Chemistry, Manufacturing and Controls: Perspectives on Donor Screening In Vitro Diagnostics Regulated by OBRR

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Office of Blood Research and Review

CBER

Outline of Talk

- Applicable Regulations and Chemistry, Manufacturing and Controls (CMC) guidance documents
- Content of CMC
  - Critical areas of the CMC will be covered (Quality Systems: design controls and process controls/validation, and conformance lots…)
  - Points to consider with examples based on frequent issues observed during the review

CMC Across the Product Lifecycle

CMC is a critical component of a submission that describes the development and manufacture of an IVD in a **controlled** and **reproducible** manner

- **IND**
  - Brief CMC section (materials, components, controls, assembly)
  - Awareness that even at the IND stage CMC is critical
  - Changes to CMC need to be reported to FDA in Annual Reports (ARs)
- **BLA** (1)
  - Summary of contents in the CMC section of the BLA
  - Focus of this presentation (Serology/NAT assays)
- **Post-approval/Post-licensure/Post Market Commitments** (2, 3)
  - Changes need to be reported to FDA as PAS/CBEs/AR

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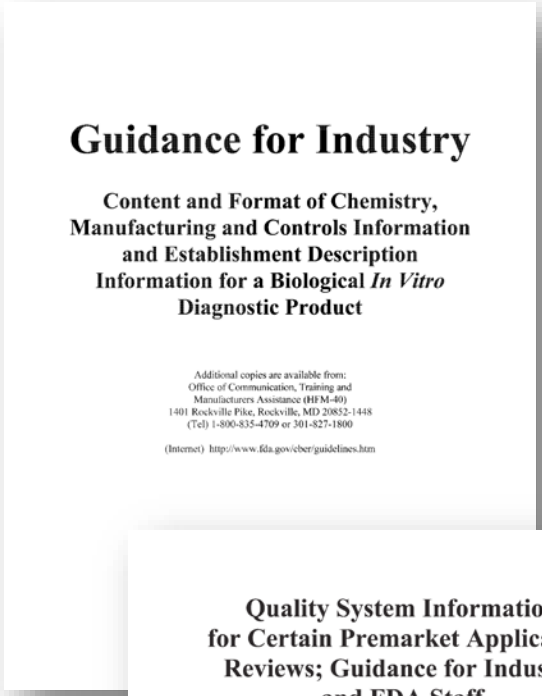
Applicable Regulations

- 21 CFR 210 and 211 (cGMPs)
- 21 CFR 610
  - Specific requirements for blood donor screening devices for infectious diseases (e.g., Lot release testing)
  - Other applicable requirements in 21 CFR 600 through 680
- 21 CFR 820 (Quality Systems)
  - Provides a framework, thus **descriptive not prescriptive**

Applicable Guidance

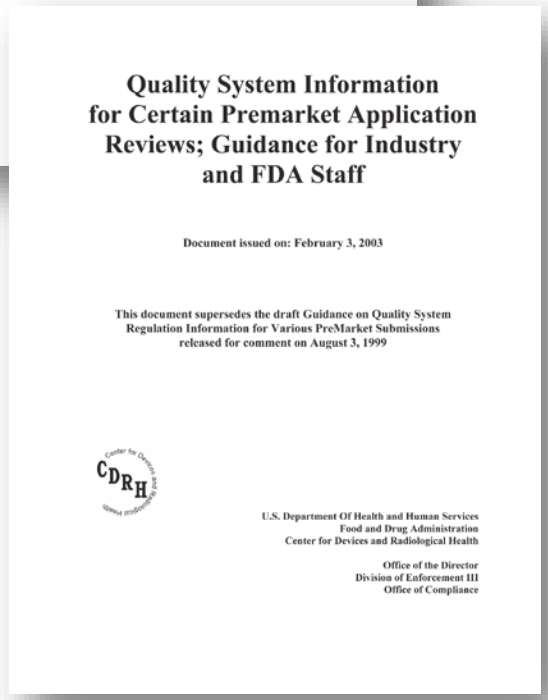


Guidance for Industry

Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Biological *In Vitro* Diagnostic Product

Additional copies are available from:
Office of Communication, Training and
Manufacturers Assistance (HFM-40)
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 1-800-835-4709 or 301-827-1800

