FDA Regulation of OCT

CDR Brad Cunningham, MSE, RAC
Chief,
Diagnostic and Surgical Devices Branch
Office of Device Evaluation
Center of Devices and Radiological Health

It is a Medical Device if it:

- Diagnoses, Cures, Mitigates, Treats or Prevents a Disease or Condition, or
- Affects the Function or Structure or the Body, and
- Does Not Achieve Intended Use Through Chemical Action, and
- Is Not Metabolized

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview

Device Classifications

- CLASS I
  - » Simple design, low risk
  - » General Controls
  - » Most exempt from premarket submission
- CLASS II
  - » More complex, higher risk
  - » General Controls plus Special Controls
  - » Premarket Notification [510(k)]
- CLASS III
  - » Most complex, highest risk
  - » General Controls and Pre-market Approval (PMA)

Class I: General Controls

- Prohibition of adulterated or misbranded devices
- Good Manufacturing Practices (GMPs)
- Registration of manufacturing facilities
- Listing of device types
- Record keeping
- Repair, replacement, refund
- Most Class I devices now exempted from Premarket notification [510(k)]

4

Class II: General Controls *plus* Special Controls

- Performance standards (e.g., ANSI, ASA, ISO, ASTM)
- Guidance documents
- Device tracking
- Patient registry
- Most require Premarket Notification [510(k)] to show substantial equivalence to a legally marketed "predicate" device

5

Class III: General Controls plus PMA

- Typically reserved for devices that:
  - » Support/sustain human life, or
  - » Have substantial importance in preventing health impairment, or
  - » Potential unreasonable risk of illness or injury
- Requires Premarket Approval (PMA)

6

Ophthalmic Examples

CLASS I	CLASS II	CLASS III
• VA chart	• Daily wear CL	• IOLs
• Perimeter	• Ophthalmic Camera	• Excimer lasers
• Topographer	• Phaco instruments	• Viscoelastics
• Haploscoope	• OCT	• Endotamponades
• Eyeglasses	• SaMD Devices	• Retinal Implants

7

Premarket Applications for Devices

Application Type	Review Standard	Applies To:
Premarket Notification [510(k)]	Substantial Equivalence	Class II devices (some Class I)
De Novo Classification Request	Probable benefit/risk General and/or Special Controls	Class I and Class II devices
Premarket Approval (PMA)	Reasonable assurance of safety and effectiveness	Class III devices
Humanitarian Device Exemptions (HDE)	Safety and probable benefit	Devices for small populations

8

510(k)

- Section 510(k) of F.D. & C. Act
- Marketing clearance application
- Allows FDA to Determine Substantial Equivalence (SE) to a predicate device (currently on U.S. market)

9

A Device is Substantially Equivalent if:

- In comparison to a legally marketed device it:
  - » Has the same intended use, and
  - » Has the same technological characteristics as the predicate device,
    OR
  - » Has the same intended use, and
  - » Has different technological characteristics and the information in the 510(k):
    - ○ Does not raise new questions of safety and effectiveness, and
    - ○ Demonstrates it is as safe and effective as the predicate

10

De Novo Classification Process

- Established in 1997 (FDAMA)
  - » Provided regulatory authority for FDA to classify devices that were automatically classified into Class III per Section 513(f)(1) (new devices) to Class I or II using criteria of Section 513(a)(1)(A-B)
  - » Excludes devices already classified into Class III (e.g., PMA-approved devices)
- Modified in 2012 to streamline and increase efficiency in process (FDASIA):
  - » Removed requirement for sponsor to submit 510(k) prior to submission of de novo request.
  - » Created two pathways for de novo submissions: post-510(k) NSE and direct de novo.

