Combination Products and CGMP Case Studies

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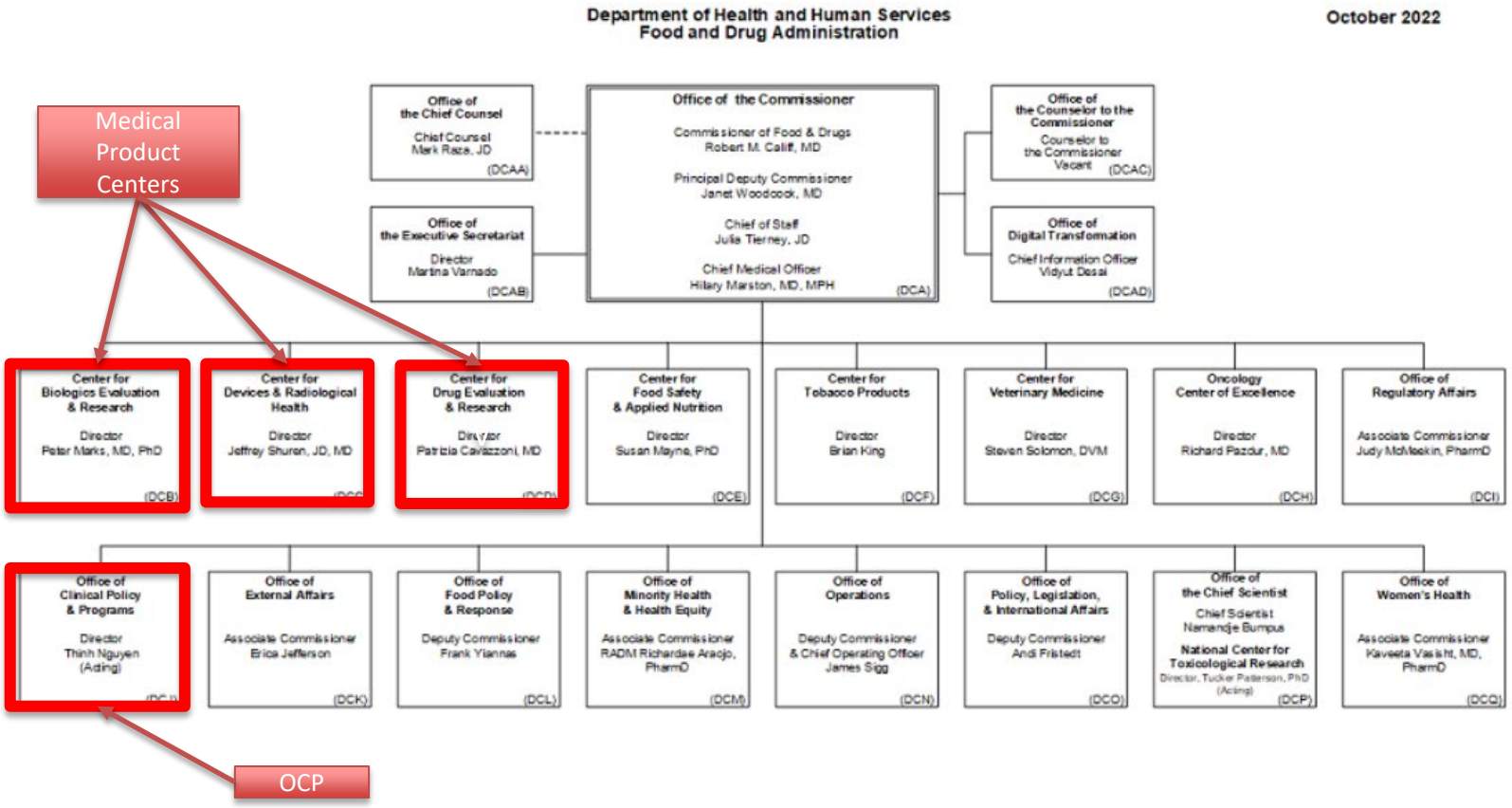
Background: Marketing Submissions to FDA

