October 2018 FDA Update

Brendan O'Leary
Division Director
Division of Program Operations and Management
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Today's Agenda:

- Introduction & Staffing Changes
- Final Guidance Update
- Draft Guidance Update
- Breakthrough program is taking off
- CLIA Waiver Program improvements continue

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Introducing OIR's new Director, Tim Stenzel, MD, PhD

- **As a student,** studied microbiology and immunology at Duke, chemistry at Grinnell College
- **As an academic researcher,** created Duke's Clinical Molecular Diagnostics Laboratory and researched performance evaluation and quality assurance for genetic testing
- **As a developer,** created/launched numerous diagnostics, including NGS + CoDx
- **As an executive,** served in leadership roles at Invivoscribe, Quidel, Asuragen, Vysis/Abbott Molecular, and now FDA

Director	Timothy Stenzel
Deputy Dir. for New Product Evaluation	Donald St. Pierre
Deputy Dir. for Patient Safety and Product Quality	Vacant
Deputy Dir. for Personalized Medicine	Stayce Beck (Acting)
Deputy Dir. for Radiological Health	Robert Ochs
Associate Dir. for Programs and Performance	Elizabeth Hillebrenner
Associate Dir. for Strategic Initiatives	Toby Lowe
Associate Dir. for Regulatory Counsel	Scott McFarland
Chief Medical Officer	Vacant
Chief Medical Officer for Radiological Health	Donald L. Miller

Division of Chemistry and Toxicology Devices (DCTD)

Director – Courtney Lias
Deputy – Kellie Kelm

Division of Immunology and Hematology Devices (DIHD)

Director – Lea Carrington
Deputy – Vacant

Division of Microbiology Devices (DMD)

Director – Uwe Scherf
Deputy – Steve Gitterman

Division of Molecular Genetics and Pathology (DMGP)

Director – Reena Philip
Deputy – Yun-Fu Hu

Division of Mammography Quality Standards (DMQS)

Director – Helen Barr
Deputy – Preet Sudhaker (Acting)

Division of Program Operations and Management (DPOM)

Director – Brendan O'Leary
Deputy – Vacant
PMO – Scott McCall

Division of Radiological Health (DRH)

Director – Thalia Mills (Acting)
Deputy – Michael O'Hara
Deputy – Ting Song (Acting)

OIR by the numbers: We're proud of our talented, well-educated, and professional staff

About **290** Scientists & Engineers

- **>20** MDs
- **>150** PhDs
- **>40** Masters

CDRH by the numbers:

>90%

external customer satisfaction rating

100%

of MDUFA 4 FDA-Days Goals Met

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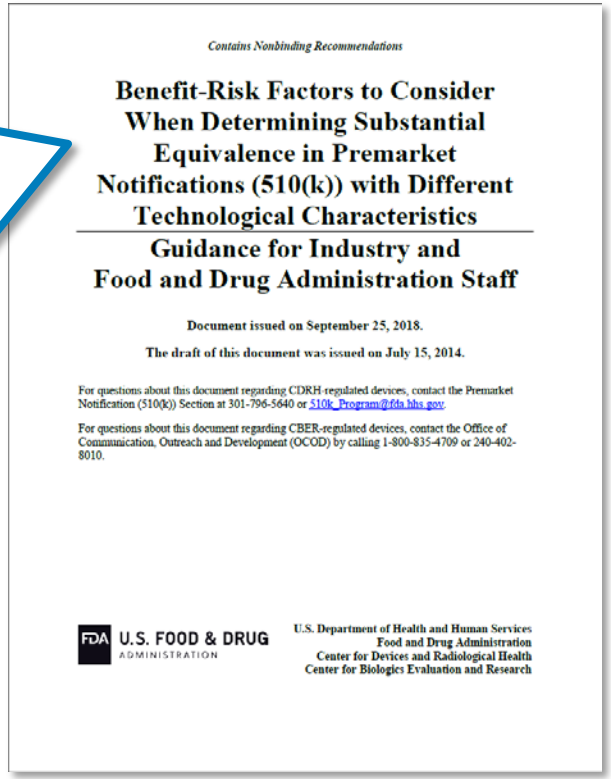
Final Guidances advance novel and risk-based regulatory approaches

1. Benefit-Risk for 510(k)
2. Voluntary Consensus Standards
3. LOINC Codes
4. NGS design, development and analytical validity
5. Genetic Variant Databases as sources of clinical evidence

New Benefit-Risk guidance is loaded with recommendations for diagnostics

For diagnostic devices specifically, benefit(s) in reference to the nature of the public health impact, could be based on a number of factors including:

- Identification of a specific disease;
- Provision of diagnosis at different stages of a disease;
- Prediction of future disease onset;
- Improvement of patient workflow;
- Increase in efficiency or examination;
- Provision of reproducible and quantifiable results contributing to the optimization of therapy and treatment; and
- Improvement of patient outcome (e.g., well-being, health status, safety of patients) by facilitating fewer missed diagnoses (or the right diagnosis the first time, hence the correct treatment plan) and/or identification of patients likely to respond to a given therapy and therefore enable treatment of the disease or reduce/prevent its spread, which can often be measured through the use of PROs.