11

De Novo Classification Process

- Special controls alone, or general and special controls, provide reasonable assurance of safety and effectiveness
- Review time is 150 days (55% for FY2019)
  - » Establishes a new "device type" along with classification, regulation, and product code
  - » Device is eligible to serve as a predicate for new medical devices, where appropriate [510(k) process]

12

Optical Coherence Tomography

- **21 CFR 886.1570 (ophthalmoscope regulation)**
  - » "An ophthalmoscope is an AC-powered or battery-powered device containing illumination and viewing optics intended to examine the media (cornea, aqueous, lens, and vitreous) and the retina of the eye."
- **Product Code**
  - » OBO: "Viewing, imaging, measurement, and analysis of ocular structures. Diagnostic device to aid in the detection and management of various ocular diseases."
  - » Class II
- **Premarket Notification Pathway [510(k)]**
  - » First OCT clearance in December 1994
  - » 48 clearances (OBO product code)

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

13

Indication for Use (IFU)

- General description of the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended [21 CFR 814.20]
  - – Diagnostic Device Indications
    - » Imaging only (qualitative)
    - » Measurement (quantitative), but not disease specific
    - » Aid in the diagnosis of a specific disease
    - » Diagnosis of a specific disease
    - » Screening

14

510(k)-Cleared OCT Indications

- Viewing/Visualization
  - – Posterior: Macula, retina; retinal nerve fiber layer; optic disc, sclera; geographic atrophy; vitreous and choroid
  - – Anterior: cornea; a/c angle; lens; sclera; conjunctiva
  - – OCT Angiography: vascular structures of the retina and choroid
- Quantification
  - – Posterior: Retinal thickness; Retinal nerve fiber layer; 3D measurements; Optic disc parameters (including cup-to-disc ratio); Ganglion cell layer plus inner plexiform layer
  - – Anterior: corneal thickness; corneal epithelial thickness; corneal stromal thickness; pachymetry; corneal power; anterior chamber depth
  - – OCT Angiography measurements of vascular density and foveal avascular zone
- – Diagnostic Aid
  - – Retinal diseases; macular edema; macular hole; cystoid macular edema; retinal detachment; age-related macular degeneration; diabetic retinopathy; central serous retinopathy; Glaucoma

15

OCT Indications Not Currently Cleared

- Stand-alone diagnosis
- Screening
- Photoreceptor imaging
- Measurements:
  - Specific to intraocular inflammation (quantitative)
  - Drusen Volume / atrophy
  - Ellipsoid Zone
  - Junctional Zone

16

OCT Performance Characterization for Premarket Review

- Precision
  - » Repeatability
  - » Reproducibility
- Agreement
- Reference database

17

Precision Testing: Repeatability

- Test-retest within a short period of time – usually the same testing session
  - » Provides "within-subject variability"
- Testing to establish "reliability" of a measurement
  - » Same operator
  - » Same device
  - » Same scan mode, pattern, etc.

18

Precision Testing: Reproducibility

- Test-retest with greatly changed conditions including different time, measuring device, operators, etc.
- Provides overall variability
- Testing to establish "reliability" of the device using different:
  - » Operator; device; settings; testing times, etc.

19

Precision Testing

- How close are repeated measurements on the same object (eye) under the specified testing conditions?
  - » Standard deviation
  - » % coefficient of variation (SD/mean x 100)
- Patient selection
  - » evaluate separately in diseased and healthy subjects

20

OCT Testing: Agreement

- Systematic differences between new device results and predicate
  - » mean differences
  - » SD of the difference
  - » Absolute difference
  - » Regression
- Limits of Agreement
  - » For each eye, calculate the difference between the new device result and the predicate device result
  - » Mean of differences ± 2 x (SD of differences)
- No simple criteria for how close results need to be

21

OCT Innovation

- Continued evolution of OCTs
  - » New Indications
  - » Improved technology for faster scans, deeper imaging capability
  - » Reference database types
  - » New measurements
- Digital Health and Artificial Intelligence

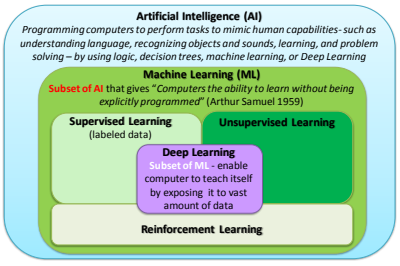
22

CDRH Digital Health Big Picture

- Increase patient and health care provider access to digital health solutions that are
  - » High Quality
  - » Safe and Effective
  - » Patient-centered
- Adapt regulatory science to evolving technological landscape

23

Artificial Intelligence & Machine Learning



24

Artificial Intelligence – Discussion Paper

- Discussion paper posted on April 2, 2019
  - https://www.fda.gov/downloads/MedicalDevices/DigitalHealth/SoftwareasaMedicalDevice/UCM635052.pdf
- Key driving factors
  - » Currently use "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" as guidance for changes to SaMD
  - » "Locked" algorithms Vs "adaptive" algorithms
  - » Traditional regulatory paradigm not designed for adaptive AI/ML
- Critical question: when does a continuously learning AI/ML SaMD require a premarket submission for an algorithm change?