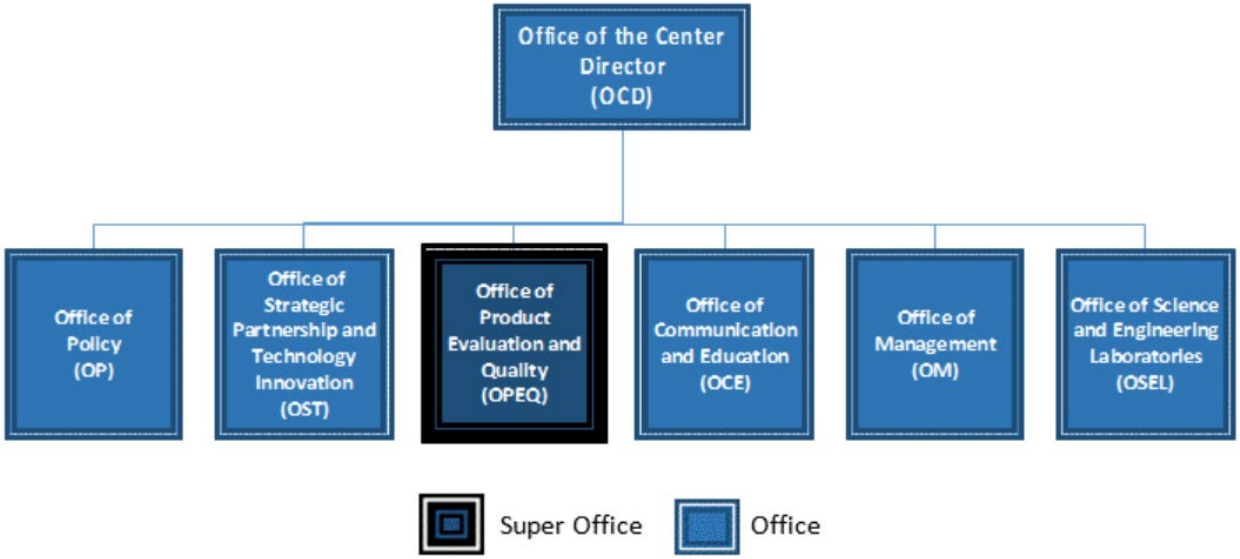
- One marketing application is typically used for single-entity and co-packaged combination products
- Application type is typically aligned with the PMOA and lead center:
  - CDER-led: New Drug Applications (NDA), Abbreviated New Drug Applications (ANDA), Biologics License Applications (BLA)*
  - CDRH-led: Premarket Approval Application (PMA), Premarket Notification (510(k)), De Novo
  - CBER-led: BLA*, PMA, 510(k), De Novo**
- See also Final guidance, Principles of Premarket Pathways for Combination Products

* Some therapeutic biological products are reviewed by CDER and others by CBER, see Transfer of Therapeutic Products to the Center for Drug Evaluation and Research
** Some devices related to blood and cellular products are reviewed by CBER.

FDA Organization Chart



Center for Devices and Radiological Health



FDA Review of Combination Product Premarket Submissions

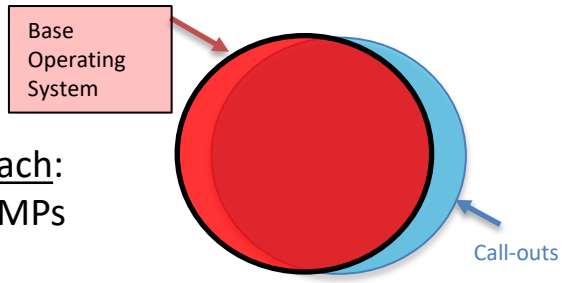
- FDA assesses the safety and effectiveness of the combination product as a whole
- Lead center for the combination product:
  - Serves as Sponsor's primary point of contact
  - Lead center's processes and procedures are typically used (e.g., meetings, review timelines, etc.)
  - Engages expertise in other centers via the intercenter consult process (See SMG 4101 Inter-center Consult Request Process)
- The Office of Combination Products is involved in jurisdiction/assignment, cross-cutting policy, novel issues, and facilitating the review process

