Overview of the Office of Blood Research and Review Device Regulation

Anne Eder, M.D., Ph.D.

Office of Blood Research and Review

CBER

Overview:

- Office of Blood Research and Review (OBRR)
- Regulation of devices in OBRR
- Guidance, Advisory Committees, Standards
- What's new? Resources for developers
- Today's meeting – Outline

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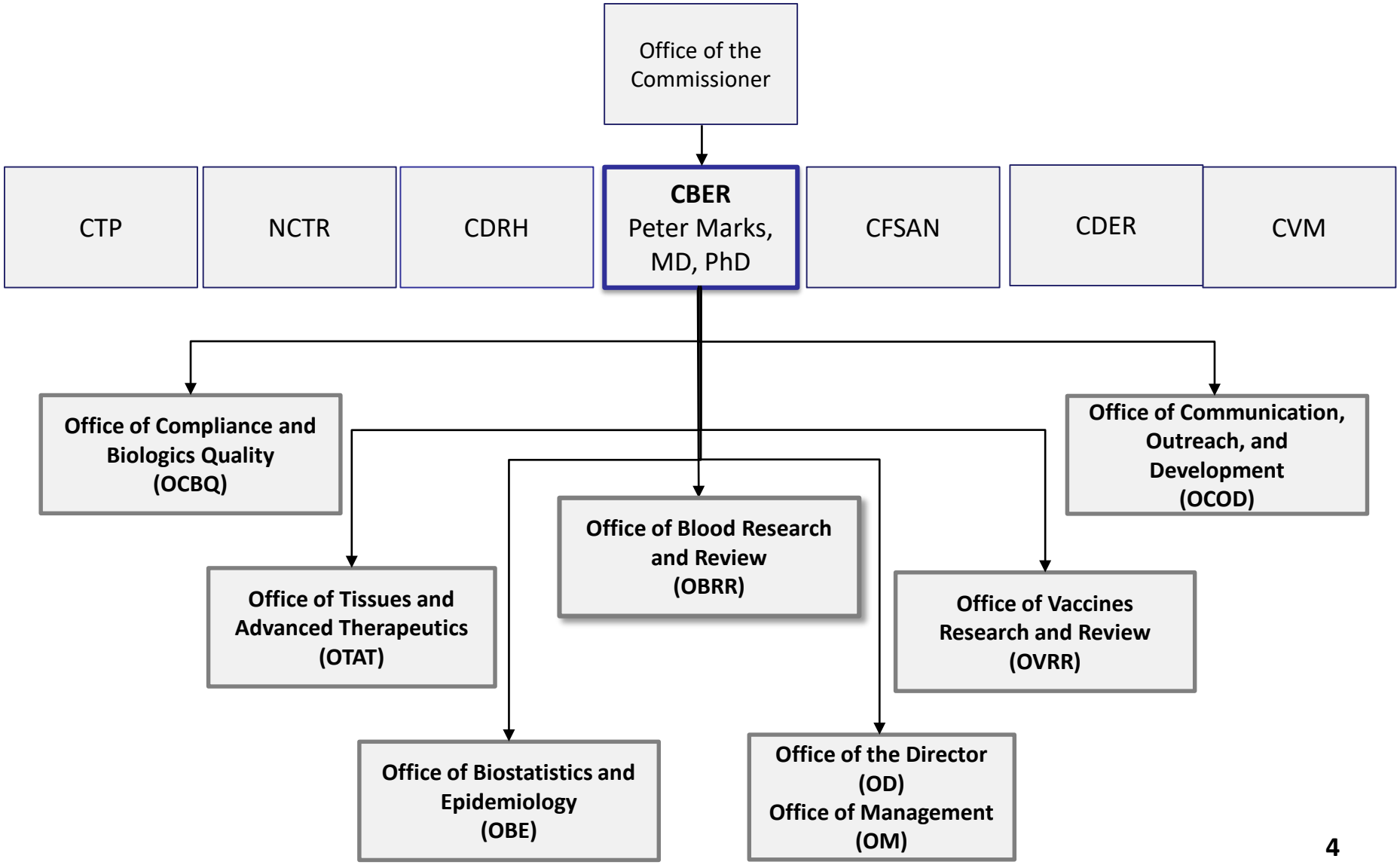
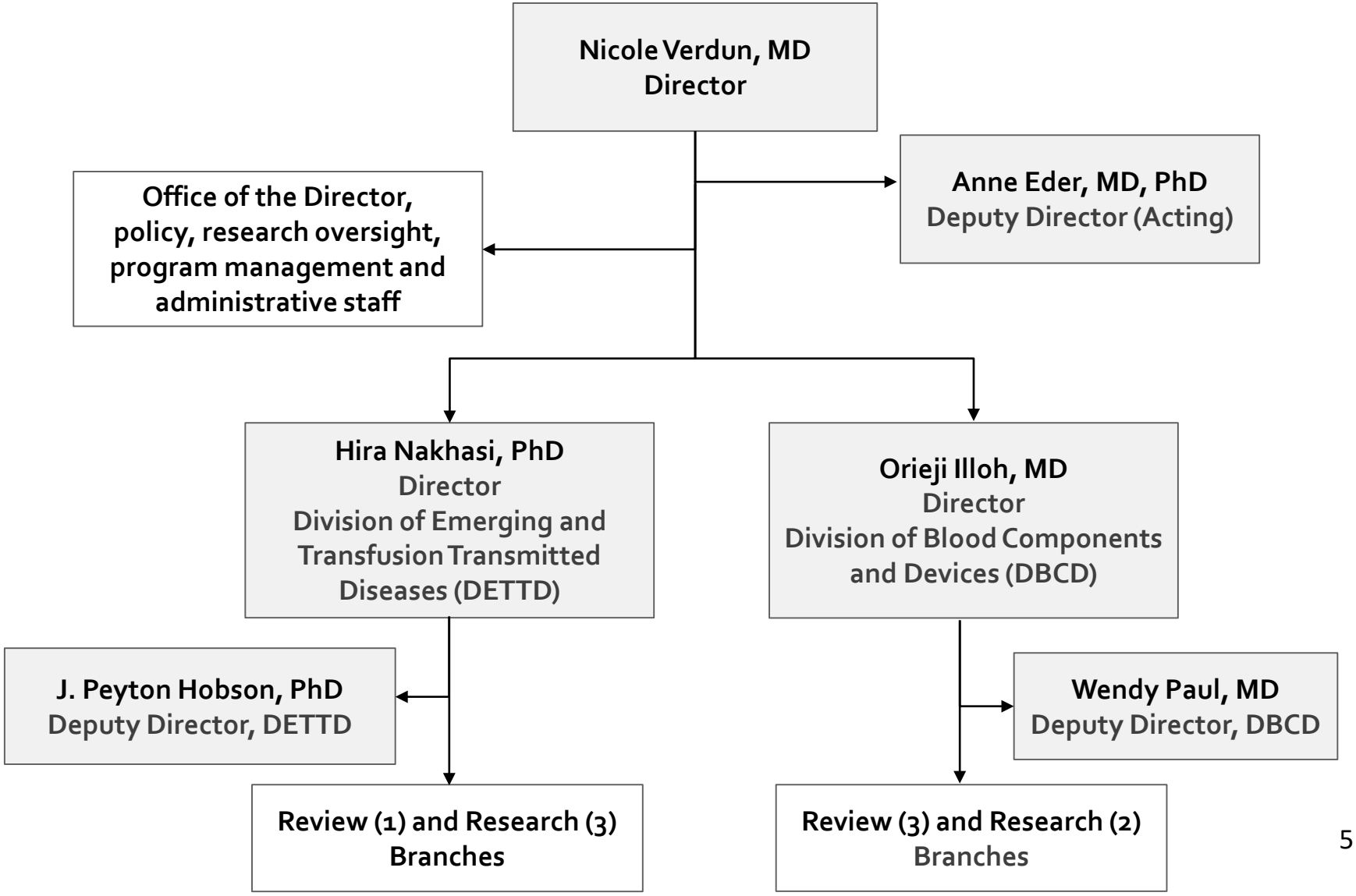
CBER Organizational Chart



