What Post-Marketing Issues Should I Be Considering?

Fundamentals of Digital Health Regulation

FDLI Virtual Course

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FDA Strategies for Cutting Edge Technologies

Agenda

- Registration and Listing
- Modifications to a Device
- Labeling Requirements
- Quality System Regulations: Key Principles for Software
- Adverse Events/Product Problems
- Discussion and Questions

Registration and Listing: Who Must Register and List?

- If a digital health product is a "device," registration and listing requirements apply to:

Category	Registration	Listing
Manufacturer, Contract Manufacturer	Yes	Yes
Initial Importer	Yes	No
Relabeler or Repackager	Yes	Yes
Specification Developer	Yes	Yes

Registration and Listing: How to Register and List?

- All registration and listing information must be submitted electronically via FDA's FURLS system (https://www.access.fda.gov/oaa/)
- Pay registration user fee
  - Fee for FY 2024 is $7,653
- Submit registration and listing information
- Step-by-Step instructions available at: https://www.fda.gov/medical-devices/device-registration-and-listing/how-register-and-list

Registration and Listing: When to Register and List?

- **New devices:** Within 30 days "of an establishment beginning an activity or putting a device into commercial distribution"
  - If a device requires premarket clearance or approval, wait until such premarket authorization is issued
- **Annually:** Once per year, between October 1 and December 31

Registration and Listing: Updates

- Annual registration information must be submitted even if no changes have occurred
  - Review listing information
- At any point during the year, FURLS account holders can update registration and listing as changes occur
  - Examples include:
    - A registered manufacturer introduces a new device
    - A new establishment begins manufacturing a listed device

Modifications to a Device

- Document all modifications to a device
- Internal documentation must comply with the Quality System Regulation (QSRs) (21 C.F.R Part 820)
  - Manufacturers of finished devices must review and approve changes to device design and production
  - Process to demonstrate a manufactured device meets the changes in the design and production specifications
  - Internal records are subject to inspection

Modifications to a Device: 510(k)

- **A new 510(k) is required if a device modification:**
  - Could significantly affect the safety or effectiveness; or
  - Change or modify the intended use of the device
- **Modifications that require a new 510(k) include:**
  - Modifications intended to significantly improve the safety or effectiveness of the device
  - Control mechanism, operating principle, or energy changes
  - Changes in wireless communications or patient/user interface *that significantly affect the use of the device*

Modifications to a Device: 510(k)

- FDA has specific guidance for software changes
  - Same general principles as other 510(k)s
  - Specific software changes that require a new 510(k):
    - Introduces a new risk/modifies an existing risk that could result in significant harm and that is not effectively mitigated
    - Creates or necessitates a new risk control measure or modifies a risk control measure for a hazardous situation that could result in significant harm
    - Could significantly affect the clinical functionality or performance specifications directly associated with the intended use

Modifications to a Device: PMA

- Some changes may require a new PMA:
  - A design change that causes a different intended use, mode of operation, *and* technological basis of operation;
  - A change in the patient population that will be treated with the device; or
  - A change so significant that a new generation of the device will be developed
    - If a manufacturer anticipates any of these changes, they should consult with FDA. It is much more likely that changes can be addressed through a PMA Supplement.

Modifications to a Device: PMA

- Modifications that require a PMA Supplement include:
  - A new indication for use
  - Changes in manufacturing method or quality control procedures
  - Changes in the performance or design specifications, circuits, components, ingredients, principles of operations, or physical layout of the device
- See 21 C.F.R. § 814.39 for information about types of PMA supplements

Labeling Requirements: Instructions for Use

- Every device has an Intended Use
- Device labels must have Instructions for Use, or "Adequate Directions for Use," under 21 C.F.R. § 801.5
  - Adequate Directions for Use means directions "under which the layman can use a device safely and for the purposes intended"

Labeling Requirements: Instructions for Use

- Adequate Directions for Use include:
  - Statements of all purposes for which, and conditions under which, the device can be used;
  - Quantity for each use and usual quantities for persons of different ages and physical conditions;
  - Frequency and duration of administration;
  - Time of administration in relation to other factors;
  - Route or method of application; and
  - Any preparation necessary for use
- What does this mean for software and digital health products?

Labeling Requirements: Unique Device Identification System

- The Unique Device Identification System is intended to adequately identify devices sold in the U.S.
  - Most device labels must have a unique device identifier (UDI) that can be read by humans and machines
  - UDIs must be submitted to the Global Unique Device Identification Database (GUIDID)
  - Specific requirements for stand-alone software regulated as a device (see 21 C.F.R. § 801.50)

Quality System: General QSRs

- The Quality System Regulation (QSR) is Good Manufacturing Practices for devices (21 C.F.R. Part 820)
- Manufacturers must establish and follow quality systems to help ensure that their devices consistently meet applicable requirements and specifications
- The regulation provides the general framework that all manufacturers of finished devices must follow
- **An FDA final rule, which will harmonize QSRs with ISO 13485, is pending**