Background on Combination Product CGMPs

- CGMPs = Current Good Manufacturing Practices
  - Regulatory requirements that help ensure manufacturing and other processes are appropriately monitored and controlled.
- Drugs, devices and biological products have separate regulations covering current good manufacturing practices (CGMPs):
  - Drugs: 21 CFR 210 and 21 CFR 211 ("Drug CGMPs")
  - Devices: 21 CFR 820 ("Device Quality System Regulation")
  - Biological Products: 21 CFR 600 – 680
- To provide clarity on how CGMPs apply to combination products, FDA issued a regulation and associated guidance:
  - Final Rule (78 FR 4307) Issued January 2013
  - Final Guidance Published January 2017

Combination Product CGMPs

- Combination Product CGMP Rule (21 CFR part 4, Subpart A) allows for "streamlined" approach for manufacturers*:
  - Device QS regulation-based streamlined approach:
    Compliance with 21 CFR 820 Device Quality System (QS) Regulation
    PLUS
    21 CFR 211 Drug CGMPs call-outs
  - Drug CGMP-based streamlined approach:
    Compliance with 21 CFR 211 Drug CGMPs
    PLUS
    21 CFR 820 Device QS Regulation call-outs



- If biological product constituent part, also comply with 21 CFR 600-680. If product includes HCT/P, also comply with 21 CFR 1271.

* "Manufacturer" includes, but is not limited to, designing, fabricating, assembling, filling, processing, testing, labeling, packaging, repackaging, holding, and storage

Combination Product CGMPs Streamlined Approach

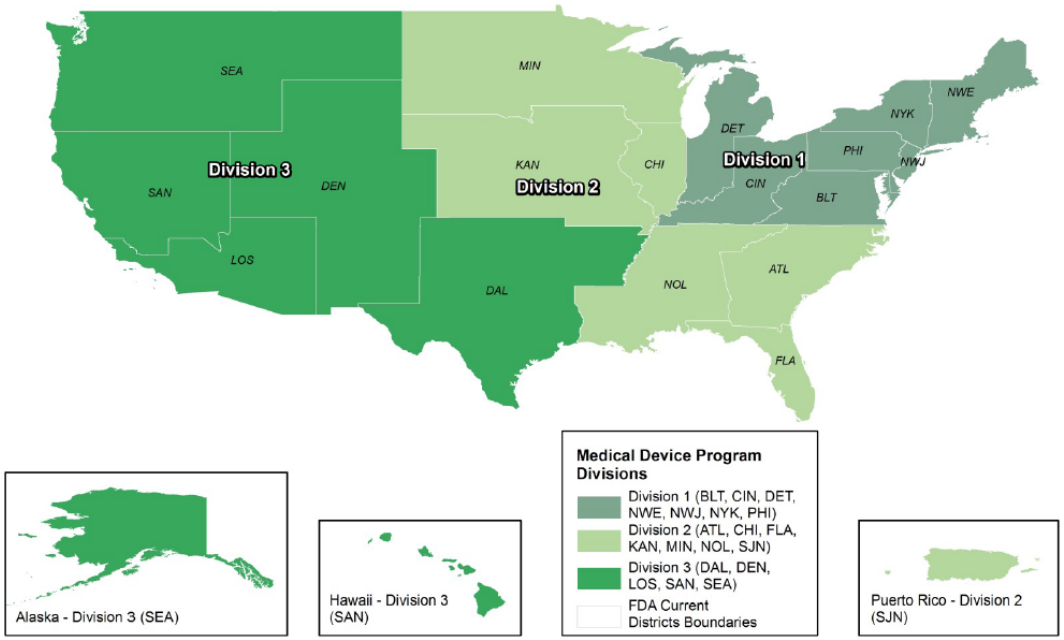
21 CFR Part 4.4(b)(1) Drug CGMP w/ QS Regulation call-outs (Drug CGMP-based streamlined approach):

- 820.20 (management responsibility)
- 820.30 (design controls)
- 820.50 (purchasing controls)
- 820.100 (CAPA)
- 820.170 & 820.200 (installation & servicing [as applicable])

21 CFR Part 4.4(b)(2) QS Regulation w/ drug CGMP call-outs (Device QS regulation-based streamlined approach):

- 211.84 (incoming testing)
- 211.103 (yield calculation)
- 211.132 (tamper-evident packaging for OTC)
- 211.137 (expiration dating)
- 211.165 (finished product testing)
- 211.166 (stability testing)
- 211.167 (special testing)
- 211.170 (reserve samples)