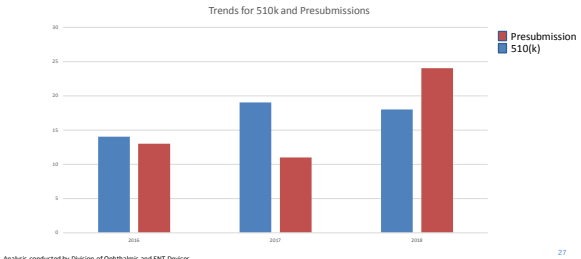
25

Artificial Intelligence – Proposed Regulatory Framework

- Types of modifications
  - » Type i → modifications related to performance; no change in intended use or input type
  - » Type ii → modifications related to inputs; no change in intended use
  - » Type iii → modifications related to the intended use
- SaMD Pre-Specifications (SPS)
  - » Delineates the proposed types of modifications to the SaMD
- Algorithm Change Protocol
  - » Describes the methods for performing & validating the changes in SPS
- » Total Product Life Cycle Approach and Good Machine Learning Practices
  - » Accepted practices in ML/AI algorithm design, development, training, and testing that facilitate the quality development and assessment of ML/AI-based algorithms
  - » Real World Performance monitoring

26

OCT Submissions



Analysis conducted by Division of Ophthalmic and ENT Devices

27

OCT Submissions

- MDUFA IV goal FY' 2019 - "total time to decision" (TTD) -120 TTD
  - » Traditional 510k submissions:
    - » CY 2018: 144 days
- Observations
  - » Misunderstood testing types and methods needed to validate device performance to support substantial equivalence
  - » Repeated requests for additional information, resulting hold decisions and longer review times

28

OCT Pilot Program

- Federal Register October 23, 2018[1]
- Why?
  - » Improve consistency of premarket submissions
  - » Improve predictability of the 510(k) process
  - » Design, develop, and refine testing recommendations

[1] https://www.federalregister.gov/documents/2018/10/23/2018-23059/fostering-medical-innovation-voluntary-pilot-program-to-streamline-review-of-premarket-notification

29

Methods and Goals

- Methods
  - » Selection of 9 participants (completed)
  - » Eligibility criteria
    - Submit 510(k) for OCT device within one year of joining the pilot program
    - Commitment to a fully-interactive review process
    - Commitment to incorporate FDA feedback and testing recommendations in the 510(k) submission
- Goals of the pilot program
  - » Improve consistency & predictability of the 510(k) review process for OCT devices
  - » Reduce TTD for OCT 510(k) submissions
  - » Increase collaboration between FDA and stakeholders to refine testing recommendations

30

Initial Testing Recommendations: Basic Device Information and General Testing

- Device Description
  - » Hardware
  - » firmware
  - » Software
  - » Auxiliary hardware and software features
- Fundamental device information and testing
  - » Biocompatibility
  - » Electrical, Thermal, and Mechanical Safety
  - » Electromagnetic Compatibility
  - » Optical Radiation Hazards Analysis

31

Initial Testing Recommendations: Non-Clinical Performance Testing

- Spatial Performance Testing (lateral and axial considerations)
- Sensitivity (S/N, depth attenuation)
- OCT Angiography (for quantitative vascular parameters)
- Validation of Auxiliary Functions

32

Initial Testing Recommendations: Clinical Performance Testing

- All OCT devices
  - » Image quality indicators; imaging protocol considerations, study eligibility criteria/clinical characteristics of study population
- Visualization-only OCTs
  - » Non-OCTA qualitative image grading study
  - » OCTA qualitative image grading study
- Quantitative OCTs
  - » Identify all scan patterns responsible for quantitative output
  - » Validate any [new] segmentation algorithm and/or [new] quantitative parameters
  - » Precision and Agreement

33

OCT Pilot Program: Next Steps

- Collaboration with nine participants to further refine initial testing recommendations with the goal to reduce TTD

34

Workshop Goal For Today

Facilitate innovation of laser-based imaging modalities

35