OBRR Organizational Chart



Devices Reviewed by OBRR

DETTD

- Blood donor screening and supplemental tests

  Babesia, Chagas, CMV, HBsAg, HBc, anti-HBV, HCV, HIV, Syphilis, WNV, Zika
- Source Plasma donor screening tests
- Retroviral diagnostic tests (HIV/HTLV)
  - Diagnosis
  - Monitoring
  - Supplemental

DBCD

- Blood grouping reagents
- Reagent Red Blood Cells
- Anti-Human Globulin
- Automated immunohematology analyzers
- Molecular erythrocyte typing tests
- HLA, HNA, HPA - antigen and antibody test kits
- Bacterial detection tests

Offices that Review or Contribute to OBRR Submissions

- Office of Biostatistics and Epidemiology (OBE)
- Office of Compliance and Biologics Quality (OCBQ)
  - Manufacturing, CMC, Quality Systems
  - Lot release
  - Compliance, adverse event reporting, labeling
  - Inspections
- Office of Tissues and Advanced Therapy (OTAT)
  - Cadaveric claims (heart beating or non-heart beating)
- Office of Product Evaluation and Quality (OPEQ), OHT7 (formerly OIR), Center for Devices and Radiological Health (CDRH): CLIA categorization

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In Vitro Diagnostics (IVDs) are:

- Reagents, instruments, and systems used in diagnosis of disease or other conditions…in order to cure, mitigate, treat, or prevent disease.
- Intended for use in the collection, preparation, and examination of specimens taken from the human body.
- Medical devices per 201(h) of Food, Drug, & Cosmetic (FD&C) Act
- May also be biologic products subject to section 351 of Public Health Services Act

[21 CFR 809.3]

Governing Acts and Regulations

Most OBRR devices are regulated under two acts and two sets of regulations

- Public Health Service Act (42 U.S.C. sec. 351):
  - Blood and blood products are therapeutic biological products
  - Tests used to ensure that blood is pure, potent, safe, effective
  - Regulated under 21 CFR 600s
- Food, Drug and Cosmetics Act (21 U.S.C. sec. 301):
  - In vitro diagnostic devices
  - Regulated under 21 CFR 800s

Device Review is Based on the Intended Use

Intended Use (IU) includes:

- What indication?
- What population?
- What samples?
- What mode of operation?
- What other clinical information?

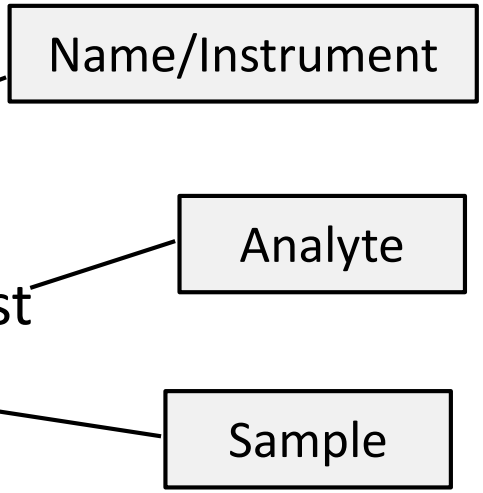
Intended Use

ACME® WNV test for use on Acme® 103i Systems, is a qualitative in vitro nucleic acid screening test for the direct detection of West Nile virus (WNV) RNA in human plasma.

This test is intended for use to screen donor samples for WNV RNA in plasma samples from individual human donors, including donors of whole blood and blood components, as well as other living donors.

This test is not intended for use as an aid in diagnosis of WNV infection.

Intended Use



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Limitation

Basis of Pre-market Device Review: Safety and Effectiveness

Safety

…the **probable benefits to health** from use of the device for its **intended uses and conditions of use**, when accompanied by adequate directions and warnings against unsafe use, **outweigh any probable risks.** [21 CFR 860.7(d)(1)]

Effectiveness

…the use of the device for **its intended uses and conditions of use,** when accompanied by adequate directions for use and warnings against unsafe use**, will provide clinically significant results.** [21 CFR 860.7(e)(1)]

Safety/Risks to Health

- **A false negative test result:**
  - Wrong result in compatibility testing: Transfusion of incompatible blood to a patient causing hemolytic transfusion reaction
  - Negative result in infectious disease testing: Transfusion of blood from infected donor causing disease in recipient
- **A false positive result:**
  - RhD+ result in RhD-negative pregnant woman resulting in missing RhD immunoglobulin shot and possible hemolytic disease of fetus and newborn
  - Positive for infectious disease: unnecessary follow-up testing, additional diagnostic studies, and psychological stress to the donor

IVD Submission Types

	Class I	Class II		Class III	BLA
Decision	Marketed	510(k) cleared (SE/NSE)	De Novo Granted	PMA approved	Licensed
Marketing Authorization Standard	Registered and listed, cGMP	Predicate Device Substantial equivalence	Safety and effectiveness	Safety and effectiveness	Safety and effectiveness
Risk-based Inspections	Risk-based	Post-market	Post-market (may be pre)	Pre-, post-market, BIMO	Pre-, post-market, BIMO
Interactions	NA	Interactive Review (IR), Additional information (AI) request	IR, AI	IR, Major Deficiency letter (MDL)	IR, Complete response (CR)
Time to decision (FDA days)	NA	90 days	150 days	180 days 320 for panel track	10 months 6 months (priority)