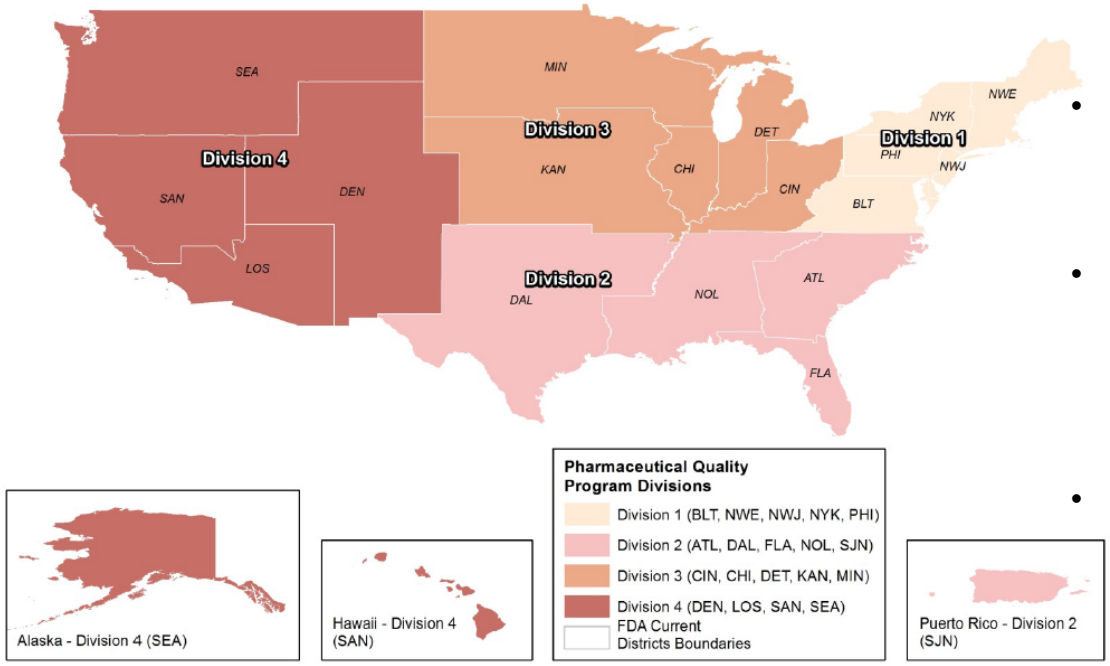
Office of Medical Devices and Radiological Health Operations (OMDRHO) in Office of Regulatory Affairs (ORA)



- Division 1
  - Director: Joseph Matrisciano, Stoneham, MA
- Division 2
  - Director: Blake Bevill, Maitland, FL
- Division 3
  - Director: Shari Shambaugh, Dallas, TX

Foreign Inspections: Akbar Zaidi, Operations and Mammography Staff Director: Rhonda Mecl

Office of Pharmaceutical Quality Operations (OPQO) in Office of Regulatory Affairs (ORA)



