combined with the device constituent parts.
    - component parts and drug product containers and closures requirements (21 CFR 211 Subpart E),
      - leachables, biocompatibility and extractables on primary container (drug-device compatibility)
      - To be expanded and considered for remaining device constituent components.
    - Valid statistical techniques

21 CFR Part 4 cGMP Requirements: Design Controls (820.30)

- For CP manufactures
  - Design Validation:
    - Performed under defined operating conditions on initial production units, lots or batches.
      - Finished combination product
    - Conformance to defined user needs and intended uses include testing of production units under actual or simulated conditions of use
      - Human Factors (Home use, lay users, IFU, PIL, etc…)
    - Include software validation and risk analysis, where appropriate
  - CP Risk Management
    - No negative drug-device interactions
    - Pre- and post-market activities
      - use related risks (HF, usability studies, etc…)
      - changes to the design or manufacturing process
      - capture information from quality sources from all facilities involved

21 CFR Part 4 cGMP Requirements: Design Controls (820.30)

- For CP manufactures
  - Change control
    - Design and development, and manufacturing
    - Some difference to change controls expected per 21 CFR 211
      - Draft guidance, “Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA.”
    - Clearly established process - multiple sites and suppliers of constituent parts.
    - Verifying/Validating/CAPA effectiveness
  - Design transfer
    - Critical specifications
      - Controlled process qualification/validation
      - Manufacturing controls/Critical to Quality (CtQ) attributes considerations
      - Supplier controls
      - Final acceptance activities
  - Notes
    - Class 1 devices/legacy devices DC exempt.
    - Class 1 device/legacy devices + drug = CP, not exempt.

21 CFR Part 4 cGMP Requirements: Design Controls (820.30)

For DDS manufactures

- A finished design for a DDS approved for one drug should not be used for a new drug without proper evaluation/validation with that new drug. (platform devices)
- Validation shall be performed on the final CP with the specific drug and for the intended use.
- A quality agreement and/or CP specific design control procedures
  - Difference between the design control requirements for the device constituent part vs those required for the overall CP.

21 CFR Part 4 cGMP Requirements: Supplier Controls (820.50)

- For CP manufactures
  - “Virtual firms”
  - Supplier Controls procedures -
    - Control of multiple sites
    - Covers all suppliers including service provides (specification developers, consultants, etc…)
    - Risk based supplier evaluation/selection
    - Extent of control
      - Audit frequency
      - Acceptance activities (sampling plan) – purchasing data
      - Records of acceptable suppliers

21 CFR Part 4 cGMP Requirements: Supplier Controls (820.50)

- For CP manufactures
  - Quality Agreements
    - CAPA
      - Purchasing record evaluation/trending
      - Criteria for CAPA triggers
      - Non-conformance reviews
      - Complaint reviews
    - Notification of changes (design/manufacturing) for review/approval before implementation to ensure they will not affect the final CP (different in drug GMPs)
    - Post-market surveillance reporting requirements (record keeping/sharing/reporting)
- For DDS manufactures
  - Informing customers/owner of changes before implementation
  - Informing customers of potential concerns learned from feedback received from other customers or similar products

21 CFR Part 4 cGMP Requirements: CAPA (820.100)

- For CP manufactures
  - Overall organization
    - Monitoring and evaluation of quality data from all levels (including suppliers)
      - Complaints Handling
        - uniformity of handling
        - linkage with MDR
        - recall assessment
      - Non-conforming materials, audits, change control, manufacturing data, purchasing records, etc…
    - Trending criteria for CAPA triggers
  - Communication
    - Internal parties (quality plan)
    - Suppliers (quality agreements)

21 CFR Part 4 cGMP Requirements: CAPA (820.100)

- For CP manufactures
  - Procedures for the
    - Identification of existing and potential causes of nonconforming practices and products;
    - Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and,
    - Verification or validation of the actions taken.
  - More prescriptive in comparison to drug/biologic cGMP (21 CFR 211.198(b) and 211.22) - (21 CFR 600.14 and 21 CFR 606.171).
- For DDS manufactures
  - Quality agreement to clearly identify information to be communicated to sponsor for trending/approval/sharing (i.e. for CAPA, complaints, PMSR)
  - Approval of changes resulting from CAPAs from sponsors before implementation

21 CFR Part 4 cGMP Requirements: Drug Requirements (210/211)

- Generally, more prescriptive then device production and process controls and acceptance activity requirements. (21 CFR 820)
- Testing and approval or rejection of components, drug product containers, and closures (21 CFR 211.84)
- Calculation of yield (21 CFR 211.103)
- Tamper-evident packaging for OTC drugs (21 CFR 211.132)
- Packaging and labeling operation (21 CFR 211.130)
- Expiration dating (21 CFR 211.137)
- Testing and release for distribution (21 CFR 211.165)
- Stability and reserve samples requirements (21 CFR 211.166(b) and 21 CFR 211.170, respectively)
- Retention and holding requirements (21 CFR 211 Subparts E and H)
    - To assure that drug components are still acceptable for further processing
    - Affected by drug products that have sterility and hold dates
    - Retention for effective complaint investigation.