BIMO: Bioresearch Monitoring

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BIMO: Bioresearch Monitoring

Change Management for Marketed Devices

	510(k)[a]	PMA[b]	BLA[c]
Major changes May effect safety and effectiveness (S&E) Require pre-approval	New 510(k)	180-day, Panel track, Manufacturing site change	Comparability, efficacy, Labeling, Manufacturing (PAS)
Moderate changes- Little effect on S&E- Notification	Special 510(k), abbreviated 510(k)	30-day notice, Real time, Labeling, CBE	CBE, CBE-30
Minor changes- No effect on S&E	CLIA categorization (CR)	Annual report	Annual report

References

[a]https://www.fda.gov/media/99812/download

[b]https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modifications-devices-subject-premarket-approval-pma-pma-supplement-decision-making-process

[c]https://www.fda.gov/regulatory-information/search-fda-guidance-documents/changes-approved-application-biological-products

Representative Changes

	510(k)	PMA	BLA
Major New 510(k), 180-day, panel track	•New antibody •Remove limitation	•New antibody •Mfg site change	•New key reagents •Mfg site change
Moderate 30DN, CBE, CBE-30, special 510(k)	•Add clinical data •Update reference range	•Add QC step •New cleaning process	•Automate process •Labeling changes
Minor CLIA categorization, Annual report	•Add a limitation •Clarify instructions	•Extend stability per approved protocol •Tighten specifications	•Add timepoints to stability protocol •Labeling changes

References
[a]https://www.fda.gov/media/99812/download
[b]https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modifications-devices-subject-premarket-approval-pma-pma-supplement-decision-making-process
[c]https://www.fda.gov/regulatory-information/search-fda-guidance-documents/changes-approved-application-biological-products

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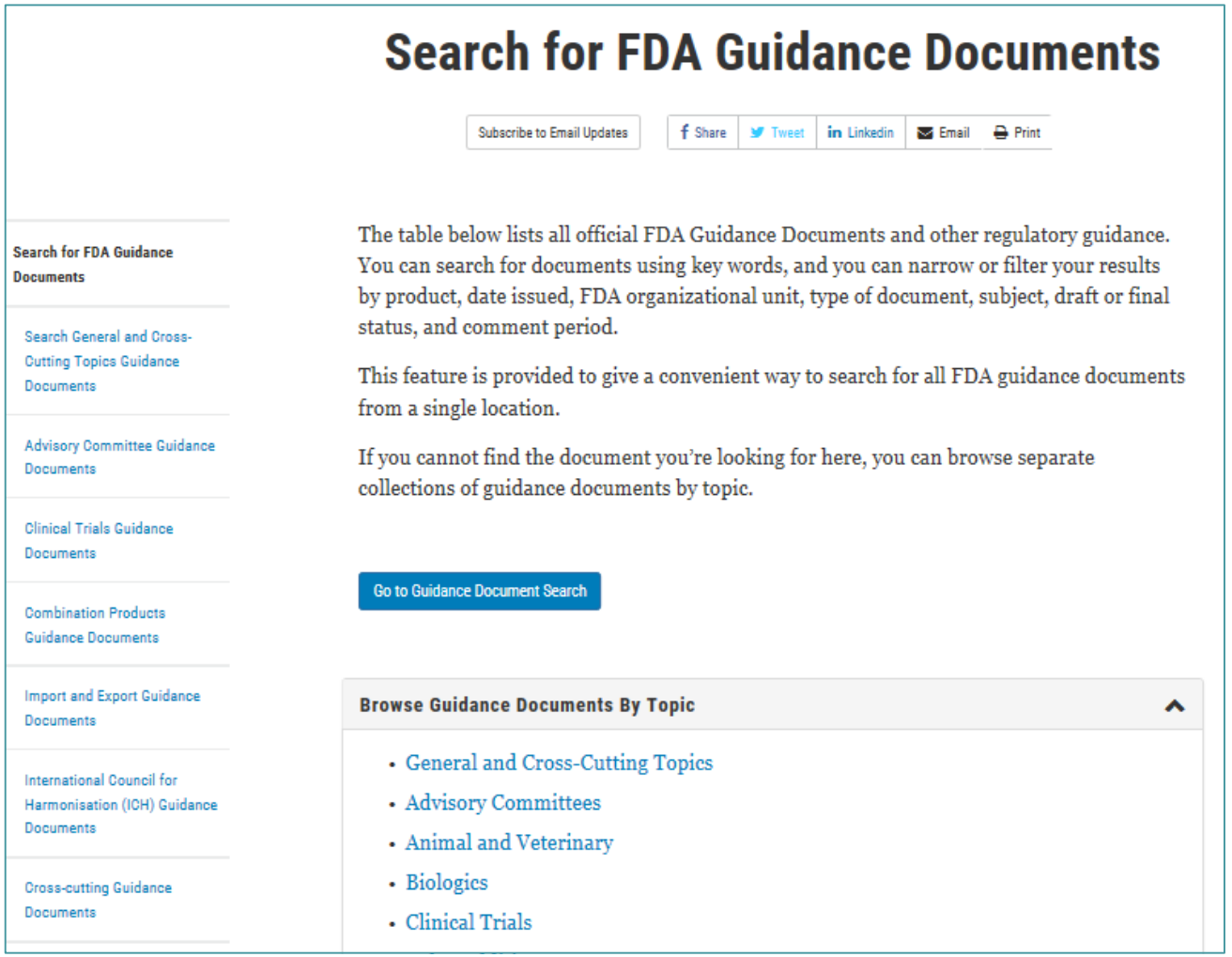
FDA Guidance Homepage