Contains Nonbinding Recommendations

Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 25, 2018.

The draft of this document was issued on July 15, 2014.

For questions about this document regarding CDRH-regulated devices, contact the Premarket Notification (510(k)) Section at 301-796-5640 or 510k_Program@fda.hhs.gov.

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD) by calling 1-800-835-4709 or 240-402-8010.

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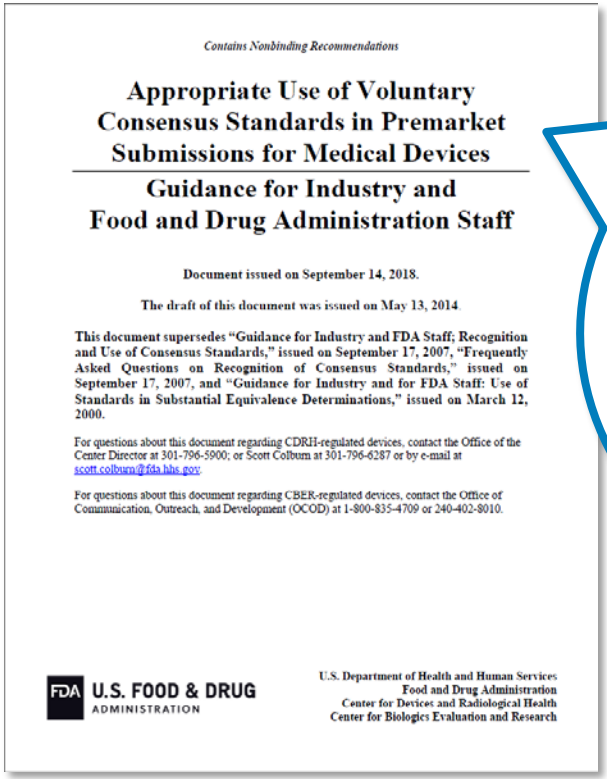
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

FDA continues increased emphasis on standards, implementing *Cures* legislation



Contains Nonbinding Recommendations

Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 14, 2018.

The draft of this document was issued on May 13, 2014.

This document supersedes "Guidance for Industry and FDA Staff; Recognition and Use of Consensus Standards," issued on September 17, 2007, "Frequently Asked Questions on Recognition of Consensus Standards," issued on September 17, 2007, and "Guidance for Industry and for FDA Staff: Use of Standards in Substantial Equivalence Determinations," issued on March 12, 2000.

For questions about this document regarding CDRH-regulated devices, contact the Office of the Center Director at 301-796-5900; or Scott Colburn at 301-796-6287 or by e-mail at scott.colburn@fda.hhs.gov.

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.

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Food and Drug Administration
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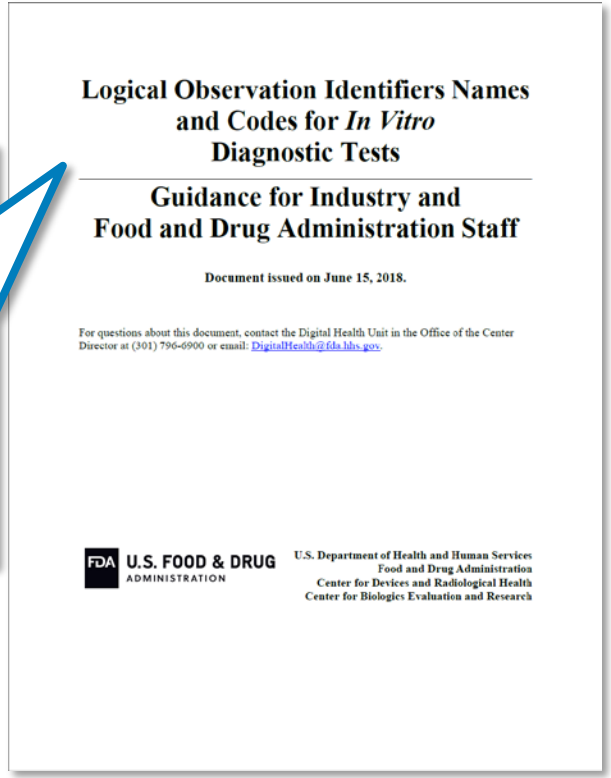
"The use of consensus standards can increase predictability, streamline premarket review, provide clearer regulatory expectations, and facilitate market entry for safe and effective medical products."

