Part III: What Post-Marketing Issues Should I Be Considering?

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Agenda

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

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
See 21 C.F.R. Part 807. *See also* https://www.fda.gov/medical-devices/device-registration-and-listing/who-must-register-list-and-pay-fee		

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
  - 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 this 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
  - Also 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: 510(k)

- Generally, a new 510(k) is required if a device modification:
  - Could significantly affect the safety or effectiveness of the device; or
  - Change or modify the intended use of the device

Modifications to a Device: 510(k)

- 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 affects the use of the device*

Modifications to a Device: 510(k)

- For IVDs, modifications that require a new 510(k) include:
  - Changes that alter the operating principle
  - Changes that are identified in a device-specific final guidance or regulation
  - Design verification and validation activities that produce unexpected issues of safety and effectiveness
    - *See* FDA, "Deciding When to Submit a 510(k) for a Change to an Existing Device: Guidance for Industry and Food and Drug Administration Staff," (Oct. 25, 2017).

Modifications to a Device: 510(k)

- All modifications to a device – whether they require a new 510(k) – must be documented
- Internal documentation must comply with the Quality System regulation (21 C.F.R Part 820)
  - 21 C.F.R. §§ 820.30 and 820.70 require manufacturers of finished devices to review and approve changes to device design and production, and document the changes and the internal approvals in the device master record (21 C.F.R. § 820.181)
  - There must be a process to demonstrate that the manufactured device meets the changes in the design and production specifications (*See* 21 C.F.R. § 820.75)
  - These internal records are subject to review by an FDA Investigator during an inspection (*See* 21 U.S.C. § 374(e))

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):**
    - **Change that introduces a new risk/modifies an existing risk that could result in significant harm and that is not effectively mitigated**
    - **Change that creates or necessitates a new risk control measure or modifies a risk control measure for a hazardous situation that could result in significant harm**
    - **Change that could significantly affect the clinical functionality or performance specifications directly associated with the intended use**
      - *See* FDA, "Deciding When to Submit a 510(k) for a Software Change to an Existing Device: Guidance for Industry and Food and Drug Administration Staff," (Oct. 25, 2017).

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

Modifications to a Device: PMA

- Different changes require different PMA Supplements

Supplement Type	Reference	Description
PMA Panel-Track Supplement	21 C.F.R. § 814.39(c)	Significant change in design or performance of the device, or a new indication for use; Substantial clinical data are necessary to provide reasonable assurance of safety and effectiveness
PMA Supplement (180-Day Supplement)	**21 C.F.R. § 814.39(a)**	**Changes that affect the safety and effectiveness of the device;** **Clinical data provided in support of the original device approval should still support the change;** **Only new pre-clinical testing is needed to support safety and effectiveness**
Real-Time Supplement	FD&C Act § 737(4)(D)	Minor change to the device; Applicant requested and FDA has granted a meeting to jointly review and determine the status of the Supplement

Modifications to a Device: PMA

Supplement Type	Reference	Description
Special PMA Supplement – Changes Being Effected	21 C.F.R. § 814.39(d)	Change that enhances the safety of the device or the safety in the use of the device; For certain labeling changes; Changes may be placed into effect before receiving FDA's written approval order
30-Day Notice/135-Day PMA Supplement	21 C.F.R. § 814.39(f)	Modifications to manufacturing methods or procedures that affect safety and effectiveness; If the change qualifies as a 30-Day Notice, the change may be made 30 days after FDA receives the Notice; If not, the Notice becomes a 135-Day Supplement
PMA Manufacturing Site Supplement	21 C.F.R. § 814.39(a)(3)	Use of a different facility or establishment to manufacture, process, or package the device; Will require a 180-Day Supplement if the facility or establishment change affects the safety and effectiveness of the finished device and the site was not already approved with the PMA

Modifications to a Device: PMA

- PMA Annual Reports
  - Approval orders require periodic reports, at annual one-year intervals from the date of approval
  - Key component of Annual Reports:
    - Changes required to be reported to FDA under 21 C.F.R. § 814.39(b) and the changes described in 21 C.F.R. § 814.39(a)
      - *See* FDA, "Annual Reports for Approved Premarket Applications (PMA): Guidance for Industry and Food and Drug Administration Staff," (Dec. 16, 2019).

Labeling Requirements: Instructions for Use

- Every device has an Intended Use
- Device labels must also 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 of dose for each use and usual quantities for persons of different ages and physical conditions;
  - Frequency of administration;
  - Duration of application;
  - 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. from manufacturing through distribution to patient use
  - When fully implemented, most device labels will have a unique device identifier (UDI) that can be read by humans and machines
  - FDA's goals: to improve patient safety, modernize post-market surveillance, and facilitate innovation

Labeling Requirements: Unique Device Identification System

- FDA has a UDI Draft Guidance open for comment through Dec. 13, 2021
  - FDA, “Select Updates for Unique Device Identification: Policy Regarding Global Unique Device Identification Database Requirements for Certain Devices: Draft Guidance for Industry and Food and Drug Administration Staff,” (Oct. 14, 2021)
- Under this draft guidance, FDA states it does not intend to enforce UDIs on Class I devices and devices considered consumer health products

