Introduction to FDA's Role in Regulation of Alzheimer's Diagnostic Tests

ALZHEIMER'S DISEASE CENTER PROGRAM, DIVISION OF NEUROSCIENCE, NIA/NIH Spring Meeting

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Disclosures

I have no financial conflicts to disclose

Disclaimer

This presentation is intended for informational purposes only and does not constitute legal or regulatory advice. Please see the Federal Food, Drug, and Cosmetic Act and 21 CFR Subchapter H for a full list of requirements by FDA

Outline

1. Introduction to how FDA regulates in vitro diagnostic tests
2. Our experience with Alzheimer's tests

CDRH Mission

The mission of the Center for Devices and Radiological Health (CDRH) is to protect and promote the public health.

We assure that patients and providers have timely and continued access to **safe, effective, and high-quality medical devices** and safe radiation-emitting products.

We provide consumers, patients, their caregivers, and providers with understandable and accessible **science-based information** about the products we oversee.

We facilitate medical device innovation by advancing regulatory science, providing industry with **predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices.**

https://www.fda.gov/MedicalDevices/default.htm

In Vitro Diagnostic (IVDs) Are Medical Devices [21 CFR 809.3]:

1. Reagents, instruments, and systems used in diagnosis of disease or other conditions…
2. In order to cure, mitigate, treat, or prevent disease…
3. Intended for use in the collection, preparation, and examination of specimens taken from the human body

Tests/assays that can consist of (for example only):

A. Reagents (antibodies, primers, buffers, enzymes)
B. Instruments or readers (mass spectrometer, spectrophotometer, DNA sequencer, PCR machine)
C. Software for data generation, analysis, reporting of results
D. That are used to detect or quantify something (protein, DNA, RNA, metabolite, drug)
E. That are used to manage patient care either with or without a prescription (diagnosis, prognosis, prediction, monitoring)

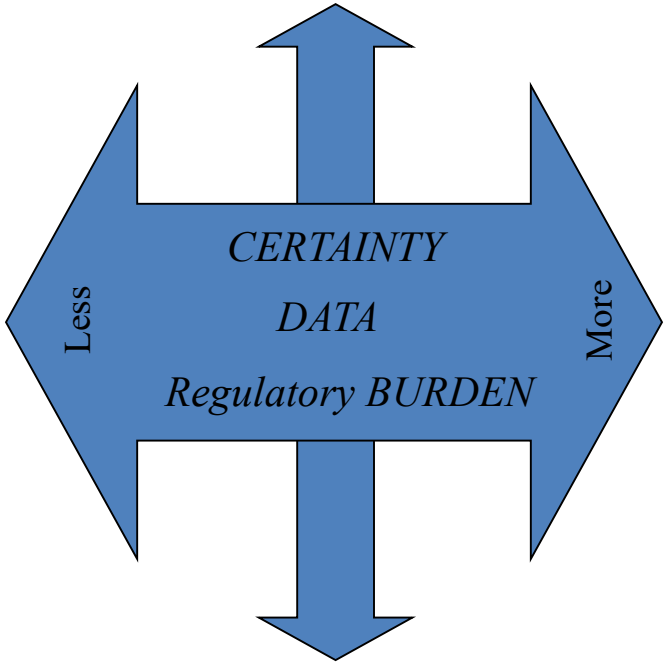
Devices Are Evaluated According to Risk

For IVDs, risk is assessed by the impact of a false positive or false negative result on patients

1. Class I: low risk (e.g., mass spectrometer)
2. Class II: moderate risk (most IVDs: 510(k) or De Novo)
3. Class III: high risk (e.g., screening for cancer: PMA)