We've clarified expectations for communicating LOINC codes for unapproved uses

- Upon receipt of an "…individual, unsolicited request…"
- "…where the manufacturer's response provides the appropriate LOINC coding…"
- "FDA does not intend to consider that response as evidence of the firm's intent that the product be used for unapproved or uncleared uses."*



Logical Observation Identifiers Names and Codes for *In Vitro* Diagnostic Tests

Guidance for Industry and Food and Drug Administration Staff

Document issued on June 15, 2018.

For questions about this document, contact the Digital Health Unit in the Office of the Center Director at (301) 796-6900 or email: DigitalHealth@fda.hhs.gov.

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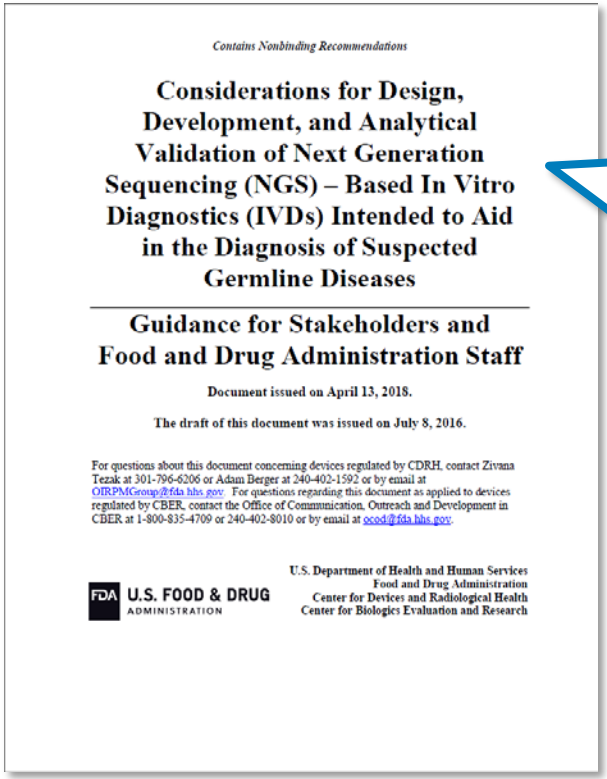
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

*** Read this guidance for full context. It's only 8 pages long.**

FDA believes innovative diagnostics merit innovative regulatory paradigms



Contains Nonbinding Recommendations

Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS) – Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases

Guidance for Stakeholders and Food and Drug Administration Staff

Document issued on April 13, 2018.

The draft of this document was issued on July 8, 2016.

For questions about this document concerning devices regulated by CDRH, contact Zivana Tezak at 301-796-6206 or Adam Berger at 240-402-1592 or by email at OIRPMGroup@fda.hhs.gov. For questions regarding this document as applied to devices regulated by CBER, 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.

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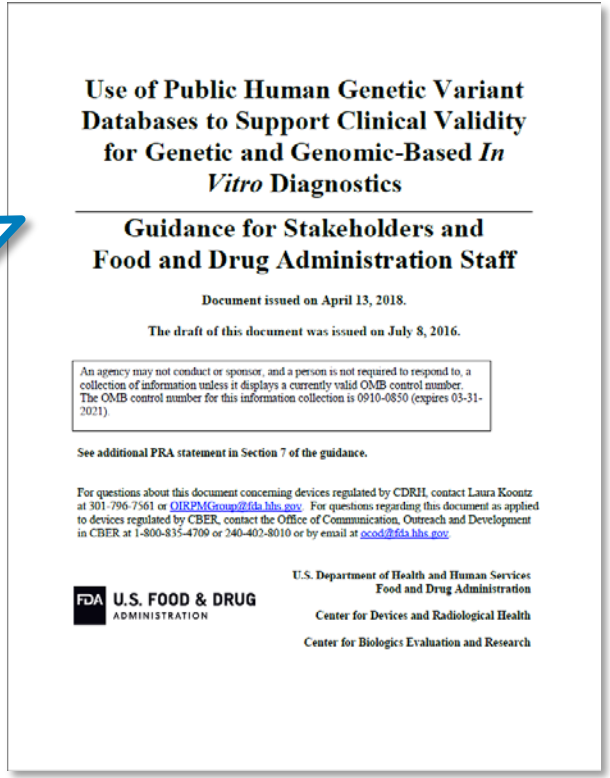
"FDA's vision is that NGS-based tests can be developed, validated, and offered for clinical use through a process that leverages appropriate standards, quality systems controls and community assessment of clinical validity to streamline the premarket review process."

