PDA & West Present: Combination Products Combination Product Development & Regulatory Best Practices: Drug/Biologic PMOA Perspective

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Topics

21 CFR 4, CGMP for Combination Products: Impact on Development

- Overview of the Rule and Available Resources
- Combination Product Design Controls and PFS Example
- Management Responsibility, CAPA, Purchasing Controls

Drug/Biologic PMOA Combination Product Regulatory Submissions

- Regulatory Strategy
- Common Review Issues
- Submission Content – structure, data expectations, use of platform data

21 CFR 4, CGMP for Combination Products:

Impact on Development

Merging Pharma/Device Differences

PHARMA

Quality by Design: Design Space defined based on **process** (inputs/parameters) as function of impact to CQA

Product manufacturing **(PROCESS)** variability has greatest impact on finished product: Control biologic/chemical variability

GMP focus on **product**: 'components, drug products…'

DEVICE

Design controls: Design Space defined based on **physical** aspects as a function of impact on device performance

Physical and mechanical variation **(PRODUCT DESIGN)** has greater impact on finished product: Control dimensional/functional variability

GMP focus on **responsible party**: 'manufacturers of devices…'

Packaging system development for pharma, device and combination products merge these differences into an integrated approach that satisfies the requirements all of the constituents

21 CFR 4(A): CGMP for Combination Products

- Manufacturer of **single-entity** or **co-packaged** combination products shall:
  - Comply with all applicable CGMP requirements for the constituents contained within the combination product, *OR*
  - Adopt a streamlined approach, as follows:
    - Select the base system for the manufacturer (e.g., Drug GMP, Device QSR), and then show compliance with additional provisions:

Note – frame of reference is for the responsible party (device GMP approach)

Drug GMP Streamlining Approach:

- 820.20 Management Responsibility
- 820.30 Design Controls
- 820.50 Purchasing Controls
- 820.100 CAPA
- 820.170 Installation
- 820.200 Servicing

Device QSR Streamlining Approach:

- 211.84 Testing and approval or rejection of components, drug product containers, and closures[1]
- 211.103 Calculation of yield[2]
- 211.132 Tamper-evident packaging requirements for the OTC human drug products
- 211.137 Expiration dating
- 211.165 Testing and Release for distribution
- 211.166 Stability Testing
- 211.167 Special Testing Requirements
- 211.170 Reserve Samples

Clarifications from FDA Guidance on CGMP for Combination Products:

[1] Device components that are part of the container/closure only

[2] Drug constituent part only

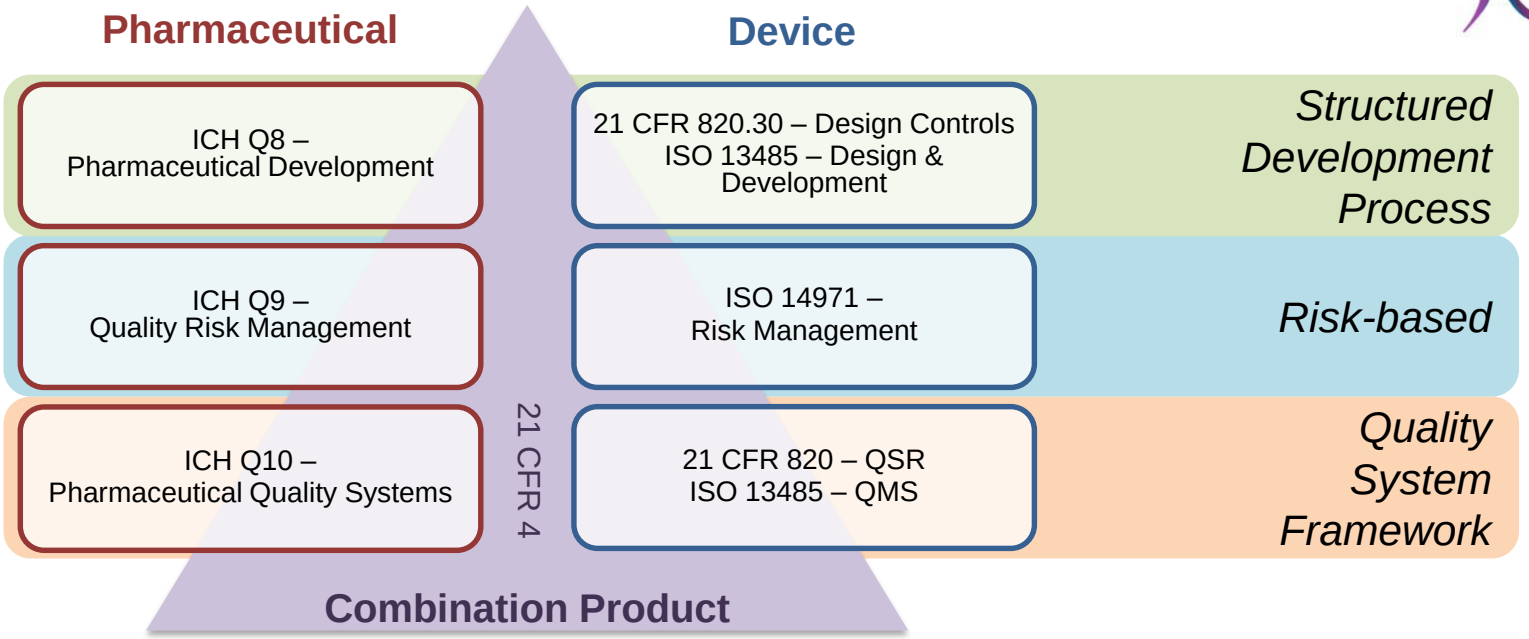
Highlights from Part 4(A) Resources: CGMP for Combination Products

