

Division of Manufacturing and Product Quality (DMPQ)'s Perspective on Chemistry, Manufacturing, and Controls for *In Vitro* Devices (IVDs)

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Presentation Outline

- Overview of DMPQ
 - Who we are
- DMPQ's review scope of IVDs
 - What we review
- Deficiencies in IVD applications and other submissions
 - Potential areas for deficiency letter items

Overview of DMPQ

- DMPQ is within the Office of Compliance and Biologics Quality
- Perform reviews and pre-license/pre-approval inspections of applications and other submissions in concert with all product offices in CBER. Submission review includes:
 - Investigational New Drug applications (INDs)
 - Marketing applications (i.e., Biologics License Applications, Premarket Approval Applications, New Drug Applications, and Abbreviated New Drug Applications)
 - Supplements

DMPQ Review Scope for IVD

- Quality systems
- Facility
- Contamination/cross-contamination controls
- Equipment
- Microbial process controls
- Manufacturing process and sterilization
- Container Closure System
- Labeling and Packaging/Kitting
- Shipping
- Categorical Exclusion from Environmental Assessment
- Standards

Quality Systems

- DMPQ's review of Quality Systems is focused on the following major topics (note, list is not all inclusive):
 - Management responsibility, per CFR 820.20
 - How inspection, measuring, and test equipment is routinely calibrated, inspected, checked, and maintained, per CFR 820.72
 - Purchasing controls, per CFR 820.50
 - Receiving, in-process, and final acceptance activities, per CFR 820.80
 - Nonconforming product, per CFR 820.90
 - Corrective and Preventative Action (CAPA) system, per CFR 820.100
 - Labeling and Packaging control, per CFR 820.120 and 820.130

Submissions should include a summary and related procedures for the subject device covering the Quality Systems

Facility

- Overview of facilities being used for production (physical address and FEI #/registration # along with operations performed (i.e., component manufacturing, final kit packaging)). All facilities should be listed on FDA Form 356h.
- Room/area classification where operations are performed
- Floor Diagrams of facility
- Flow Patterns (i.e., product, personnel, equipment, waste)
- General description of utilities (i.e., water system, HVAC system, etc.)

- Facility design should reflect the risk assessment with respect to environmental controls
 - What is the risk of false positive and/or negative due to environmental conditions

Contamination /

Cross-Contamination Controls

- Description of segregation, contamination, and cross-contamination controls, including:
 - Facility controls (i.e., airlocks, pressure differentials)
 - Procedural controls (i.e., line clearance, changeovers)
 - Sanitary controls (i.e., gowning, facility and equipment cleaning and/or sterilization)
- List of other products manufactured at facility
- Risk assessment
 - Perform to determine what controls to implement
 - Controls should reflect the outcome of risk assessment

Equipment

- General description of equipment design, operation of equipment, location in facility
- List of equipment utilized in device manufacture including identifying: shared or dedicated, product contact, single use vs multi-use, qualified or calibrated
- Equipment performance qualification
- Description of equipment cleaning procedure and cleaning validations

Microbial Process Controls

- Bioburden
 - Description of in-process and final release bioburden process testing locations
 - Process limit for each test location
 - Method validation if not following USP
 - Does the risk assessment support bioburden limits?
- Preservative effectiveness studies, and/or microbial interference characterization study

Manufacturing Process and Sterilization

- Manufacturing Process
 - Description and flow diagram of manufacturing process along with summary of equipment used
 - Procedures and validations supporting rework
- Sterilization (if applicable)
 - Identify manufacturer who performs sterilization
 - Type (i.e., gamma, e-beam, terminal)
 - Method validation or standard reference

Container Closure System

- Description of container(s) and closure system for finished product(s) and FFMU product(s)
- Validation summary report for container closure integrity testing (i.e., torque test, burst test, peel test, laser weld, etc.) for finished product(s) and FFMU product(s)

Labeling and Packaging/Kitting

- Labeling
 - Description of labeling process (manual or automatic, control of labels)
 - Relabeling procedures (if applicable)
- Packaging/Kitting
 - Description of final kit packaging activities
 - Facility location, equipment, segregation practices
 - Release activities and finished product testing
 - Use of desiccant for moisture sensitive part(s)

Shipping

- Description of shipping containers and transport conditions for FFMU and/or final device kit packages
- Summary validation report for shipping validation
 - Studies can be performed in real conditions or simulated. Simulated studies should represent worst-case conditions.
- Recommend performing stability testing on samples prior to and after shipping as part of validation activities.

Categorical Exclusion from Environmental Assessment

- When the approval of a submission introduces a new or modified product into the market, or results in an overall increase of production of already licensed product, an environmental assessment (EA) or categorical exclusion (CE) for such an assessment must be submitted by the applicant.
- A CE describes a category of actions that does not typically result in individual or cumulative significant environmental effects or impacts.
 - 21 CFR § 25.31 for drugs and biologics (including biologic devices submitted as a BLA)
 - 21 CFR § 25.34 for devices (including biologic devices submitted as a PMA)
- The CE claim must include statements by the sponsor or applicant that:
 - The action requested qualifies for a CE, with a citation to the regulations for the specific CE that is claimed, and
 - To the applicant’s knowledge, no extraordinary circumstances exist that would warrant the preparation of an EA. [21 CFR § 25.15(d)]

Standards

- If elect to conform to one or more FDA-recognized consensus standards, should submit a “Declaration of Conformity” to the standard(s) (21 U.S.C. 360d(c)(1)(B)).
 - Link to FDA-recognized consensus standards:
<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm>

Using Same Manufacturing Process or Facility

- State if using the same facility, manufacturing process, and/or control processes as other US licensed products
 - Such as cleaning, segregation, containment, line clearance, change over and prevention of contamination, cross-contamination and mix-ups, floor diagrams, flow patterns, facilities, utilities, equipment, container/closure system, and shipping process
- State if there are any changes to the Quality System procedures and device design controls
 - If no changes, do not need to submit existing procedures
- If there are any changes from existing US licensed product, list changes and provide supporting documents

Supplements

- Ensure utilizing the correct reporting category
 - BLAs: Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products; Draft Guidance for Industry (December 2017)
 - PMAs: Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process; Guidance for Industry and FDA Staff (December 2008)

Common Deficiencies with IVD submissions

- Missing or incomplete Quality Systems information from BLAs and PMAs
- Incomplete list of manufacturers, raw material suppliers, design controls holder, and/or sterilizers
 - Need to provide summary of operations at each site along with address, FEI #, and/or registration #.
- Unclear table of contents and location of studies for review
- Providing data without summary explanation of criteria and results (aka data dumping)
 - Information needs to be clear and concise
- All documents and diagrams must be in English and also legible
- Deviations (process, equipment) must be explained and resolved
- Equipment qualification summaries and/or reports not provided
- For device supplements, use of incorrect reporting category

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