Genetic Variant Database Guidance advances innovative paradigm for showing clinical validity

"publicly accessible databases of human genetic variants can serve as sources of valid scientific evidence to support the clinical validity of genotype-phenotype relationships"



Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based *In Vitro* Diagnostics

Guidance for Stakeholders and Food and Drug Administration Staff

Document issued on April 13, 2018.

The draft of this document was issued on July 8, 2016.

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 valid OMB control number. The OMB control number for this information collection is 0910-0850 (expires 03-31-2021).

See additional PRA statement in Section 7 of the guidance.

For questions about this document concerning devices regulated by CDRH, contact Laura Koontz at 301-796-7561 or OIRPMGroup@fda.hhs.gov. For questions regarding this document as applied to devices regulated by CBER, 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

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U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

Today's Agenda:

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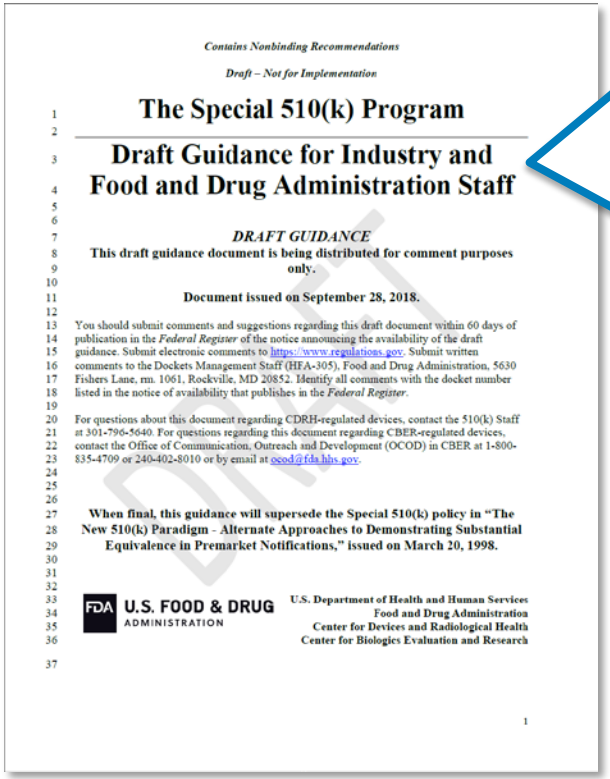
- Draft Guidance Update
- Breakthrough program is taking off
- CLIA Waiver Program improvements continue

Comment and monitor Draft Guidances to help us set our future direction

1. Special 510(k) program expansion
2. Recognition and Withdrawal of Standards
3. 3rd Party Premarket Review Program
4. Consideration of Uncertainty in Benefit-Risk
5. Q-Submission Program
6. Multiple Functions

We've proposed expanding the Special 510(k) Program



Contains Nonbinding Recommendations

Draft – Not for Implementation

The Special 510(k) Program

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on September 28, 2018.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document regarding CDRH-regulated devices, contact the 510(k) Staff at 301-796-5640. For questions regarding this document regarding CBER-regulated devices, contact the Office of Communication, Outreach and Development (OCOD) in CBER at 1-800-835-4709 or 240-402-8010 or by email at ocod@fda.hhs.gov.

When final, this guidance will supersede the Special 510(k) policy in "The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications," issued on March 20, 1998.