- **21 CFR 4 (Sub-part A) Preamble** (Jan 2013):
  - Pre-filled syringe is a combination product ***(and always has been!)***
  - Application of CGMP based on scope of manufacturer responsibilities
- **AAMI TIR 48:2015 – QMS Recommendations on the Application of 21CFR 4**:
  - Interpretation and application of Part 4
  - Considerations when adopting a streamlined approach – detailed tables to guide the transition from QSR or Drug GMP to streamlined quality system
  - Narrative sections with considerations for the application of design control and risk management to combination products
    - Interface between the different groups within an organization responsible for the drug, device, etc.
    - Aligning drug and device development processes
    - ICH Q9 and ISO 14971 risk management comparison and analysis

Highlights from Part 4(A) Resources: CGMP for Combination Products

- **CGMP Requirements for Combination Products Guidance** (Jan 2017):
  - Clarifies terminology/applicability – manufacturer, component vs. constituent part, drug container vs. delivery devices, convenience kits
  - Coordination of CGMP compliance across facilities
    - Manufacturing one type of constituent part - needs only comply with CGMP requirements for the constituent part, **BUT – quality system should take into account considerations for the combination product as a whole**
    - Requirements for product (e.g., design controls) vs. process (e.g., CAPA)
    - **Coordination of responsibilities across the facilities**
  - Robust sections on how to implement streamlining approaches
    - ***Note – useful insights for both Drug CGMP & Device QSR based systems***
    - **Design Controls – relates to the combined use of the constituent parts → not just the device portions of the combination product!!**
    - Extensive scenarios provide guidance on how to comply for co-packaged and single entity products

Combination Product Development Aligned with QbD



Adapted from : Donna French, Genentech, WCBP 2016

Design Control for container/closures that are also devices

- Design controls need to be in place for **both** the device constituent parts and the combination product
  - May exist in separate or combined Design History Files
- How to implement? How is this different from standard container/closure suitability assessments?

  →*NOT THAT DIFFERENT!*
  - Many of the same assessments are performed
  - Much of the same data is used to satisfy container/closure requirements as are used to satisfy design control considerations
- Design controls provide for a standardized, systematic, prospective, iterative model for device design and development to ensure that the device is **safe and effective**

Pre-filled Syringe as a Combination Product

- Piston Syringes historically regulated as devices
  - Product Code – FMF
  - 21 CFR 880.5860, Class II
- Pre-filled Syringes were historically registered as container closure systems for the drug product contained therein
- 21 CFR 4 clarified intention to enforce pre-filled syringes as combination products subject to CGMPs.
  - “syringe is a device used to deliver another medical product…Accordingly, a prefilled syringe is a combination product and subject to this rule” (preamble)

Is 211.84 required for device components?