Each risk class has its own standard of evidence and requirements for review

Striking the Balance

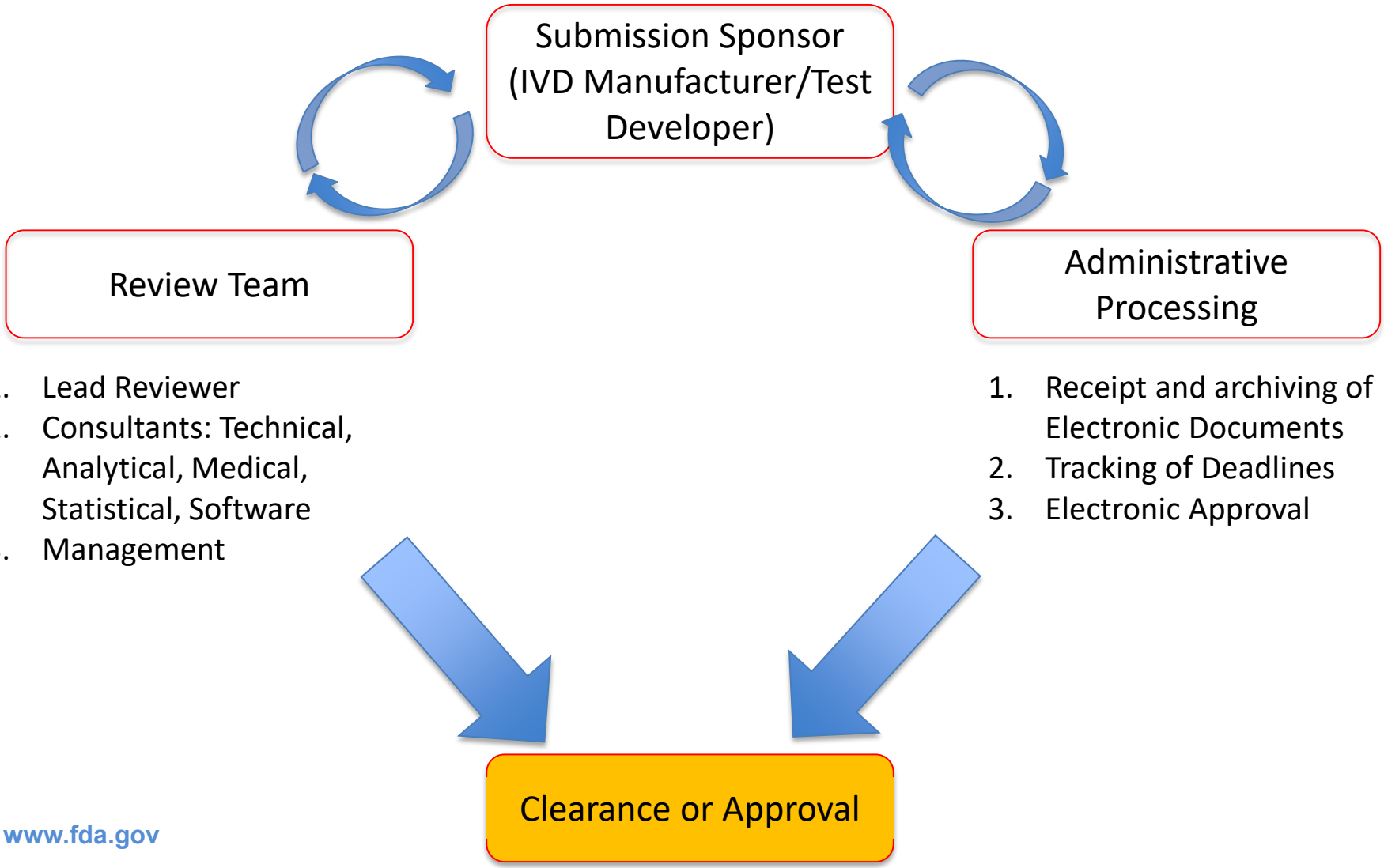


Least Burdensome Principle: the minimum amount of information necessary to adequately address a regulatory question or issue through the most efficient manner at the right time.

What Does FDA Review in a Submission?