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U.S. Department of Health and Human Services
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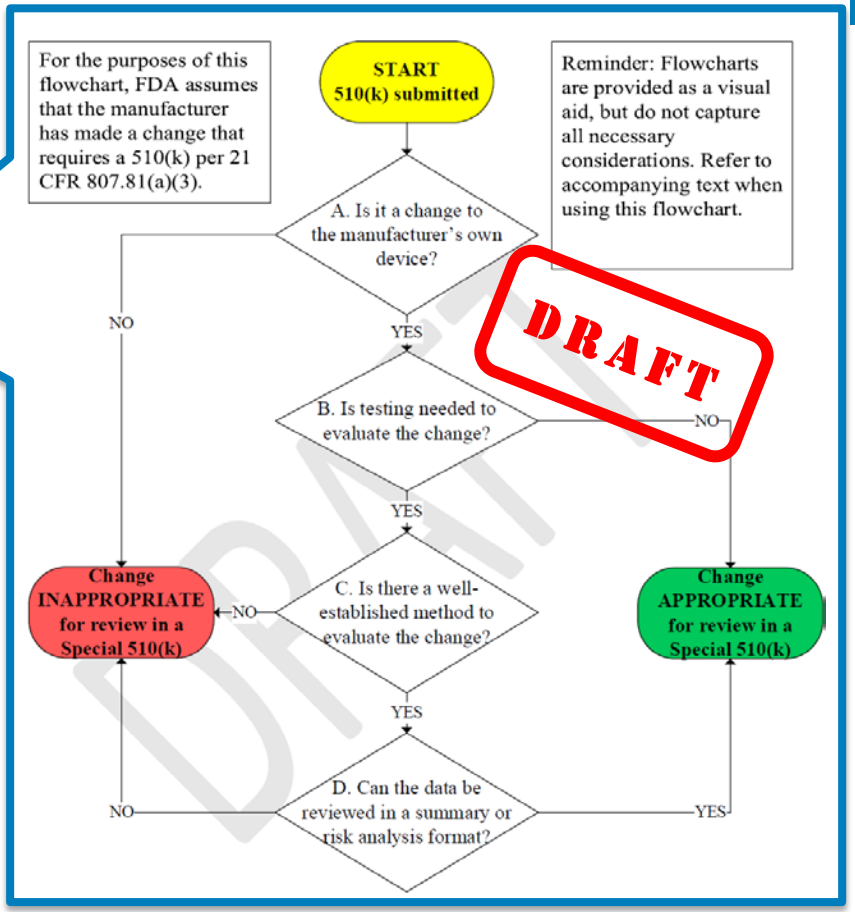
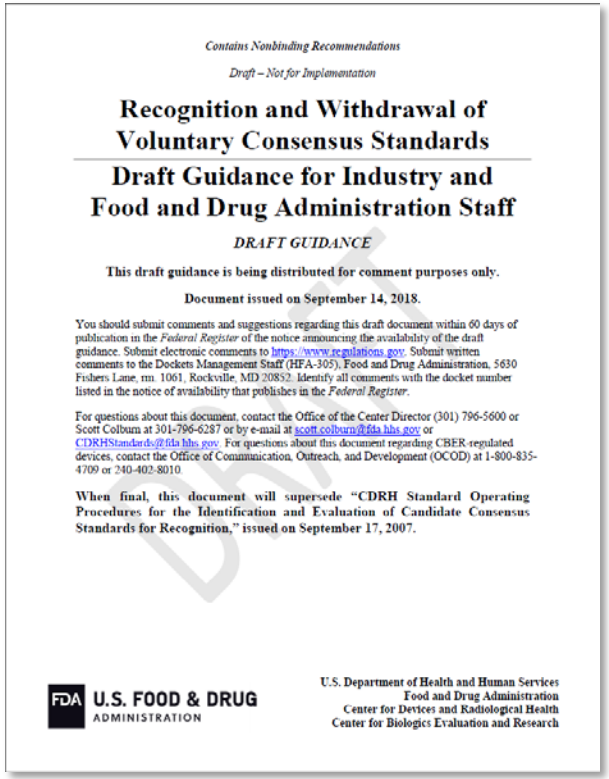


Draft guidance would improve transparency of standards recognition



Contains Nonbinding Recommendations

Draft – Not for Implementation

Recognition and Withdrawal of Voluntary Consensus Standards

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance is being distributed for comment purposes only.

Document issued on September 14, 2018.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact the Office of the Center Director (301) 796-5600 or Scott Colburn at 301-796-6287 or by e-mail at scott.colburn@fda.hhs.gov or CDRHStandards@fda.hhs.gov. 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.

When final, this document will supersede "CDRH Standard Operating Procedures for the Identification and Evaluation of Candidate Consensus Standards for Recognition," issued on September 17, 2007.