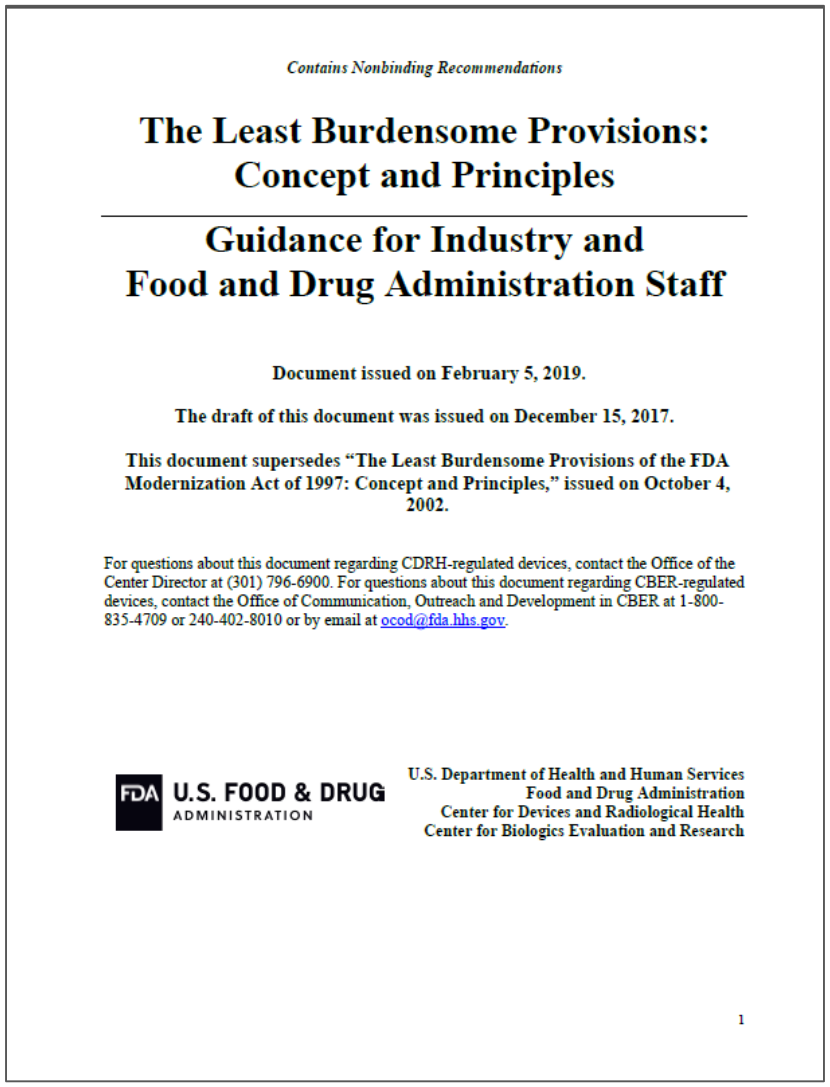


https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch

Least Burdensome Guidance

Finalized Feb. 2019

"Least burdensome": the minimum amount of information necessary to adequately address a relevant regulatory question or issue through the most efficient manner at the right time.