Quality System: QSR Requirements

- **Design Controls**
- Document Controls
- Purchasing Controls
- Production and Process Controls
- Identification and Traceability
- Acceptance Activities
- Non-Conforming Product
- Corrective and Preventative Action (CAPA)
- Labeling and Packaging
- Handling, Storage, and Distribution
- Quality Audit
- Management
- Personnel
- **Records:**
  - **Design History File**
  - **Device Master Record**
  - **Device History Record**
  - **Complaint Files**

Quality System: Software Design Controls

- Under 21 C.F.R. § 820.30, software is subject to applicable device design controls
- Design controls apply to all Class II and III devices, and Class I devices that are automated with computer software
- Control the design process to assure that device specifications meet user needs and the intended use of the device
- Main elements: Design Inputs, Design Outputs, Design Review, Design Verification, **Design Validation,** and **Design Changes**

Quality System: Documents and Records

- Records required under the QSR include the Device Master Record, the Device History Record, and Complaint Files
- All records must be maintained for whichever period is longer:
  - The expected life of the device; or
  - At least 2 years from the date of release for commercial distribution

Quality System Records: DMR and DHR

Device Master Record (DMR) 21 C.F.R. § 820.181	Device History Record (DHR) 21 C.F.R. § 820.184
The DMR is the compilation of records containing the **procedures and specifications** for a finished device	The DHR is the compilation of records containing the **production history** of a finished device
It contains: - Device specifications, including software specifications; - Production process specifications; - Quality assurance procedures and specifications, including acceptance criteria and the quality assurance equipment to be used; - Packaging and labeling specifications; and - Installation, maintenance, and servicing procedures and methods	It contains: - The dates of manufacture; - The quantity manufactured; - The quantity released for distribution; - The acceptance records, which demonstrate the device is manufactured in accordance with the DMR; - The primary identification label and labeling used for each production unit; and - Any UDI, UPC, and any other device identification(s) and control number(s) used

Quality System Records: Complaint Handling

- A complaint is any written, electronic, or oral communication that **alleges** deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution
- All manufacturers must:
  - Maintain complaint files
  - Establish a formal complaint handling unit
  - Establish and maintain procedures for receiving, reviewing, and evaluating complaints

Quality System Records: Complaint Handling

- Requirements for procedures include:
  - Complaints are reviewed and evaluated to determine if an investigation is needed
    - If no investigation is performed, document why and who made the decision
  - Complaints are evaluated to determine whether there is a reportable event, i.e., a Medical Device Report (MDR), under 21 C.F.R. Part 803
  - Complaints representing an MDR must be promptly reviewed, evaluated, and investigated. These complaints must be maintained in separate complaint files or otherwise clearly identified

Quality System Records: Complaint Handling

- Records of complaint investigations must include:
  - Information that identifies the device and the reported event
  - If related to an MDR:
    - Whether the device failed to meet specifications
    - Whether the device was being used for treatment or diagnosis
    - If applicable, the relationship between the device and the reported event

Adverse Events/Product Problems: Mandatory Device Reporting

- There are mandatory adverse event reports for manufacturers, importers, and device user facilities
- Manufacturers must report to FDA:

What to Report to FDA	When
When the device caused or contributed, or may have caused or contributed to, a death or serious injury	Within 30 calendar days of becoming aware of the event
When a malfunction occurs that, if it occurs again, it would be likely to contribute to a death or serious injury	Within 30 calendar days of becoming aware of the event
An event designated by FDA	Within 5 business days of becoming aware of the event
An event that requires remedial action to prevent an unreasonable risk substantial harm to public health	Within 5 business days of becoming aware of the event

Adverse Events/Product Problems: Correction, Removal and Recall

- **Correction** = Repair, modification, adjustment, relabeling, destruction, or inspection of a device, without physically removing it to another location

- **Removal** = Physical removal of a device from its point of use to another location for repair, modification, adjustment, relabeling, destruction, or inspection

- **Recall** = A firm's removal or correction of a distributed device that FDA considers to be in violation of the laws it administers, and against which FDA would initiate legal action

Adverse Events/Product Problems: Reports of Corrections and Removals

- Under 21 C.F.R. Part 806, manufacturers and importers must report corrections and removals to FDA:
  - If the correction or removal was initiated to reduce a risk to health posed by the device; or
  - To remedy a violation of the FD&C Act caused by the device, which may present a risk to health

Adverse Events/Product Problems: Recalls

- Recalls are classified by the relative degree of health hazard presented
  - **Class I** Recall: There is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse consequences or death
  - **Class II** Recall: Use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote
  - **Class III** Recall: Use of, or exposure to, a violative product is not likely to cause adverse health consequences

Adverse Events/Product Problems: Recalls

- Recalls can be voluntary or mandatory
- If a recall is initiated, a firm should develop a recall strategy
  - FDA will evaluate this recall strategy
- Other recall requirements:
  - Health Hazard Evaluation
  - Recall Letter
  - Recall Status Report

Thank You!

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