Regulatory Considerations for Radiological Software

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Division of Radiological Health

- Regulates diagnostic and therapeutic radiological medical devices (e.g., CT, MRI, image analysis software)

- Consult on the use of radiological equipment and diagnostic imaging in drug and device clinical studies

Note: Aspects of the talk may generalize to non-radiological software; however, we recommend talking to the lead center/division based on the intended use of your application (e.g., drug development, genomics, Health IT, biomarker qualification)

Topics

- Radiological software regulated as a medical device
- Use in investigational studies
- Marketing for clinical practice
- Software validation

Is the software a medical device?

- Section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act

  "…intended for use in the diagnosis…cure, mitigation, treatment, or prevention of disease in [humans]…or intended to affect the structure or any function of the body…" *(simplified)*

Note: the definition of a medical device is based on the intended use (regardless whether the device is distributed freely, only used in a clinical study, or commercialized). The regulatory requirements that apply to a medical device depend on investigational use and/or marketing for clinical practice.

Examples of software regulated as a medical device

- Picture archiving and communication system (PACS) intended for a hospital's image storage, retrieval, and viewing functions

- Software intended to allow a clinician to overlay digital templates of orthopedic implants onto x-ray images for pre-operative planning

- A computer algorithm intended to both identify and prompt lung nodules on CT exams and also to provide a probability of malignancy score to the clinician for each potential lesion as additional information

Examples of software not regulated as a medical device

- Software intended to automate office operations, such as patient scheduling or sending a follow-up satisfaction survey

- A digital library that is intended to provide access to electronic copies of radiological medical textbooks and reference images

Reference: Mobile Medical Applications

Considerations for use of radiological software (medical device) in investigational studies…

Considerations for investigational studies

- Understand the requirements and the risk posed by the software in the study
- Understand any Institutional Review Board and/or FDA oversight requirements for the use of human data and significant risk devices
- Consider seeking FDA feedback on study protocols that will be used to support a future regulatory submission

References:

- Institutional Review Board Oversight
- Device Advice: Investigational Device Exemption (IDE) (21 CFR 812)
- Requests for Feedback: Pre-submission
- 21 CFR Part 11

Example: PACS for a clinical study

- Researchers are developing a PACS for centralized management of images acquired as part of a multi-center clinical study. The repository would allow other researchers to access the data for analysis and research – without impacting patient/subject care.

- The software development and testing can be done following best practices using phantoms and sample images.

- The use of the system to store data for the clinical study may trigger additional requirements related to the protection of information, cybersecurity, and auditing.

Reference: Guidance for Industry Computerized Systems Used in Clinical Investigations

Example: Study Enrollment

- A medical device manufacturer proposes to use lesion size as an enrollment criteria in a clinical study to support approval of their cancer therapy device for lesions 1-2 cm in diameter.

- There are a number of research or clinical workstations with software tools to measure lesion size. Validation of the tool selected for the specific task should be performed.

- The manufacturer could submit a pre-submission to FDA to discuss their proposed clinical study with justification that the inclusion criteria is appropriate given their technology and intended patient population.

Example: Study Endpoint

- A medical device manufacturer would like to use lesion size as a surrogate endpoint in a regulatory submission to support approval of their cancer therapy device.

- The evidence to support use as a surrogate endpoint would likely be much higher than the study enrollment example. The validation of the biomarker should be independent of the data use to develop the biomarker value (e.g., cut-off). While there is FDA cleared software to measure lesion size, it does not mean that the software is cleared to perform lesion measurement as a surrogate endpoint for that specific therapy and study population.

- The manufacturer could submit a pre-submission to discuss their proposed clinical study with justification that the image biomarker would be a meaningful surrogate endpoint.

Reference: Clinical Trial Imaging Endpoint Process Standards

Example – Imaging Companion Diagnostic

- Software intended to measure liver iron concentration to aid in the identification and monitoring of non-transfusion-dependent thalassemia patients receiving therapy with deferasirox.

- This is a “companion diagnostic” since the drug could only be used clinically (if approved) if the software is also cleared/approved
  - a radiologist cannot perform the task visually, no other software is cleared/approved for this measurement, and investigational device regulations would still apply to the unapproved software

- The testing required a range of clinical data, and inter-center collaboration on drug and device reviews. Pre-submission discussions with the centers for a similar use is highly recommended.