- **Pharmaceutical Components** – any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product. 21 CFR 210.3
  - In scope of Pharmaceutical GMPs (210/211)
- **Device Components** – any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device. 21 CFR 820.3 (c) → e.g., not a finished device
  - Manufacturers of device components not subject to QSR
  - Manufacturers of finished devices have requirements related to components within QSR

What if device component is ALSO part of container closure?

Device Component Part of CCS:

- 211.84 Applies

Device Component Not Part of CCS:

- 211.84 exempt per the FDA GMP Combination Product Guidance

21CFR211.84 requires sampling, testing of each component lot according to spec. Allows for component supplier CoA acceptance with mfg performing identity testing upon receipt with validation of supplier results at appropriate intervals

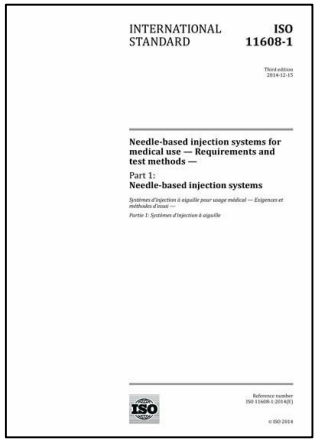
Comparison of Design Controls to CCS Suitability

Design Control Element	Traditional Drug Development	Design Control Approach
Design & Development Planning	Master project plan	D&D Plan
Design Input	Target Product Profile, Regulations/Guidance Documents	User Requirements, Design Input Requirements
Design Output	Specification, Drawings, MBR	Specification, Drawings, MBR/DMR
Design Review	Development Go/No Go decision points	Formal Design Reviews, Independent Reviewer
Design Verification	Characterization studies, suitability studies	DVT, functionality assessment
Design Validation	Use in clinical studies	Actual or Simulated (Human Factors) Use Testing
Design Transfer	Tech Transfer/MBR	Tech Transfer/DMR
Design Changes	Change control	Change control
Design History File	Drug development project files	DHF

Design Verification

- **Verification that the Outputs meet the Inputs → *Did I make the product right?***

- **Confirmation via studies, tests, inspections, and analyses**
  - Bench tests (conformance to standards)
  - Dimensional verification
  - Comparison to established product
  - May leverage results on components to demonstrate that the combination product meets the requirement (e.g., biocompatiblity, force measurement)


INTERNATIONAL STANDARD ISO 11608-1

Third edition 2014-12-15

Needle-based injection systems for medical use — Requirements and test methods —

Part 1: Needle-based injection systems


INTERNATIONAL STANDARD ISO 11040-8

First edition 2016-11-15

Prefilled syringes —

Part 8: Requirements and test methods for finished prefilled syringes

Pharmaceutical Suitability vs. Design Verification

Category	Suitability Requirement	Pharma Suitability Source(s)*	Device Source(s)*
Protection	Protection from moisture, light and microbial contamination, container integrity	ICH M4Q – CTD; 3.2.P.2.4 ICH Q1B – Photostability ICH Q1A(R2) – Stability ICH Q8(R2) – Pharm Dev ICH Q5C – Stability of Biotech USP <71>, <1211>, <1207> Ph. Eur. 2.6.1	EU Annex 1 ISO 11607, 11135, 11137, 11737, 16142, 17665, 14937
Compatibility	Product and container/label interaction (sorption, leaching, extracting)	ICH M4Q - CTD; 3.2.P.2.4 USP <1663>, <1664> ICH Q8(R2) – Pharm Dev ICH Q5C – Stability of Biotech ICH Q1A(R2) – Stability	ISO 10993
Safety	Safety of materials	ICH Q8(R2) – Pharm Dev USP <87>, <88>, <381>, <660>, <661>, <1031> Ph. Eur. 3.1, 3.2	ISO 594, 9626, 10993, 11040, 23908
Performance	Demonstration of reproducible and accurate dose delivery	ICH Q8(R2) – Pharm Dev ICH Q1A(R2) - Stability USP <1> Ph. Eur. 2.9.17	ISO 11608, 7864, 9626
	Usability Engineering		ISO 62366 ANSI/AAMI HE 75

*Plus numerous global pharmaceutical and device guidance documents related to development, manufacturing and testing of these products