(Internet) http://www.fda.gov/cber/guidelines.htm



Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff

Document issued on: February 3, 2003

This document supersedes the draft Guidance on Quality System Regulation Information for Various PreMarket Submissions released for comment on August 3, 1999

CDRH

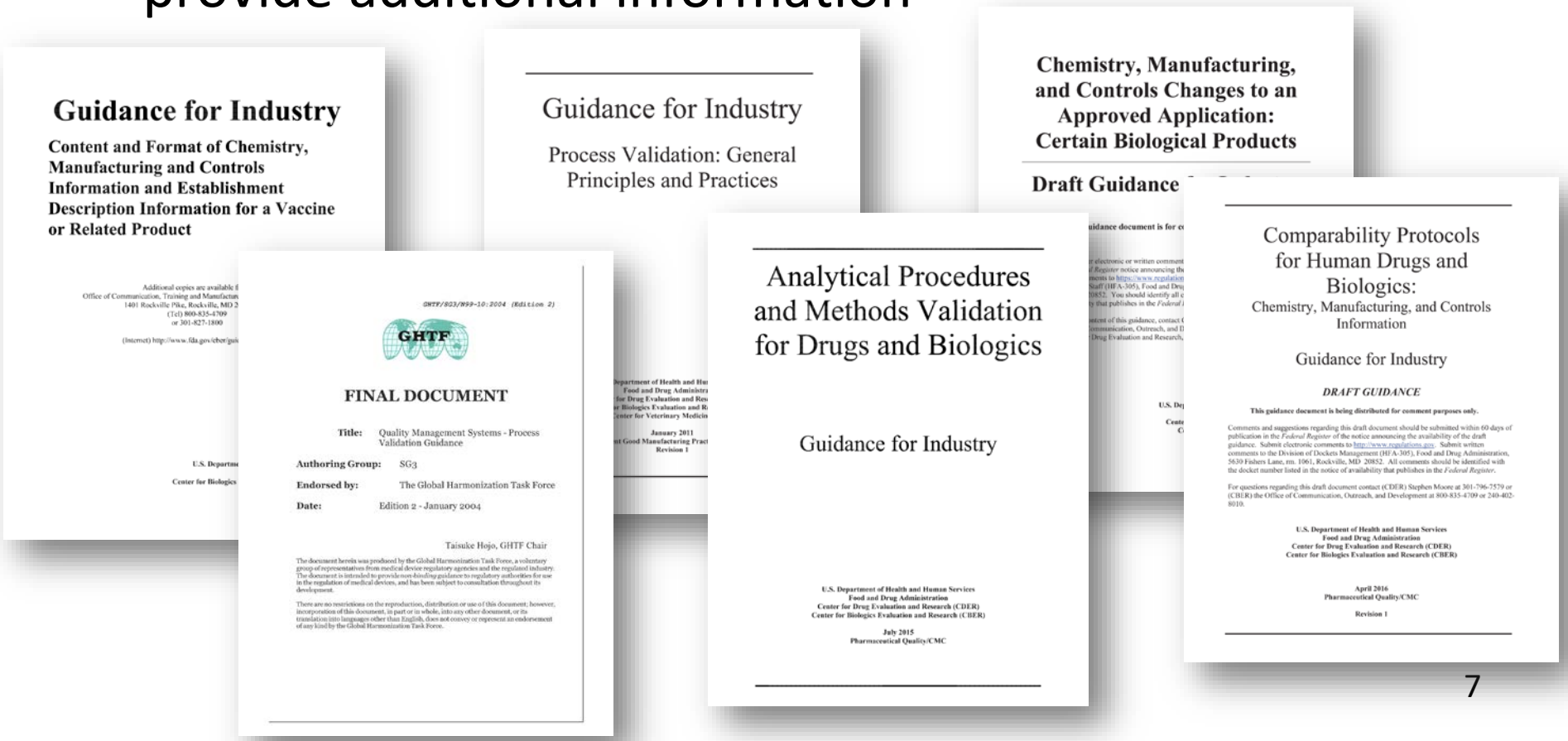
U.S. Department Of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Office of the Director
Division of Enforcement III
Office of Compliance