Quality Systems: Key Principles for Software

- The Quality System Regulation (QSR) is the GMP 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
- Manufacturers have flexibility to determine specific elements and procedures appropriate for their device

Quality Systems: Significant Requirements

- Management Controls (21 C.F.R. § 820.20)
  - Management with executive responsibility shall:
    - Establish its policy and objectives for, and commitment to, quality
    - Ensure that the quality policy is understood, implemented, and maintained at all levels of the organization
      - 21 C.F.R. § 820.20(a)

Quality Systems: Management Controls

- Management with executive responsibility shall appoint a member of management as the “management representative”
- The management representative must ensure that QSRs are effectively established and maintained, and report on the performance of the quality system to management with executive responsibility for review
- Management with executive responsibility shall review the effectiveness of the quality system at defined intervals, with sufficient frequency, according to established procedures
  - 21 C.F.R. §§ 820.20(b)(3), (c)

Quality Systems: Management Controls

- There are additional QSR requirements for:
  - Quality audits
    - Establishing procedures, conducting, documenting/ reporting, reviewing (21 C.F.R. § 820.22)
  - Personnel
    - Appropriate education, background, training, and experience; establishing procedures for and conducting training; documenting training; personnel review (21 C.F.R. § 820.25)

Quality Systems: Significant Requirements

- Software Design Controls (*See* 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 (as well as other specific Class I devices)
  - Control the design process to assure that device specifications meet user needs and the intended use of the device

Quality Systems: Software Design Controls

- General Requirements:
  - Establish procedures to control device design
    - Define, document, implement
  - Maintain procedures to control device design
    - Review, approve, update
      - 21 C.F.R. § 820.30(a)
- Main elements:
  - Design inputs, design outputs, design review, design verification, design validation, and design changes

Quality System: Software Design Controls

- **Design Inputs** are the physical and performance characteristics of a device that are used as the basis for device design
- Procedures must be established and maintained to:
  - Ensure requirements are appropriate by addressing user needs and intended use in measurable terms
  - Address incomplete, ambiguous, or conflicting requirements
  - Document, review, and approve input requirements
    - 21 C.F.R. § 820.30(c)

Quality System: Software Design Controls

- **Design Outputs** are the results of a design effort
- Procedures must be established and maintained to:
  - Define and document design output to allow adequate evaluation of design input
  - Reference definable and measurable acceptance criteria
  - Identify design outputs essential for proper function
  - Review, approve, and document design output before release
    - 21 C.F.R. § 820.30(d)

Quality System: Software Design Controls

- **Design Review** is a documented, comprehensive, systematic examination to:
  - Evaluate the adequacy of the design requirements
  - Evaluate the capability of the design requirements
  - Identify any problems
- Formal, documented Design Reviews must be performed according to established procedures
- Results of the design review must be documented in the Design History File (DHF)
  - 21 C.F.R. § § 820.30(e)

Quality System: Software Design Controls

- **Design Verification** is confirmation by examination and objection evidence that output meets input requirements
- Establish and maintain procedures to:
  - Confirm design verification through measurable means
  - Review, approve, and document design verification in DHF
    - 21 C.F.R. § 820.30(f)

Quality Systems: Software Design Controls

- **Design Validation** is the establishment by objective evidence that specifications conform with user needs and intended use
- Establish and maintain procedures to:
  - Define operating conditions
  - Describe requirements for initial production units, lots, batches, or their equivalents
  - Describe actual or simulated use conditions
    - 21 C.F.R. § 820.30(g)

Quality Systems: Software Design Controls

- 21 CFR §820.30(g) specifically mentions software validation:
  - **Design validation shall include software validation and risk analysis, where appropriate. The results of the design validation, including identification of the design, method(s), the date, and the individual(s) performing the validation, shall be documented in the DHF.**
- FDA also has a guidance: FDA, “General Principles of Software Validation; Final Guidance for Industry and FDA Staff,” (Jan. 11, 2002).

Quality Systems: Software Design Controls

- Establish and maintain procedures to identify, document, validate, verify, review, and approve **Design Changes** before they are implemented
  - Depending on the scope and impact of the change, it may require a new submission to FDA
  - Plan for future changes
    - 21 C.F.R. § 820.30(i)

Quality Systems: Significant Requirements

- Complaint Handling (21 C.F.R. § 820.198)
  - 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 Systems: Complaint Handling

- Procedures must ensure:
  - All complaints are processed consistently and in a timely manner.
  - Oral complaints are documented when received.
  - 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: 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
- Complaint files must be reasonably accessible to the manufacturer

Quality Systems: Significant Requirements

- Corrective and Preventative Actions (CAPA) (21 C.F.R. § 820.100)
  - Purpose of the CAPA system:
    - To identify and investigate actual and potential product and quality problems
    - To take appropriate and effective corrective or preventative action
    - To verify or validate the effectiveness of the corrective and preventative actions
    - To communicate corrective and preventative actions to the appropriate parties
    - To provide information for a management review
    - To document activities