Management Responsibility, §820.20

- Incorporate §820.20 Management Responsibility into a drug-GMP streamlining quality system by:
  - Management with executive responsibility establish, implement and maintain a policy describing a company's commitment to quality and quality objectives
  - Ensure that responsibility, authority, and interrelation of all personnel who manage, perform, and assess work affecting quality is well-established
    - Documented in procedures and organizational charts
  - Provide adequate trained resources
  - Identify management representative responsible for periodically reviewing the effectiveness of the quality system (against policy), and for reporting the results to the rest of management
  - Conduct Management Reviews to ensure that the QMS is effective
  - Establish quality plan and quality system procedures and instructions
- Many of these aspects are already addressed when implementing a PQS in accordance with ICH Q10, Pharmaceutical Quality System

Corrective Action and Preventative Action, §820.100

- Closest 210/211 provision is §211.192, *Production Record Review* "Any unexplained discrepancy… shall be thoroughly investigated… written record of the investigation shall be made and shall include the conclusions and followup"
- QSR provision expands the scope beyond manufacturing activities:
  - Analyze processes, operations, records, complaints, other quality data identify existing and potential causes of nonconforming product or other quality problems
  - Investigation of root cause
  - Correct non-conformities/quality problems and verify/validate effectiveness
  - Controls to prevent recurrence

- CAPA requirements are covered with a PQS in accordance with ICH Q10, Pharmaceutical Quality System

Purchasing Controls, §820.50

- "Each manufacturer shall establish and maintain procedures to ensure that all purchased or otherwise received **product and services** conform to specified requirements."
  - "product" includes device components
- Selecting a Device Partner → Initiation of Purchasing Controls
  - Outsourcing design or utilizing an existing device platform changes the "Design" Process
    - Doesn't start from rough drawings, rather starts with selection
  - Selecting components and device constituents to be incorporated into the combination product is device design
  - Purchasing controls assure rigor during the technology evaluation and selection
    - Very important to ensure that purchasing controls are utilized as part of the start of the combination product design

Purchasing Controls

Critical for managing changes during the lifecycle of a product

- Successful implementation of purchasing controls can make for proactive rather than reactive regulatory strategy
- Vital for combination products, as most include purchased materials/components/device assemblies
- Design only as good as purchasing controls
  - ➢ without strong purchasing controls, design can change ***without you even knowing***
- Supply agreements:
  - Customers and suppliers should agree on notification and approval of changes and include these terms in agreements
  - Suppliers should ensure that THEIR suppliers have adequate change control programs in place

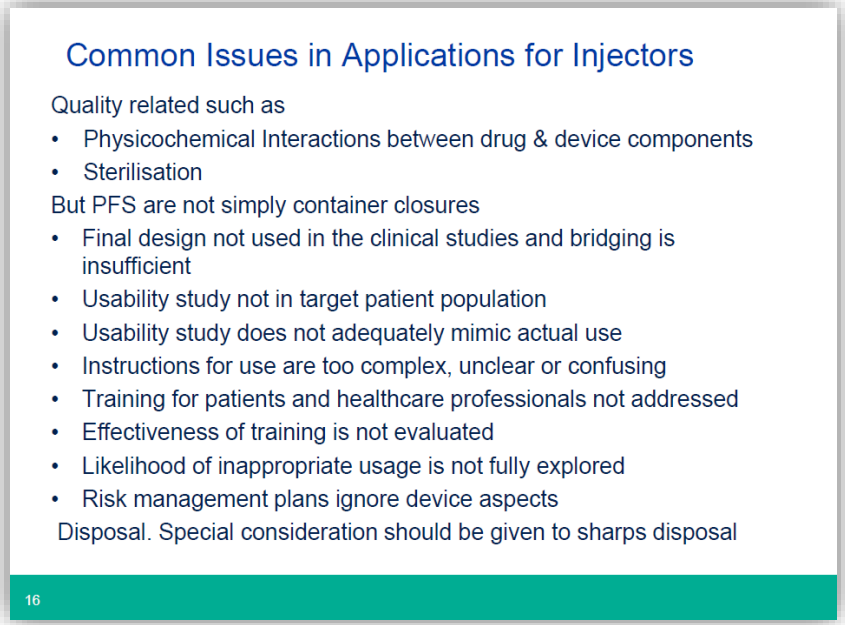
Drug/Biologic PMOA Combination Product Regulatory Submissions