Contains Nonbinding Recommendations

The Least Burdensome Provisions: Concept and Principles

Guidance for Industry and Food and Drug Administration Staff

Document issued on February 5, 2019.

The draft of this document was issued on December 15, 2017.

This document supersedes "The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles," issued on October 4, 2002.

For questions about this document regarding CDRH-regulated devices, contact the Office of the Center Director at (301) 796-6900. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development in CBER at 1-800-835-4709 or 240-402-8010 or by email at ocod@fda.hhs.gov.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

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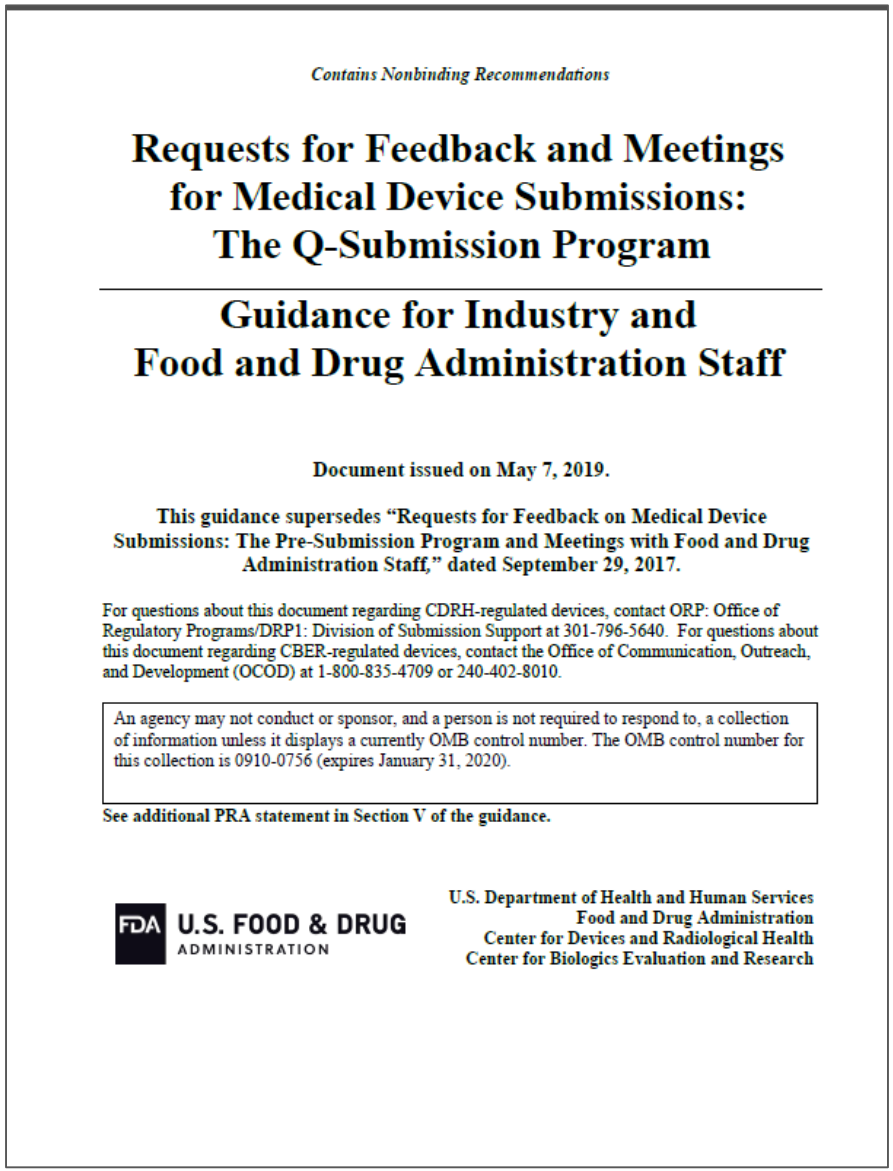
The Q-submission Program

Finalized May 2019

Changes to timelines



Contains Nonbinding Recommendations

Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program

Guidance for Industry and Food and Drug Administration Staff

Document issued on May 7, 2019.

This guidance supersedes "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff," dated September 29, 2017.

For questions about this document regarding CDRH-regulated devices, contact ORP: Office of Regulatory Programs/DRP1: Division of Submission Support at 301-796-5640. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently OMB control number. The OMB control number for this collection is 0910-0756 (expires January 31, 2020).

See additional PRA statement in Section V of the guidance.