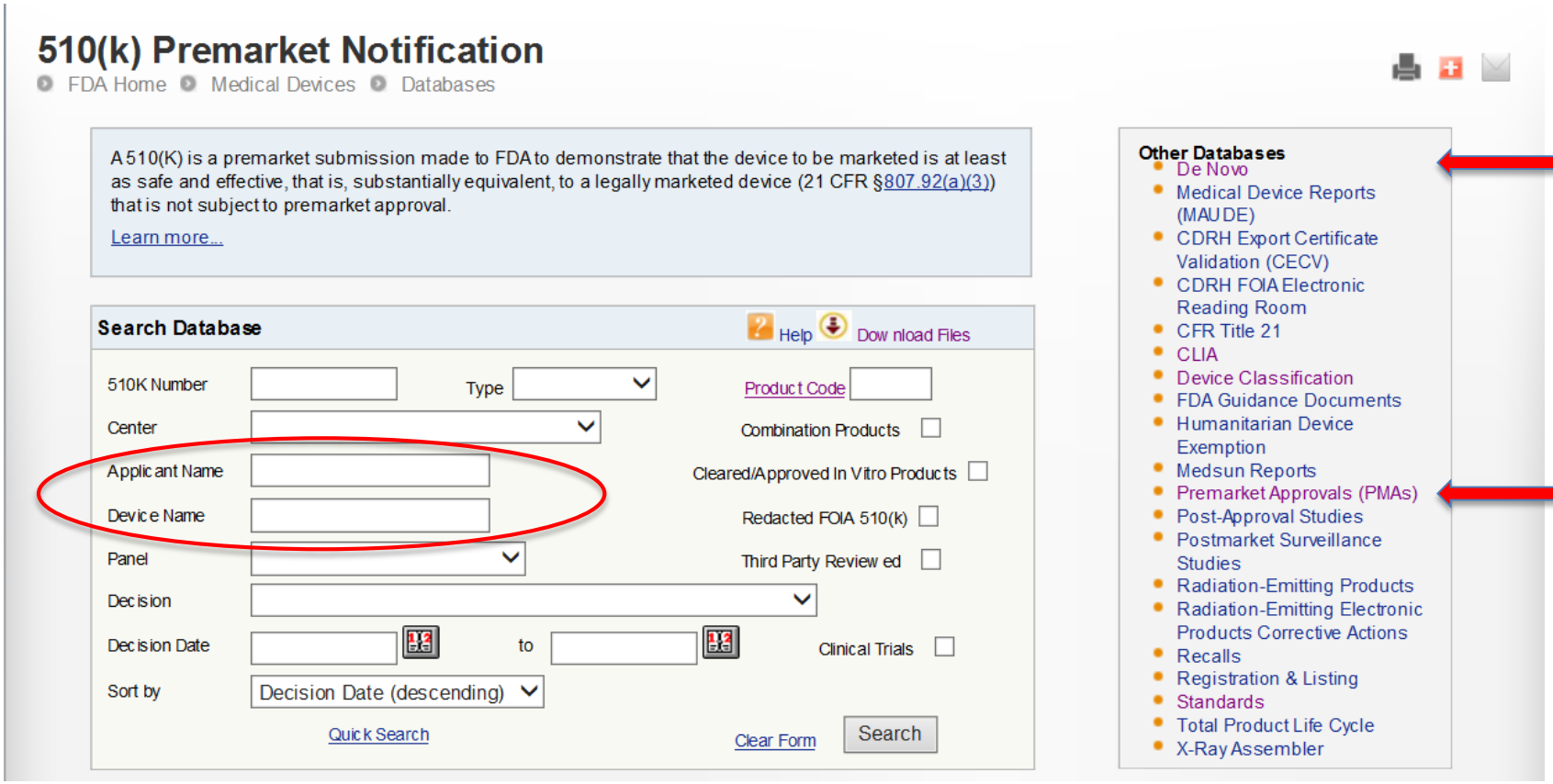
1. Intended Use/Indications for Use
2. Analytical performance testing
3. Clinical performance testing
4. Software
5. Device labeling (package insert/instructions for use/SOP)

Submissions Are Reviewed by a Large Team of Experts



Where to Find Information on Testing Performed for Marketed Devices

The 510(k), De Novo, and PMA Databases



https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

Intended Use Elements

- Assay name
- Technology
- Instrument name
- Sample matrices (serum, plasma)
- Quantitative or qualitative
- Clinical use – disease /condition
- The clinical purpose (diagnosis, prognosis, monitoring)
- The target population for whom the test is intended
- Setting (clinical laboratory, point-of-care, etc.)

Intended Use Example (cleared LC-MS assay)

Matrix

Analyte(s)

The Vitamin D 200M Assay for the Topaz System is intended for in vitro diagnostic use in the quantitative determination of total 25-hydroxyvitamin D (25-OH-D) through the measurement of 25-hydroxyvitamin D3 (25-OH-D3) and 25-hydroxyvitamin D2 (25-OH-D2) in human serum using LC-MS/MS technology by a trained laboratory professional in a clinical laboratory. The Assay is intended for use with the Topaz System. The Vitamin D 200M Assay for the Topaz System is intended to be used in conjunction with other clinical or laboratory data to assist the clinician in making individual patient management decisions in an adult population in the assessment of vitamin D sufficiency.