Developing a Regulatory Strategy

- Gather strategy inputs (experience, review memos, FOI, benchmarking, guidance, conference proceedings, industry consortia, etc)
- Understand the source of the input, any context available, age of input
- Balance these factors against the product
  - Define intended claims (e.g., sharps protection, in-use conditions, etc.) – build regulatory strategy such that planned studies will support the claims
  - Take care to not overextend the input and apply to a situation that is not relevant
- Global perspective – consider intended/likely markets
  - Design studies which will have global applicability (e.g., stability, shipping validation, process validation), or plan for supplemental studies for specific regions
- Consider intended continuous improvement plans for the project as early as possible – build submission strategies with the final product in mind
- For single-entity products (e.g., PFS, autoinjector) presented **BOTH** as a container closure system and as a combination product

Common Review Issues - Across Regions

Source: J. McMichael, FDA, CDRH, *Regulatory Challenges for Combination Products*, PDA Combination Products Interest Group Meeting, May 2017



Source: E. Baker, MHRA, *European Regulatory Update*, PDA Universe of Pre-filled Syringes EU, Nov. 2015

Opportunities for Agency Feedback

- FDA feedback/recommendations as early as Pre-IND interactions
  - Take advantage of all opportunities to present the proposed development approach and control strategy (end of phase meetings, Type C interactions)
- Comparing Pharmaceutical and Device approaches
  - DS/SP Specifications and Stability approaches are typically evaluated **multiple** times during the development of a traditional pharmaceutical product
  - It is not uncommon for a device manufacturer to have **multiple** pre-sub interactions with FDA before licensing application
- Combination product control strategy can be similarly assessed during meetings throughout product development
  - Multiple interactions will allow the company to consider the FDA feedback early and provide opportunities for dialogue where there are areas of disagreement
  - 21st Century Cures Act introduces a new meeting type:
    - **Combination Product Agreement Meeting** [per 21 U.S.C. 353(g)(2)]

Building the Submission

Guidance documents identify submission expectations, for example:

- **US:**
  - Pen, Jet and Related Injectors Guidance (June 2013)
  - Rheumatoid Arthritis Guidance (Draft, May 2013)
  - MDI and DPI Drug Products: CMC Documentation (Draft, 2018)
  - Glass Syringes for Delivering Drug &Biol. Products (11040-4 supp.) (Draft, Apr 2013)
  - Design Considerations for Devices Intended for Home Use (Nov 2014)
  - Applying Human Factors and Usability Engineering to Medical Devices (Feb 2016)
  - Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (Draft, Feb 2016)
- **EU:**
  - Inhalation and Nasal Product Guidance (Oct 2006)
  - Plastic Immediate Packaging Materials (Dec 2005)
  - MHRA Human Factors & Usability Engineering (Draft, Sept 2017)
- **ICH Guidance:**
  - Specifications, Q6A, Q6B
  - Stability, Q1A(R2), Q1B, Q1C, Q1D, Q1E, Q1F, Q5C
  - CTD, M4Q
  - Pharmaceutical Development, Q8(R2)

Importance of Telling a Good "Story" Based on Fact

- A well told scientific story in the submission will increase the readability and approvability and reduce the number of queries and reworks
  - Include informative figures and tables that are well-organized, direct and support the strategy
- The authoring team must think like a reviewer
  - ***Do not assume*** that the development approach and proposed control strategy must be acceptable because a reputable drug company has proposed it!
- The reviewer needs to be convinced through the science supporting the strategy
  - Focus on relevant data and controls
- Address alternate approaches and deviations **proactively**
  - Where the content provided deviates from current regulatory expectations, address in the submission with a strong justification
  - Don't leave it to the reviewer to uncover that the approach differs

Reviewer-Friendly Best Practices

- The submission is not a Murder Mystery…where the reviewer only completely understands the full picture after reading the entire document

  - Clearly and completely identify the control strategy early in the submission
  - Keep the discussion focused
    - Avoid scattering information in multiple sections
    - Avoid describing the strategy in multiple sections with increasing details
- Avoid using subjective terms and superlatives, 'well below' may be seen as 'barely passing' by the reviewer, let the justification speak for itself
- Draw conclusions and correlations from the data presented
  - Without the manufacturer conclusions clearly laid out in the filing, the reviewer is left to draw their own conclusions, which ***may be different*** from the manufacturer conclusions