21 CFR Part 4 cGMP Requirements: Manufacturing Considerations

- Special testing requirements (21 CFR 211.167)
- Laboratory controls (21 CFR 211 Subpart I)
  - to confirm that drug product components continue to meet specifications when combined with the device constituent parts.
- Statistical techniques procedure (21 CFR 820.250)
  - Process validation (21 CFR 820.75)
    - cannot be fully verified
    - process deviations/changes occur- revalidation where appropriate before implementation if verification is not possible or sufficient
- Change controls/Document controls (21 CFR 820.40)
  - design history files (DHF) (21 CFR 820.30), device master record (21 CFR 820.181) and device history records (DHR) (21 CFR 820.184)
  - drug master file (DMF) - the manufacturing and processing of the drug (21 CFR 314.420).

21 CFR Part 4 cGMP Requirements: PMSR (brief)

- PMSR Regulation 21 CFR 4 (effective January 19, 2017)
- For now based on application Type
  - Device application (510(k), IDE, PMA, HDE, etc…), comply with 21 CFR 803 and 806
  - Approved through NDA or ANDA, comply with 21 CFR 314
  - Marketing authorization under a BLA, comply with 21 CFR 600 and 606

21 CFR Part 4 cGMP Requirements: PMSR (brief)

- July 19, 2018 - 18 months after the effective date. More than one submission may be required.
- Device
  - 5-day reports (21 CFR 803.3/803.53)
  - Malfunction reports (21 CFR 803.50)
  - Correction and removal reports (21 CFR 806.10)
- Drug
  - Field alert reports (21 CFR 314.81)
  - 15-day reports (21 CFR 314.80)
    - 30 calendar days instead of 15 calendar for product approved/cleared under a device application
- Biologics
  - Biological product deviation reports (21 CFR 600.14/606.171)
  - 15-day reports (21 CFR 600.80)
    - 30 calendar days instead of 15 calendar for product approved/cleared under a device application

References

- FDA combination Product Website
  - https://www.fda.gov/combinationproducts/default.htm
- Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products
  - https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm429304.pdf
- Postmarketing Safety Reporting for Combination Products
  - https://www.federalregister.gov/documents/2016/12/20/2016-30485/postmarketing-safety-reporting-for-combination-products

Questions?

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About:

As a Senior Consultant at confinis ag, Mr. Viky Verna currently assists medical device and pharmaceutical companies with regulatory affairs challenges. His qualifications are firstly supported by his education, specifically, a BS and a MS in Biomedical Engineering from the University of Miami, a MS in Pharmacy and a Drug Regulatory Affairs Certificate from the University of Florida, and a Global Regulatory Affairs Certification (RAC) from Regulatory Affairs Professional Society (RAPS). Mr. Verna's experience with Combination Products started while he was at the US Food and Drug Administration (FDA). At the Center for Devices and Radiological Health (CDRH) of the FDA, Mr. Verna held several positions including (Acting) Branch Chief of the Respiratory, ENT, General Hospital, and Ophthalmic (REGO) devices branch which handles the compliance activities of drug delivery systems such as syringes. During his time at CDRH, he also served as a:

- A reviewer in the quality system working group of the Office of Compliance, where he generated and reviewed the regulatory case reports (establishment inspection report review memos) for regulatory decisions; and,
- A combination product branch lead of the REGO branch. His responsibilities included training and reviewing the work of the team, as well as developing reviewing processes and techniques to be used by the office.

After joining confinis, Mr. Verna has helped several companies of all sizes successfully understand, navigate around, and comply with the US regulatory requirements for combination products and medical devices especially for drug delivery systems. By being an expert representing Switzerland on the ISO technical committee 84, Mr. Verna has also been leveraging his expertise and experience to help develop international standards for injection and respiratory products, infusion pumps, needles and catheters.

Thank you!

Additional GMP Requirements

If the underlying Quality System is set up acc. to 21 CFR Part 820 (Quality System Regulation)		If the underlying Quality System is set up acc. to 21 CFR Part 210/211 (CGMP Regulation) aufgebaut ist	
CGMP Anforderungen	**Title**	**Folgende Anforderungen müssen kritisch auf Anwendbarkeit geprüft werden:**	**Title**
§ 211.84	Testing and approval or rejection of components, drug product containers, and closures	§ 820.20	Management responsibilities
§ 211.103	Calculation of yield	§ 820.30	Design controls
§ 211.132	Tamper-evident packaging requirements for over-the-counter (OTC) human drug products	§ 820.50	Purchasing controls
§ 211.137	Expiration dating	§ 820.100	Corrective and preventative actions
211.165	Testing and release for distribution	§ 820.170	Installation
§ 211.166	Stability testing	§ 820.200	Servicing
§ 211.167	Special testing requirements		
§ 211.170	Reserve samples		