Intended Population

Indication for Use

Analytical Performance Testing

- Precision (EP05-A3)
- Linearity/assay reportable range (EP6-A)
- Detection Limit/Analytical Sensitivity (EP17-A2)
- Cross reactivity/ Interfering substances (EP07-A3)
- Method comparison (to a predicate or reference method)
- Matrix comparison
- Stability, Traceability, Expected values for reagents, calibrators, and controls

Clinical and Laboratory Standards Institute

Clinical Performance Testing (Alzheimer's Disease Examples)

DEN160026: 23andMe Genetic Health Risk Test	1. Detect APOE4 variants in gDNA 2. APOE4 genotype associated with increased risk of late-onset AD 3. Submission supported by literature
Clinical Trial Assays	1. Measurement of beta-amyloid 2. Detection of PSEN1/PSEN2/APP variants associated with familial AD 3. Used to select patients for drug trials
Aid in the Diagnosis of Alzheimer's Disease	1. Measurement of Aβ40 and Aβ42 2. Comparison to PET imaging 3. Used in conjunction with other clinical data to evaluate patients suspected of having AD

Features of a Pre-Sub

- Voluntary interaction with the FDA
- It is free!
- Solicit comments and feedback on features of upcoming submissions, such as study design, intended use, statistical analysis approaches and regulatory path
- Always best to get FDA's *current* thinking on the clinical and analytical study design

Why Submit a Pre-Submission?

A pre-submission is a way to interact with us early and to shape your pre-market device submission in a way that facilitates clearance or approval.

Summary

1. FDA regulates in vitro diagnostic tests
2. There are a few examples of tests for Alzheimer's disease that we have seen


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Backup Slides

How to Submit a Pre-Submission

- Two copies are required (One copy must be an electronic copy (eCopy*))
- Requests are submitted through the Document Control Center (DCC)
- Address for Q-Subs:

  U.S. Food and Drug Administration

  Center for Devices and Radiological Health

  Document Control Center (DCC) WO66-G609

  10903 New Hampshire Avenue Silver Spring, MD 20993-0002
- Q-Sub applicants will receive an acknowledgement letter that contains the Q number

*http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/guidanceDocuments/UCM313794.pdf

References

- Guidance Documents:

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.Htm

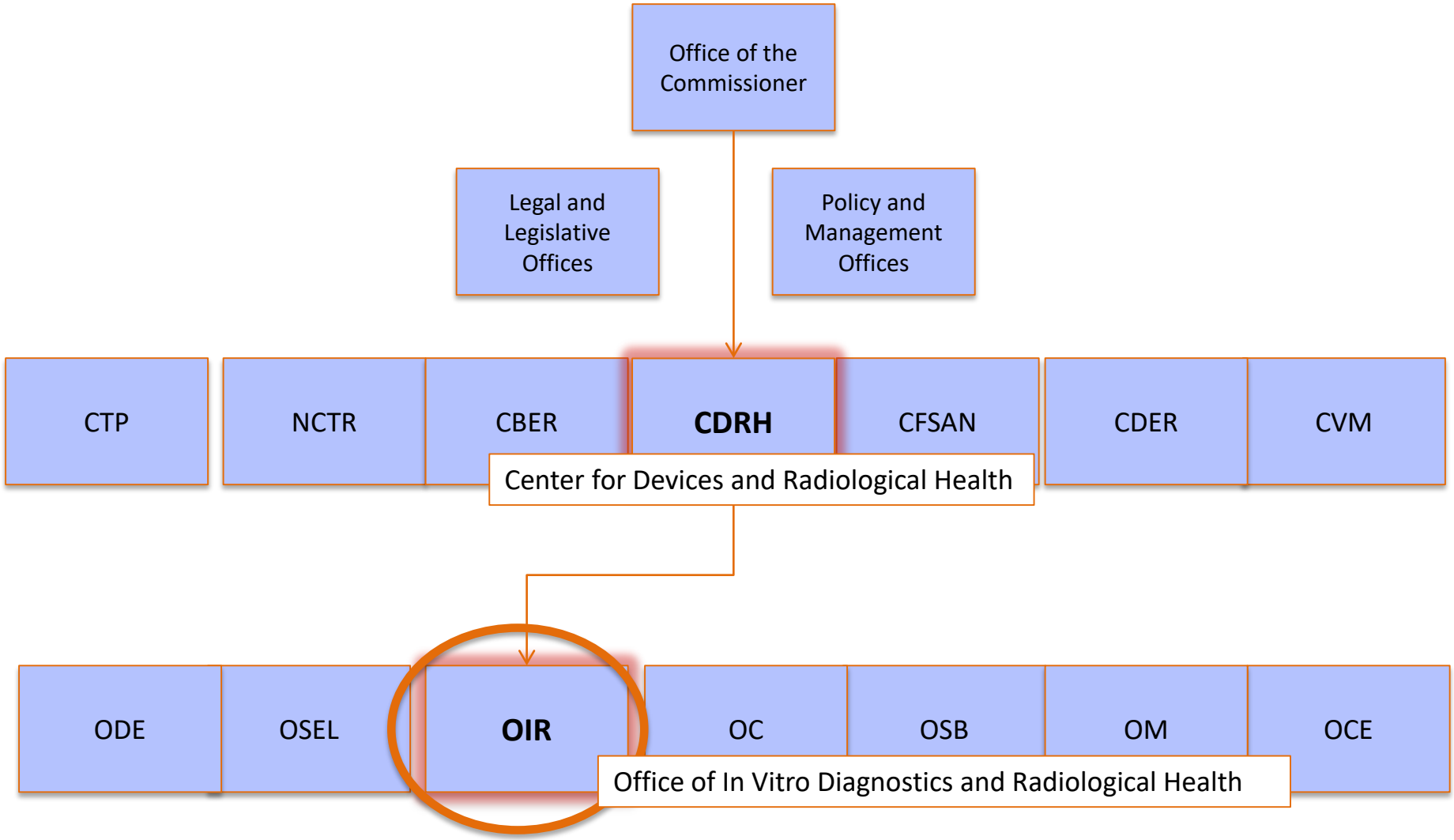
- Division of Industry and Consumer Education (DICE):