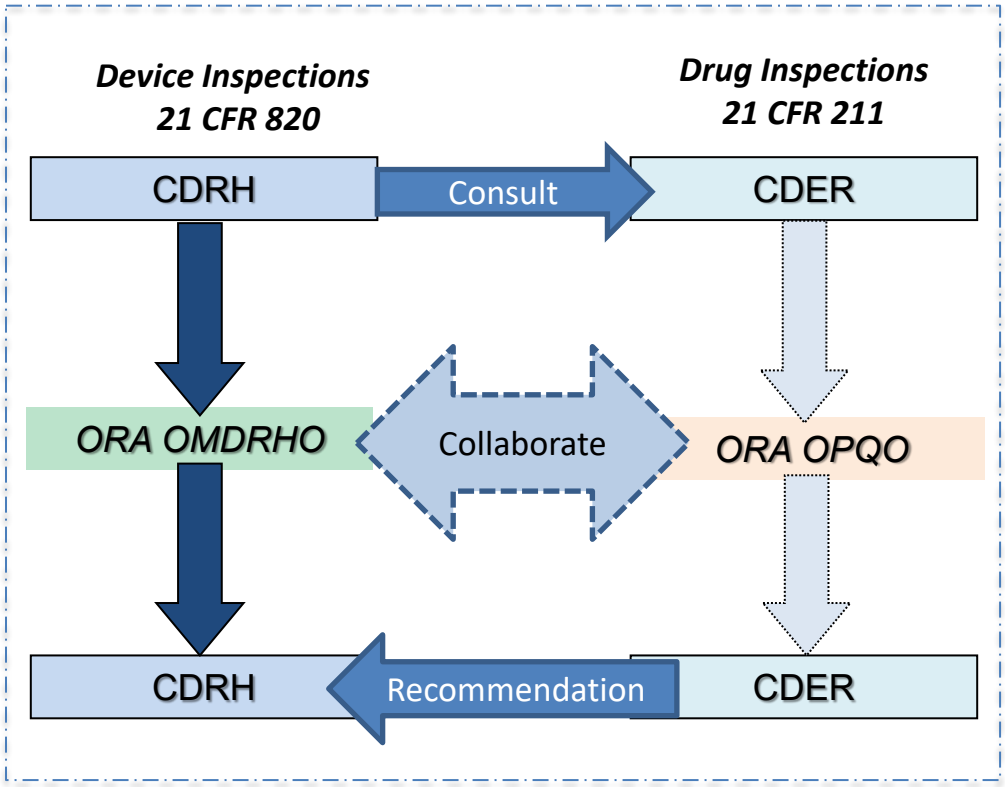
- Division 1
  - DIB: Nerizza Guerin, Chad Thompson
  - Director: Stephanie Durso
- Division 2
  - DIB: Tamala Bogan
  - Director: Vacant
- Division 3
  - DIB: Rebecca Dombrowski (Acting)
  - Director: Nicholas Lyons
- Division 4
  - DIB: Katherine Jacobitz
  - Director: Lance DeSouza

Foreign Inspections: Atul Agrawal, Kevin Gonzalez

Pre-approval Managers: Caryn McNab, Michael Tollon

Combination Product
CDRH-led Product Inspections

1. Center Review of the manufacturing information
2. Inspection requests generated by Lead Center
3. Inspections scheduled and completed by ORA
4. Establishment Inspection Report (EIR) written by ORA
5. EIR reviewed by Center(s) or ORA



Similar processes for surveillance inspections, as needed.

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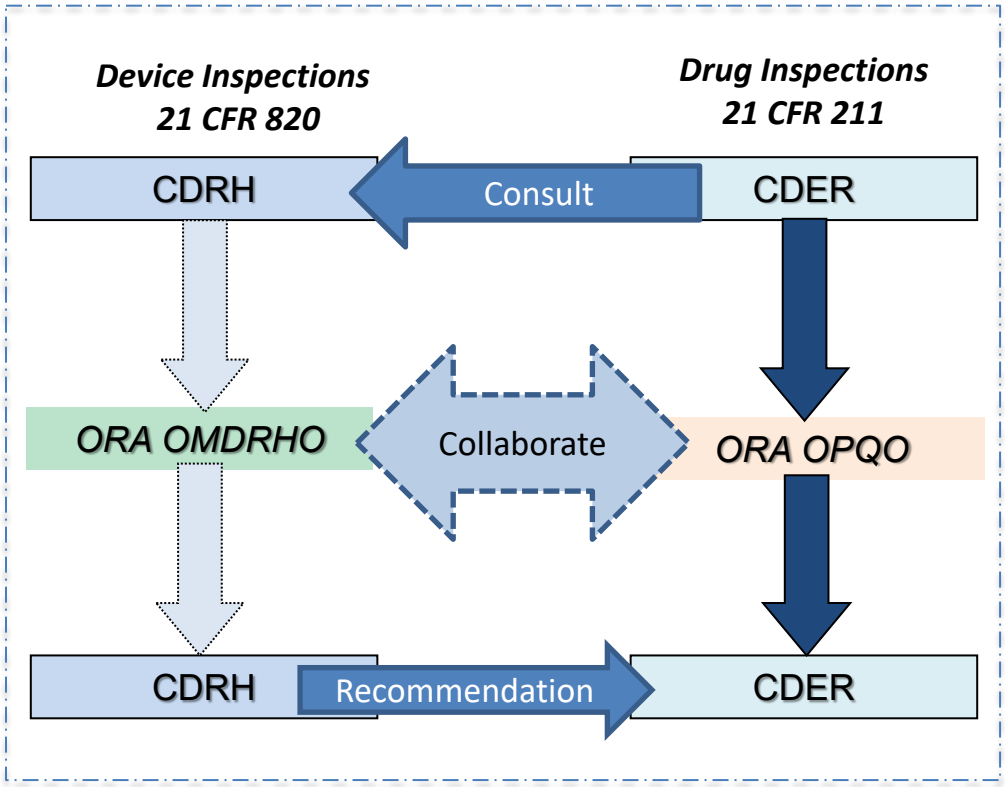