Presenting Combination Products in Filings

- Operating Principles described in more detail
  - 'Design Space' derived primarily from the design
- More emphasis on ***why*** and ***how*** the control strategy ensures essential performance

Key Submission Elements: Development Information

- Design and development information provides support for the robustness of the design and rationale for the manufacturing and control approaches (commonly placed in P.2 and/or 3.2.R)
  - **Operating principles of the combination product**
    - Typically presented with illustrations explaining the mechanics of the device functions relevant for each key use step
    - Important for the sponsor to orient the reviewer to the design of the system, the features and functions as a baseline to support the development approach and the proposed controls
      - Without sponsor providing how the system works, the reviewer may make assumptions
  - **Design controls -** Summary of design inputs, outputs, verification plan and results, design validation summary and full summative human factors report
  - **Risk management -** Key driver to explain which characteristics are essential/key/critical and to present the risks that the control strategy is intended to mitigate
  - **Assembly process development** and rationale for criticality/non-criticality of process parameters

Key Submission Elements: Manufacturing and Controls

- Justification of the control strategy (commonly placed in P.2, P.5.6 and/or 3.2.R.)
  - **Essential Performance Requirements** - approach used for designation of 'essential performance'
  - How the controls applied across the supply chain provide assurance of the essential performance of the combination product (suppliers via purchasing controls, incoming inspection, in-progress testing, release testing, stability):
    - Why the controls are the *right controls*
    - Why the *acceptance criteria* are appropriate
    - Why the control point is placed *at the right point*
- Quality System information (typically placed in P.3 and/or 3.2.R):
  - Declare which 21 CFR4 quality system(s) that the combination product development and manufacturing sites apply
  - 21 CFR 4 Quality System Summary
- Manufacturing and Controls Information: commitments which relate to how the product will be manufactured, controlled and tested throughout the lifecycle (commonly placed in P.3, P.5 and/or P.7)
  - **Established Conditions** – be mindful of which elements are considered established conditions – these will be the elements which require submissions if changed

Summary

There is NO Regulatory Crystal Ball…

The regulatory environment for combination products and delivery systems is evolving, with frequent changes to expectations

Surprises cannot be completely prevented, but there are strategies to stay current and align development and lifecycle products as the environment changes

Summary

- Design controls are required for combination products
  - Additional requirements build on currently performed container closure development activities
- Similarities between Pharmaceutical Suitability and Design Verification
  - Understanding differences is needed when planning studies
- Global regulatory requirements for combination products are evolving
  - Trend is towards increasing requirements for combination products

Questions??

Thank you!

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Some Terminology

- **Constituent -** a drug, device, or biological product that is part of a combination product. (21 CFR 4.2)
  - Constituent part retains its legal status when its combined in a combination product – regulatory requirements travel with the constituent part
  - Drug Constituent – formulation plus the primary packaging
  - Device Constituent – fully assembled/functional device
    - For single-entity injectors, often the device constituent is not formed until the combination product is assembled
    - Add-on finished devices (e.g., needle safety device) are also considered device constituents
- Device Components – means any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device. (21 CFR 820.3 (c))
  - E.g., not a finished device
- **Manufacture** - includes, but is not limited to, designing, fabricating, assembling, filling, processing, testing, labeling, packaging, repackaging, holding, and storage. (21 CFR 4.2)

Component GMP Requirements

	Pharma Components	Device Components
GMP Scope	In-scope for 210/211	Manufacturers of device components not subject to QSR, but manufacturer of finished device have requirements for components
Receipt and storage	• General req, 211.80 • Receipt/storage – untested, 211.82; approved, 211.86; rejected, 211.89 • Retesting of approved, 211.87	• Handling, 820.140 • Storage, 820.150
Acceptance and rejection	• Testing, approval or rejection, 211.84	• Acceptance, 820.80 (Receiving for purchased components and In-process for fabricated components) • Statistical Techniques, 820.250 • Nonconforming product, 820.90
Records	• Component, drug product container, closure, and labeling records, 211.184 • Master production/control records, 211.86; Batch production/control records, 211.188	• DMR, 820.181 and DHR, 820.184
Purchasing Controls	• QC Unit supplier quality, 211.22 • Oversight and control, FDASIA Sec. 711	• Purchasing controls, 820.50 • CAPA, 820.100