- BLA IVDs published in March 1999 (1)
  - Intended for use by firms which manufacture any licensed in vitro diagnostics (IVDs) used to screen donor blood
  - Part 1- CMC section for IVDs (OBRR)
  - Part 2- Establishment description section (OCBQ/DMPQ)
- PMA IVDs published in February, 2003 (4)

Additional CMC Guidance Documents

- Associated references and FDA guidance documents, parts of which may be applicable to IVD CMC, provide additional information



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- Applicable Regulations and Chemistry, Manufacturing and Controls (CMC) guidance documents

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Contents of CMC (1)

- **In Vitro Substances**: Any and all raw materials and intermediates used in the manufacture of the final in vitro product as defined in 21 CFR 820.3(c) [(1)]
  - Include information about manufacturing, testing and validation of all intermediates
  - Details of manufacturer/contractor
  - Description and characterization
  - Manufacturing process
  - In-coming material specification and test methods
  - In-process testing and controls
  - Stability

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  - Manufacturing process
  - **In-coming material** specification and test methods
  - **In-process testing** and controls
  - Stability

Inadequately documented (e.g., a missing CoA)
Acceptance criteria by manufacturer or contract mfg.
Specific and measurable (e.g., $O.D._{450} < 0.1$ vs color)

Demonstrate activity/potency
Use **Orthogonal assays**
Adhere to QC test specifications

Contents of CMC (2)

- **In Vitro Product**: The licensed product in its final form and all assembled supporting components [1]
  - Includes information about manufacturing, testing and validation of all kits and components
  - Assay kits (including supporting buffer kits or control kits)
  - Controls
    - Kit controls
    - Positive, low positive, negative controls
    - Procedural (step) controls
    - External controls
- **Manufacturing process**
  - Process validation, kit assembly, release testing, stability etc.
  - Analytical methods and specifications

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  - **Controls**
    - Kit controls
    - Positive, low positive, negative controls

Establish and adhere to specifications

Validation data must be included for review in the BLA

Adhere to release testing protocol and specifications

- **Manufacturing process**
  - **Process validation**, kit assembly, **release testing**, stability etc.
  - Analytical methods and specifications

Descriptive Narrative of the CMC

- Design controls
- Summary tables/data
- Tabular list of in vitro substances/product
  - Including those not manufactured at the sponsors facility (contract manufacturing)
- Process controls and process validation
- Reference standards/panels
- Device Master Record and executed Device History Record
- Stability
- Quality Systems
- Facilities description, contamination controls
- Manufacturing processes, equipment, labeling, shipping …

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Design Controls (1)

- **Is the design of the device appropriate?**
  - Meets user needs? Intended uses? Specified requirements?
  - Establish, maintain and document
- **What does "Design control" cover?** (4, 5)
  - **Design inputs**: Physical and performance characteristics
    - User needs and intended uses
  - **Design outputs**: Results of design effort at each stage and final IVD
  - **Design review**: Adequacy and capability to meet user needs
    - Identify problems
    - Iterative process (re-evaluate frequently; as design evolves)
    - Risk analysis

Design Controls (1)

- Is th[illegible]propriate?
  - Meets [illegible]eeds? Intended uses? Specified requirements?
  - **Establish, maintain and document!!!**
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    - Identify problems
    - Iterative process (r[illegible]
    - **Risk analysis**

Inadequately documented

Risk analysis inadequate (e.g., impact of changes to reference panels or their specifications on device quality)

Design Controls (2)

- What does "Design control" cover? (4, 5)
  - **Design verification**: Confirm by examination & provision of objective evidence (measurable means) that output meets input requirements (e.g., testing positive and negative samples)
  - **Design validation**: Establishing with objective evidence that specifications (specified requirements) conform with user needs and intended use
    - Under defined operating conditions (initial production lots/actual or simulated use condition; e.g., **early IND clinical studies**)

Design Controls (3)

- What does "Design control" cover? (4, 5)
  - **Design transfer**: Establish and maintain procedures to ensure correct design transfer into production specifications
    - Final stage of development intended to ensure all outputs are transferred
  - **Design changes**: Establish and maintain procedures for the
    - Identification, documentation, validation (and verification where appropriate), review and approval of changes
    - Evaluate before implementation
    - System to enact future changes

Design Controls (3)