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ContactDivisionofIndustryandConsumerEducation/default.htm

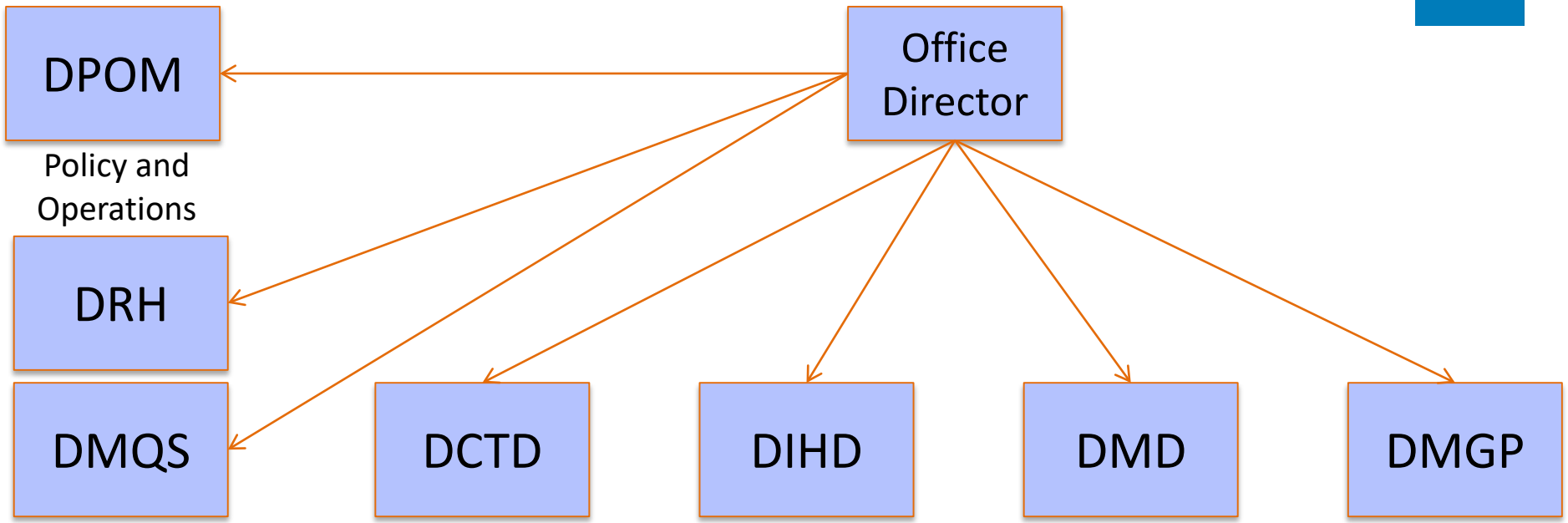
- Device Advice: Comprehensive Regulatory Assistance

https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/

FDA Organizational Structure



OIR Organizational Structure



IVD Review Divisions

- Division of Chemistry and Toxicology Devices (diabetes, cardiovascular, renal, toxicology, clinical chemistry)
- Division of Immunology and Hematology Devices (hematology analyzers, coagulation, autoimmune, neurology, allergy)
- Division of Microbiology Devices (infectious diseases)
- Division of Molecular Genetics and Pathology (most cancers, companion diagnostics, NGS)

There are ~300 Employees in OIR Today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