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Public Warning Letter Examples: Visible Particulates

Drug and Device Manufacturer of IV Containers, PCA Vials and Injectors

- Warning letter issued at site A
  - 21 CFR 820.198(c) Complaints involving a failure to meet specs were not evaluated. PCA injector and vial unit failed leak testing but lot was released.
  - 21 CFR 820.75(b)(2) Production and Process Controls, no documentation related to monitoring and control methods to monitor bioburden
  - 21 CFR 820.198(e) Complaint files. Sterile empty vials recalled due to embedded particulates. There was no review of whether there was an impact to the other related lots that were released
  - 21 CFR 820.198(a) Keeping complaints open without extensions or status updates
  - 21 CFR 820.100(a) CAPA, extended due dates without prevention of recurrence of the non-conformance while CAPA is open

- Warning letter issued at site B
  - 21 CFR 211.192 Production Record Review, not thoroughly investigating when there is a failure to meet specifications (visible particulates in injectable products)
  - 21 CFR 211.110(b) Sampling and testing of in-process materials and drug products, failed to establish valid in-process specifications (lack of defect limits for visual inspections)
  - 21 CFR 211.113(b) Control of microbiological contamination, failed to follow appropriate written procedures to prevent microbiological contamination of drug products purporting to be sterile
  - 21 CFR 211.110(d) Sampling and testing of in-process materials and drug products, failure to control rejected in-process materials under a quarantine system, to prevent their use (reinspected rejected units were placed with acceptable units without documentation of rejection or reinspection)
  - 21 CFR 211.160(b) Laboratory Controls, failed to establish laboratory controls (reserve samples not tested adequately with appropriate statistical samples)

Public Warning Letter Examples: Inadequate Design Controls and Purchasing Controls

Manufacturer of Prefilled Syringes and Autoinjectors

– Violations:
  - 21 CFR 820.30(g) Design Controls, inadequate design validation of device constituent part
  - 21 CFR 820.30(i) Design Controls, inadequate validation of design changes before implementation of a new vial adapter
  - 21 CFR 820.50(a) Purchasing Controls, not maintaining requirements that must be met by suppliers, contactors and consultants (didn't evaluate the contractors that serviced x-ray equipment)

Public Warning Letter Examples: Altered Data for Lot Release

Manufacturer of Paclitaxel API used in Cardio Devices

– Violations:
  - Failure to prevent unauthorized access or changes to data and to provide adequate controls to prevent omission of data (for infrared spectrometer data),
  - Failure of quality unit to ensure that materials are appropriately tested, and the results are reported (data altered to allow release of lots);
  - Failure of quality unit to exercise its responsibility to ensure the APIs manufactured at facility are in compliance with CGMP, and meet established specifications for quality and purity (altered data was not detected)

Public Warning Letter Examples: Autoinjectors Failing to Activate

Manufacturer of Life Saving Drug Delivered in Autoinjectors

- Violations:
  - 21 CFR211.192 Production Record Review, not investigating when there is a failure to meet specifications (failed specific lots with failed units without further investigation of other lots using same component)
  - 21 CFR 211.198(a) Complaint Files, not establishing and following procedures for handling written and oral complaints (classification scheme of complaints does not prioritize based on risk to patient)
  - 21 CFR 820.100(a)(1) CAPA, not analyzing quality data to identify quality problems and using appropriate statistical methodoloy (didn't keep track of different failure modes of rejected units, didn't use appropriate statistical methodology to analyze and detect quality problems)
  - 21 CFR 820.30(f) Design Controls, inadequate design verification
  - 21 CFR 820.30(g) Design Controls, lack of design validation and inadequate risk analysis related to design validation

Thank you!

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