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  - **Design transfer:** ensure correct desi specifications.
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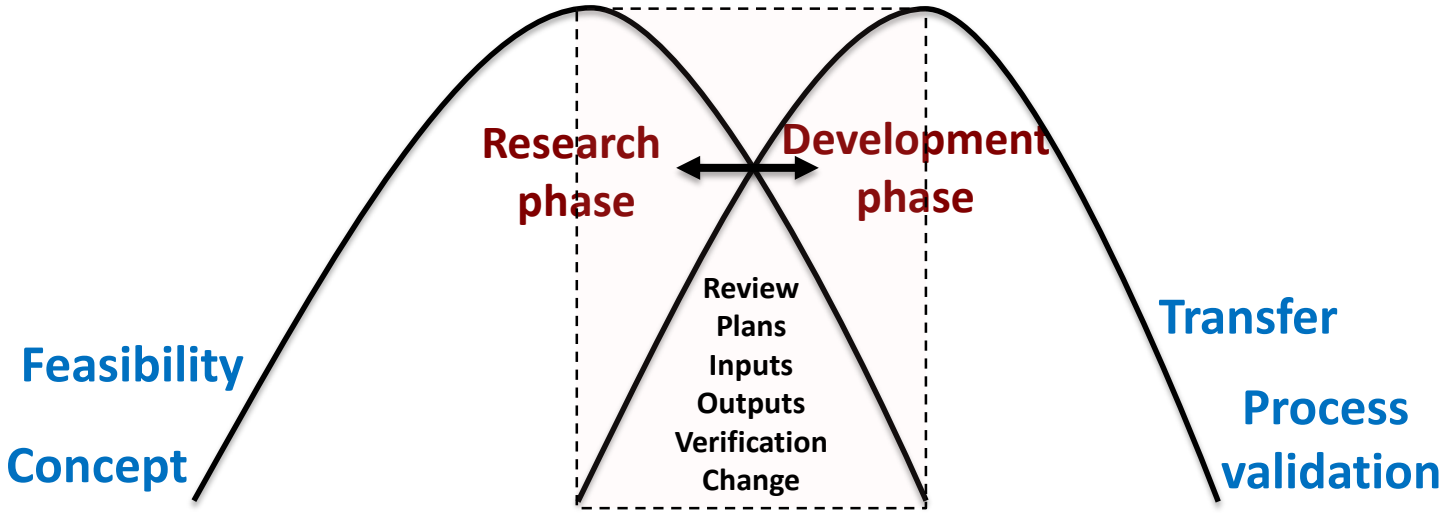
  - **Design changes:** Establish and maintain procedures for the
    - Identification verification w changes
    - Evaluate before
  - **System to enact future changes**

Critical step to document the date of design transfer from R&D to manufacturing as design changes may impact clinical studies or analytical studies.

Establishes that the **"design is fixed"** with respect to process validation

Changes should go through the complete process of design controls (input, output, review, verification, validation and transfer)

Design Controls to Process Validation



- **Design History File (DHF)** - compilation of records which describes the design history of a finished device
  - Summation of record of all design actions from start to transfer including changes
  - Brief summary in the IND (or ARs); recommend update in BLA
  - Reviewed during inspection (Design controls a key component of QSIT)

Process Controls and Validation

- **Process controls:**
  - Description of the methods used for in-process controls
  - To assure that the functional requirement of the final product is met (e.g., testing of enzyme conjugates for purity or potency)
- **Process validation:**
  - Demonstrates that, when a process is operated within specified limits, it will consistently produce product complying with predetermined (design and development) requirements (e.g., use of DoE to reduce variation) [6, 7]
  - Revalidate if changes implemented
- **Process verification:**
  - Confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled

Process Verification and Validation

- **Manufacture of antigen coated ELISA plates**
  - **Option 1**: Measure volume of antigen dispensed
    - Ultrasonic reader- non-destructive, easy but time consuming, and 100% of plates need to be read
  - **Option 2**: Perform ELISA and ensure results match control and panel member specifications
    - Destructive, easy, less time consuming but needs statistically valid sampling procedures (e.g., number of plates; test at beginning, middle and end of process…)
- **Automated liquid handling systems**
  - Dye based volume estimation, easy, accurate and fast (Design inputs)

Process Verification and Validation

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Process verification

Issues with scale up of lot size

Process validation

Revalidation may be required with scale up of lot size

Process verification

rate and fast

Reference Standards and Panels (1)

- **Used for process validation and final release**
  - Primary reference standard
  - Working reference standard
    - Qualified against primary reference standard NOT against the previous working reference standard
    - Enables primary reference standard to last through the product life cycle
- **International (WHO), CBER/CDRH and compendial (U.S.P)**[8]
  - Assay validation data using the standards should be provided
  - May have different matrix than test sample (NAT donor screening BLAs; e.g., HIV, Zika, WNV, etc.)