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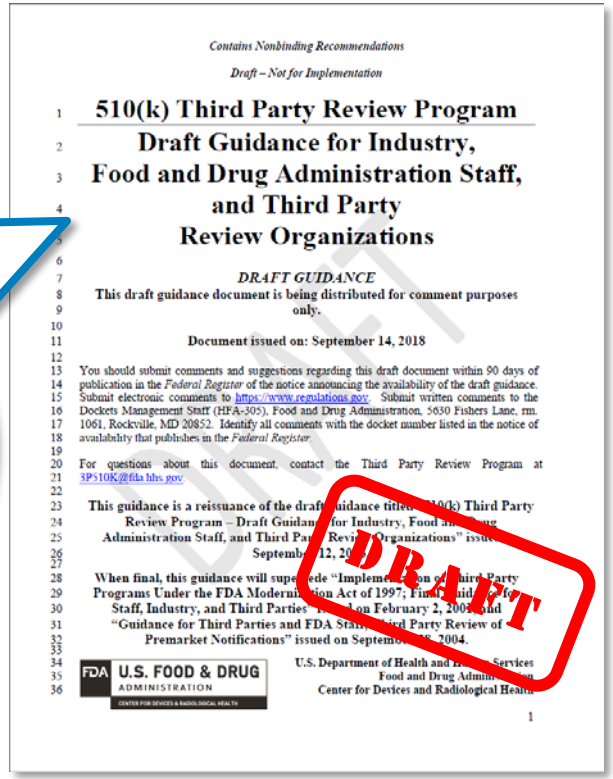
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

DRAFT

Proposed 3rd Party Review guidance would loosen clinical data restriction, reinvigorate program

"However, if a device type contains simple clinical data such as sample clinical images or tests using banked specimens, it may be eligible for 3P review. Most in vitro diagnostic (IVD) devices are eligible for 3P review..."



Contains Nonbinding Recommendations

Draft – Not for Implementation

510(k) Third Party Review Program
Draft Guidance for Industry, Food and Drug Administration Staff, and Third Party Review Organizations

DRAFT GUIDANCE
This draft guidance document is being distributed for comment purposes only.

Document issued on: September 14, 2018

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact the Third Party Review Program at 3P510K@fda.hhs.gov.

This guidance is a reissuance of the draft guidance titled "510(k) Third Party Review Program – Draft Guidance for Industry, Food and Drug Administration Staff, and Third Party Review Organizations" issued on September 12, 20

When final, this guidance will supersede "Implementation of Third Party Programs Under the FDA Modernization Act of 1997; Final Guidance for Staff, Industry, and Third Parties" issued on February 2, 2005, and "Guidance for Third Parties and FDA Staff: Third Party Review of Premarket Notifications" issued on September 2004.

DRAFT

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CENTER FOR DEVICES & RADIOLOGICAL HEALTH

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

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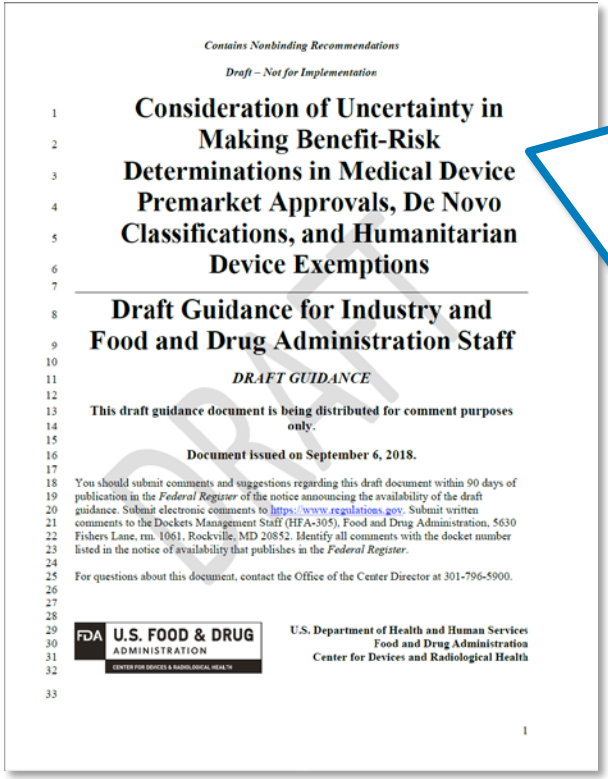
Later today: Hear how 3rd Party Premarket Review can be a key component of diagnostics regulation

"Today's framework demonstrates the FDA's continued commitment to ensuring a robust, rigorous, and streamlined third-party review process to advance timely patient access to safe, effective, and high-quality medical devices."

- *Scott Gottlieb, MD*
  23rd Commissioner of Food and Drugs

Draft "uncertainty" guidance describes possible postmarket data collection options



Contains Nonbinding Recommendations

Draft – Not for Implementation

Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on September 6, 2018.