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Guidances Applicable to Devices

- Device guidances

  https://www.fda.gov/vaccines-blood-biologics/general-biologics-guidances/devices-guidances

- Application submission guidances

  https://www.fda.gov/vaccines-blood-biologics/general-biologics-guidances/application-submissions-guidances

- MDUFA IV performance goals

  https://www.fda.gov/media/102699/download

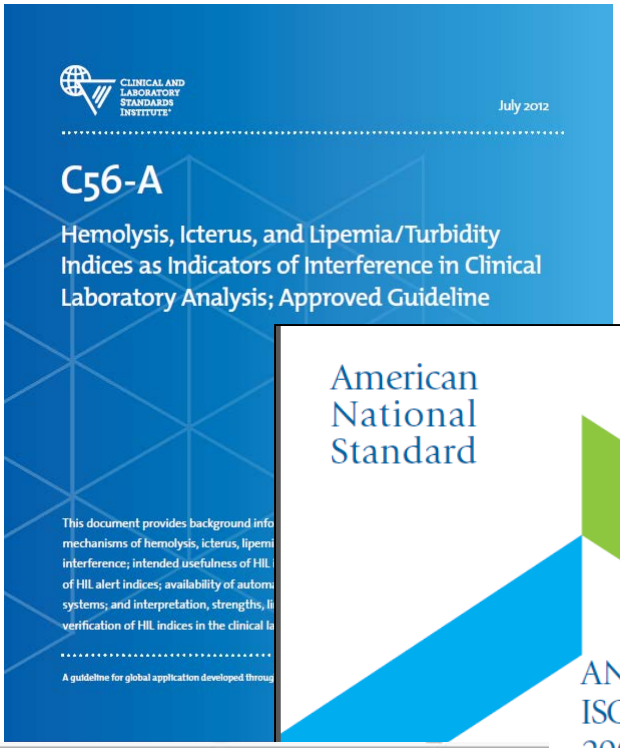
Blood Products Advisory Committee (BPAC)

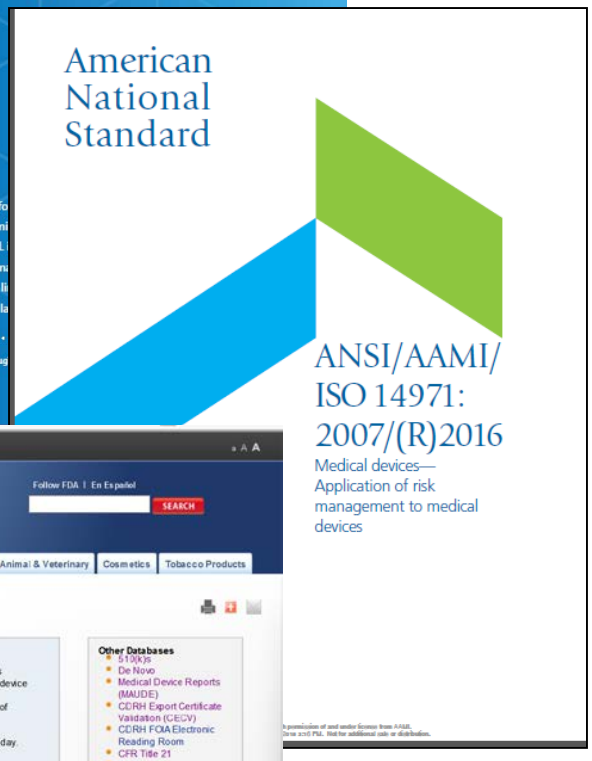
- FDA's Advisory Committees provide independent advice from outside experts on relevant issues
- Composition
  - Voting: Authorities knowledgeable in blood banking, medicine, immunology, epidemiology other professionals
  - Non-voting: Industry representative, consumer rep (device panels)
- Meet regularly to provide advice on issues of importance to FDA/CBER/OBRR
  - Specific device approvals as needed
  - Classification, reclassification of devices
  - Pathogen reduction of blood components