Reference Standards and Panels (2)

- **If no reference standard/panel available**
  - For immunoassay donor screening BLAs (e.g., emerging infectious diseases)
  - Establish in-house panel (> 3 panel members)
    - Values should bracket expected results in donor screening and cover a range of high positive, low positive and negative samples
    - Establish specifications
  - Repeatability and reproducibility should be demonstrated
  - SOP to qualify a new reference panel member should be included
    - Regeneration/reconstitution of the panel
  - Stability data for the reference standard should be provided

Reference Standards and Panels (2)

- **If no reference standard/panel available**
  - For immunoassay donor screening BLAs
  - Establish in-house panel (> 3 panel members)
    - Values should bracket expected results in donor screening
    - Critical if using this panel for in-process testing or final release of kit (e.g., SOPs)
    - **Procure enough** to last through the product review cycle and beyond
  - included
    - **Regeneration/reconstitution** of the panel
  - Stability data for the reference standard should be provided

Kit Controls

- **Kit controls are tested along with samples to verify system suitability or validity of a test performance [(1)]**
  - Positive, low positive (if used) and negative control
  - Define criteria for assay run validity
    - In IFU/Package insert
  - Qualify against reference panel/standard
    - SOP to regenerate/reconstitute
    - Specifications listed
  - Due to overlap in qualification/specifications some reference panel members may be repurposed as kit controls

Kit Controls

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  - Positive, lo (if used) and negative control
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Critical to ensure that specifications in IFU are identical across DHF, DMR, DHR and clinical testing facilities

Specification should use raw data such as O.D. for immunoassays as a change in assay cutoff can impact interpretation of kit controls (e.g., a low positive can become a negative if assay cut-off increases)

Batch Records

- **Device History Record (DHR)** - compilation of records containing the **production history** of a finished device
  - 3 conformance lots (consecutive lots), 3 DHR
  - Summary table of lot numbers of each component is helpful
    - 3 conformance lots should use 3 different lots of critical assay components
    - Include expiry dates of components
    - Include document change history and date executed for SOPs
    - Must pass CBER Lot release testing
  - Deviations/CAPA evaluated at inspection or as part of DHR

Batch Records

Executed batch records must be submitted in the BLA

Conformance lots (PV lots) may not necessarily be launch lots

At least one lot must be at full scale/maximum batch size

- **3 conformance lots (consecutive lots)**, 3 DHR
- Summary table of lot numbers of each component is

Key to assure process validation

  - 3 conformance lots should use **3 different lots of critical assay components**
  - Include expiry dates of components
  - Include
    for SOPs

All marketed lots for donor screening IVDs

  - Must pass CBER **Lot release testing**
- Deviations/CAPA evaluated at inspection or as part of DHR

Overall Take Home Message

- Regulations under 21 CFR 610 apply in addition to IVD cGMPs and Quality System regulations
- Design controls are critical
- CMC is critical during the lifecycle of the product from IND studies to approval to post marketing changes
- CMC changes need to be assessed for effect on product quality

CMC Guidance Documents

1. Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Biological In Vitro Diagnostic Product. (March 1999)
2. Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products. (December 2017)
3. Comparability Protocols for Human Drugs and Biologics : Chemistry, Manufacturing, and Controls Information (April 2016)
4. Quality System Information for Certain Premarket Application Reviews (February 2003)
5. Design Control Guidance for Medical Device Manufacturers (March 1997)
6. Quality Management Systems – Process Validation Guidance (January 2004)
7. Process Validation: General Principles and Practices (January 2011)
8. Analytical Procedures and Methods Validation for Drugs and Biologics (July 2015)

Thanks!

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