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact the Office of the Center Director at 301-796-5900.

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Food and Drug Administration
Center for Devices and Radiological Health

1

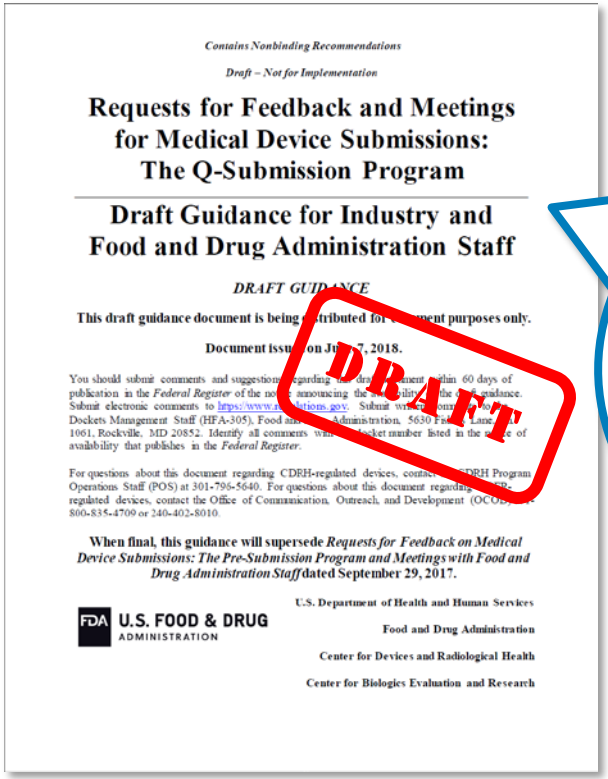
"FDA's decisions operate in the context of a broader healthcare system..."

Summary: Confidence levels and differences in sample size of premarket study

Scenario	Confidence level for both sensitivity and specificity	Number of subjects with target condition present	Study size for prevalence=20%	Postmarket data collection in light of the greater uncertainty
Case 1: Conventional Uncertainty	95%	120	600	Not applicable
Case 2: Greater Uncertainty, Modest Postmarket Data Collection	90%	80	400	Modest postmarket data collection as a condition of approval Flag postmarket data collection on FDA's website

DRAFT

Draft Q-Sub guidance would clarify differences between pre-subs, SIMs



Contains Nonbinding Recommendations

Draft – Not for Implementation

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

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on June 7, 2018.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document regarding CDRH-regulated devices, contact the CDRH Program Operations Staff (POS) at 301-796-5640. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 800-835-4709 or 240-402-8010.

When final, this guidance will supersede *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff* dated September 29, 2017.

U.S. Department of Health and Human Services

Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

FDA U.S. FOOD & DRUG ADMINISTRATION

DRAFT

Pre-Subs help improve predictability about what information is appropriate to support a marketing application before you spend precious resources on testing

Draft Multiple Function guidance would clarify a key *Cures* provision

- "Architecture decisions early in the design cycle can facilitate optimal separation and support segregation necessary for risk control."
- "The higher the degree of separation, the easier it is to independently review... the device function-under-review."
- "In the premarket review of a device function-under-review, FDA may assess the impact of other functions on the device function-under-review."

Contains Nonbinding Recommendations

Draft – Not for Implementation

Multiple Function Device Products: Policy and Considerations

Draft Guidance for Industry and Food and Drug Administration

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on April 27, 2018.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document regarding CDRH-regulated devices, contact Linda Ricci at Linda.Ricci@fda.hhs.gov or at 301-796-6325 or the CDRH Digital Health Program at DigitalHealth@fda.hhs.gov. 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.

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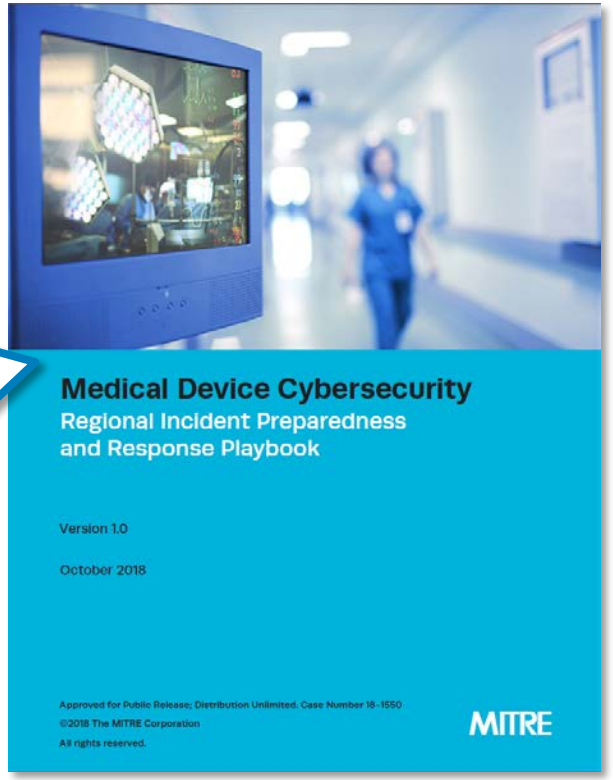
MITRE Cybersecurity Playbook* mentions manufacturers' role >40 times