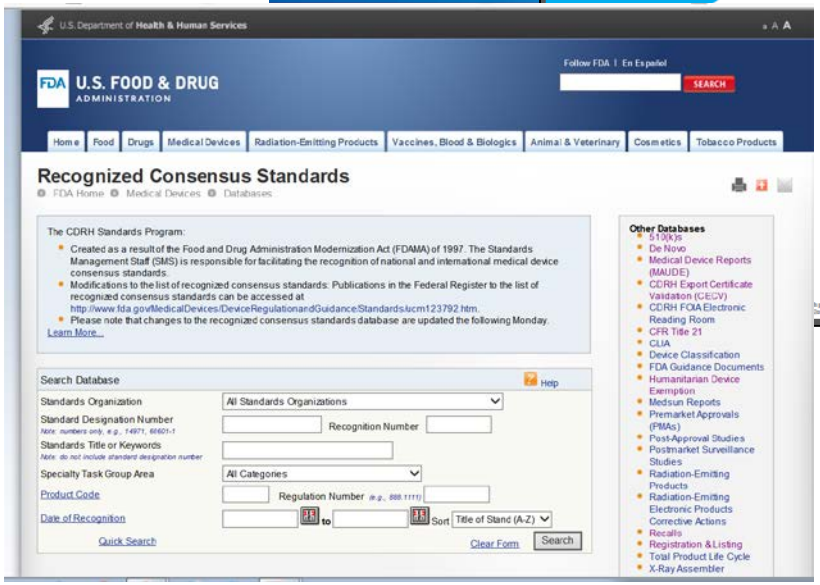
Recognized Consensus Standards

- Standards produced by experts to present best practices for specific aspects of validation
- FDA recognizes certain standards

FDA Standards Website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm







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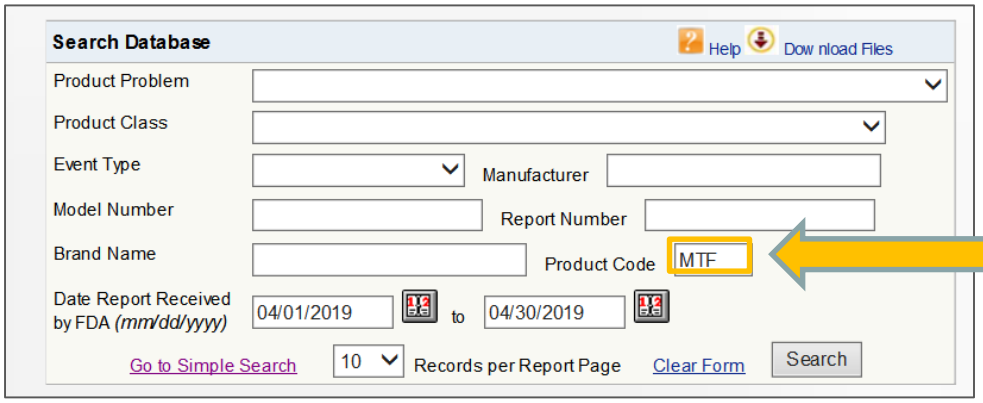
What's New? Product Codes for BLA Devices



Procode

- Random three-letter codes used for
  - Adverse event reporting
  - Searching databases
- Manufacturers will receive letters with new product codes (procodes)

Resources for Sponsors

- Reagents
  - Reference panels for development
  - Analyte reference standards for validation
  - DNA reference samples
- Workshops
  - Disease-specific: Babesia spp.
  - Technology-specific: Next-Gen Sequencing
  - Education and Outreach: IVD roundtable

CBER Office of Communications, Outreach & Development

Manufacturer's Assistance and Technical Training Branch (MATTB)

- How to submit-eCopy, etc.
- Registration and listing
- Email
- User fees

Email: Industry.biologics@fda.hhs.gov

Phone: 240-402-8020 or 1800-835-4709

Website: https://www.fda.gov/vaccines-blood-biologics/industry-biologics/manufacturers-assistance-and-technical-training-branch-mattb

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Elements Covered in the Workshop

Pre-Market:
Common Elements

PreSubmission
Iwona Fijalkowska

IND/IDE
Caren Chancey

CMC
Rana Nagarkatti
Lori Peters

Software
Lisa Simone

Lot Release
Kori Francis

BIMO
Bhanu Kannan

Pre-Licensure Inspection
Nicole Li

Not every element applies to every device

Elements Covered in the Workshop

Pre-Market:
Indication-Specific Considerations

Infectious Disease Screening

Donor-Recipient Compatibility

Analytical
Krishna Ketha

Clinical
Babita Mahajan

Cadaveric Claims
Brychan Clark

Immunohematology
Kimberly Bigler
Annette Ragosta

Molecular Tests
Zhugong (Jason) Liu

Not every element applies to every device

Elements Covered in the Workshop

Post Market

CLIA Categorization
Peter Tobin

Biological Product Deviation Reporting
Sharon O'Callaghan

Medical Device Reporting
Bima Patel

Not every element applies to every device

Thank you!

Anne Eder

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