Reference: Liver Iron Concentration Imaging Companion Diagnostic for Deferasirox

Example: Imaging Biomarker

- A company would like to have their image analysis software validated for extracting an imaging biomarker for use as a surrogate endpoint in a defined study population. The software would not be tied to a specific regulatory submission or therapy.

- FDA's Center for Drug Evaluation and Research (CDER) has a Biomarker Qualification program. FDA's CDRH has a Medical Device Development Toolkit program.

- FDA interaction is recommended since the supporting data required for acceptance will depend on many factors.

Reference

- CDER Biomarker Qualification Program
- CDRH Medical Device Development Tools

Considerations for marketing radiological software (medical device) for clinical use…

Marketing a new device

- There are differences in the premarket requirements and policies for different types of radiological medical devices

- Examples:
  - Some mobile medical apps and medical data storage products do not require FDA premarket review
  - Quantitative image analysis software would require a premarket submission, typically a 510(k) to demonstrate substantial equivalence to another device

References

- Mobile Medical Applications
- Medical Device Data Systems
- Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices

Marketing a new device

- Understand the device classification
  - Class I, Class II, Class III – depends on risk and special controls
- Understand the premarket submission type (if any)
  - 510(k), PMA, de novo, HDE, exempt
- Understand the other regulatory requirements that apply when marketing medical devices, including registration and listing and quality systems

References

- Overview of Device Regulation
- The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]

Marketing a modified device

- A premarket submission is not a one-time event!
- The criteria for a new 510(k) is if a change, or the sum of the incremental changes "could significantly affect the safety or effectiveness of the device"
- Example modifications that would likely require premarket review
  - Adding new 3D visualization package
  - Adding a new set of quantitative measurements
  - Expanding the current functions to a new anatomical regional, pathology, or modifications to a CAD algorithm that alter performance

Reference: Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)

Marketing a modified device

- Example incorporating third-party software:
  - A PACS manufacturer incorporates an open-source package to market a new brain segmentation and analysis package
  - The manufacture should define the software requirements and test methods for the new features
  - The test methods can be re-run if a newer software library is made available to ensure that the software requirements are still met
  - The modified PACS would likely require a new 510(k) for review of the safety and effectiveness of the new brain package

Reference: Off-The-Shelf Software Use in Medical Devices

Considerations for software verification and validation…

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- Basic requirements: traceability between requirements, design, hazards, cybersecurity, and risk mitigation
- Testing of basic functionality can be done with phantoms, simulations, and/or sample images

References

- General Principles of Software Validation; Final Guidance for Industry and FDA Staff
- Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices
- FDA CDRH Cybersecurity Website

Considerations for software verification and validation…

- What specific evidence is required for premarket submissions of imaging devices?
- Answer – it depends on the intended use

"this device provides tools for measuring volume" ≠ "this device may be used to measure changes in micro-lesions from CT images in patients suspected of mTBI"

- Specific uses will likely require clinical data from the specific clinical population

Example – General

- A PACS is intended for general image display and visualization of images from CT, MR, and ultrasound modalities. The software will also include a cardiac package for semi-automated segmentation of ultrasound images to compute measurements.

- General software verification and validation using sample images, phantom, and/or simulated images are appropriate to test the image storage, transfer, display and visualization.

- The semi-automated segmentation and measurements could be tested with sample cardiac images. The results with the software could be compared to the results from manual segmentation or other cleared software.

Example – Specific

- Software is intended for use in clinical screening mammography to identify areas suspicious for breast cancer for radiologist review after completing an initial read to aid breast cancer detection.

- An multi-case, multi-reader study on a clinical dataset that is independent of the device development is recommended for the regulatory premarket submission. Non-clinical testing is recommended to characterize the standalone software performance.

References

- Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions
- Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Notification [510(k)] Submissions

Summary

- There are differences in the premarket requirements and policies for different types of software (e.g., data storage and transfer, imaging analysis, computational biology)

- Search the FDA website for device specific advice, directories, and support emails
  - FDA CDRH Digital Health Website (digitalhealth@fda.hhs.gov)
  - FDA CDRH Division of Industry and Consumer Education (DICE@fda.hhs.gov)
  - FDA CDRH Management Directory

- Submit a pre-submission to seek device specific feedback!