"Through planning and practice, as well as support from and collaboration with manufacturers and regional and national partners, HDOs can be well positioned to manage medical device cybersecurity incidents."



* Not guidance.

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More breakthrough diagnostics are coming to market through FDA

>95 designated devices

- **29** diagnostics

8 devices authorized to market

- **4** PMAs approved
- **2** 510(k)s cleared
- **2** De Novos granted

Tomorrow: Hear how the breakthrough program expedited a diagnostic for concussion

"The FDA's review team worked closely with the test developer and the U.S. Department of Defense to expedite a blood test for the evaluation of mTBI that can be used both in the continental U.S. as well as foreign U.S. laboratories that service the American military."

- *Jeff Shuren, MD*
  CDRH Director

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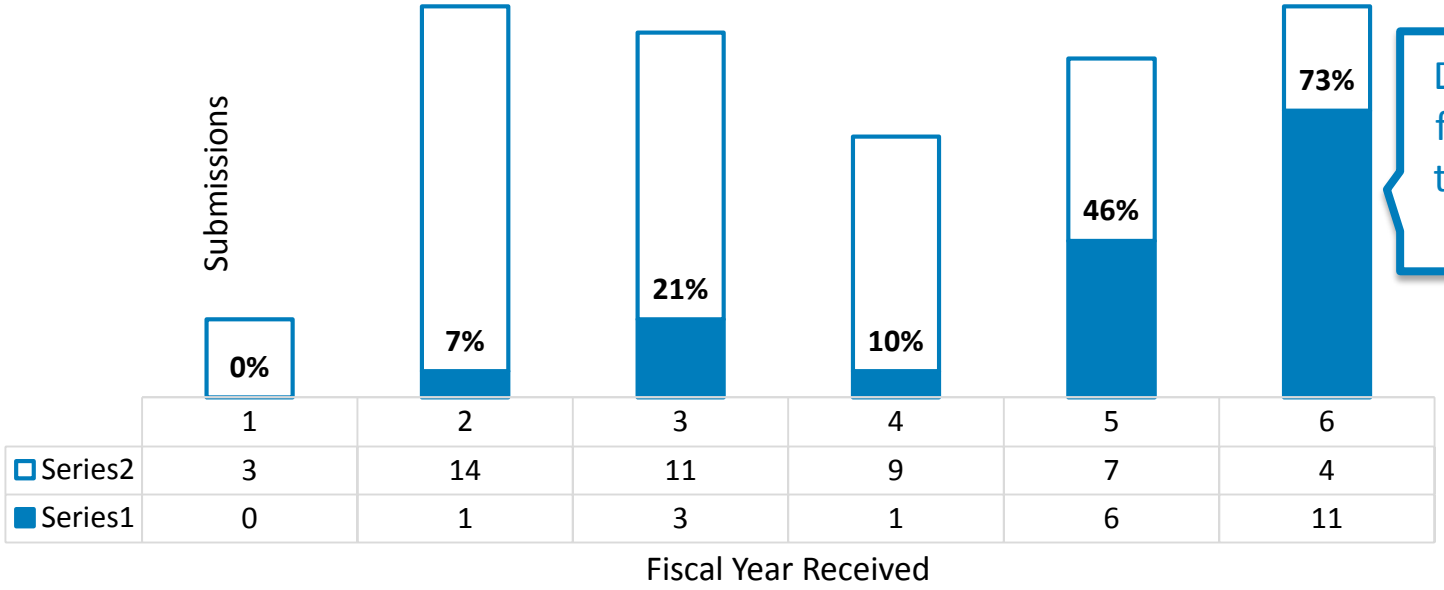
Dual CWs eclipsed standalone CWs as the preferred waiver pathway in FY18



CLIA Waiver Decision Summaries:
https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm578178.htm

Questions?

oir-policy@fda.hhs.gov