Quality Systems: CAPA

- Analysis: To identify existing and potential causes of nonconforming product or other quality problem

- Investigation: To determine the root cause of nonconformities relating to product, processes, and the quality system
  - 21 C.F.R. § 820.100(a)(2)

Quality Systems: CAPA

- Identify actions to be taken
  - Correction
  - Corrective Action
  - Preventative Action
  - No further action necessary
- Verify or validate the corrective and preventative action
  - Ensure that the action is effective and does not adversely affect the device
    - 21 C.F.R. § 820.100(a)(4)

Quality Systems: CAPA

- Implement and record changes in methods and procedures needed to correct and prevent the quality problems identified
  - 21 C.F.R. § 820.100(a)(5)
- Communicate and document CAPA information:
  - Distribute information related to the quality problems or nonconforming products to parties directly responsible for assuring quality or preventing problems
  - Submit the information for management review
  - Document all activities and the results

Quality Systems: Significant Requirements

- Records and Documents (21 C.F.R. §§ 820.40, 820.180, 820.184)
- Establish and maintain procedures to control all documents required by 21 C.F.R. Part 820
  - These documents must be available at all locations for which they are designated, used, or otherwise necessary
  - Remove all obsolete documents promptly
    - 21 C.F.R. § 820.40

Quality Systems: Documents and Records

- All records under 21 C.F.R. Part 820 must be maintained for:
  - The expected life of the device; or
  - At least 2 years from the date of release for commercial distribution
    - Whichever is longer
      - 21 C.F.R. § 820.180(b)

Quality System: Documents and Records

Device Master File (DMF) 21 C.F.R. § 820.181	Device History File (DHF) 21 C.F.R. § 820.184
The DMF is the compilation of records containing the **procedures and specifications** for a finished device.	The DHF 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.

Adverse Events/Product Problems

- Medical Device Reporting
  - 21 C.F.R. Part 803 provides mandatory reporting requirements for manufacturers, importers, and device user facilities for certain device-related adverse events
  - FDA's information and instructions for reporting is available at: https://www.fda.gov/medical-devices/postmarket-requirements-devices/mandatory-reporting-requirements-manufacturers-importers-and-device-user-facilities

Adverse Events/Product Problems:
Mandatory Device Reporting for Manufacturers

What to Report	To Whom	When
When the device caused or contributed, or may have caused or contributed to, a death or serious injury	FDA	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	FDA	Within 30 calendar days of becoming aware of the event
An event designated by FDA	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	FDA	Within 5 business days of becoming aware of the event

Adverse Events/Product Problems

- Recalls and Reports of Corrections and Removals
  - 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
    - Recalls can be voluntary or mandatory
      - *See* 21 C.F.R. Parts 7, 810
  - Removal = the physical removal of a device from its point of use to another location for repair, modification, adjustment, relabeling, destruction, or inspection
  - Correction = repair, modification, adjustment, relabeling, destruction, or inspection of a device without physically removing it to another location

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

- Develop a recall strategy
  - FDA will evaluate this recall strategy
- Other recall requirements:
  - Health Hazard Evaluation
  - Recall Letter
  - Recall Status Reports
    - FDA has a Guidance: FDA, “Product Recalls, Including Removals and Corrections: Guidance for Industry,” (March 2020).

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

- Safety Communications
  - FDA posts Medical Device Safety Communications to describe the agency's current analysis of an issue. These contain specific regulatory approaches and clinical recommendations for patient management.
    - *See* https://www.fda.gov/medical-devices/medical-device-safety/safety-communications
- Letters to Healthcare Providers
  - FDA posts letters it sends to health care providers about safety concerns with devices used in health care facilities.
    - *See* https://www.fda.gov/medical-devices/medical-device-safety/letters-health-care-providers

Enforcement and Compliance

- 21 U.S.C. § 331 provides “prohibited acts” against which FDA can take enforcement action. These include:
  - Introducing an adulterated or misbranded device into interstate commerce
  - Adulterating or misbranding any device
  - Refusing an FDA inspection or for records to be reviewed during an FDA inspection
  - Falsifying device labeling
  - Failing to register
  - Failing to comply with FDA requirements, including reports
  - Knowingly creating false records
  - Failing to maintain required records

Enforcement and Compliance: FDA Inspection

- FDA has inspection authority under 21 U.S.C. § 374
  - Intended to assess compliance with the QSR, Registration and Listing, MDRs, and Corrections and Removals
  - Post-Market, Class II and III manufacturers are inspected bi-annually
    - “High risk” Class I manufacturers are also selected for inspection

Enforcement and Compliance: FDA Inspection

- Before the inspection:
  - The investigator will call 5 days ahead to announce
    - Will likely request records and procedures
  - Do NOT make any assumptions
    - ISO certified ≠ FDA-compliant
    - Past inspections have no application

Enforcement and Compliance: FDA Inspection

- Be ready for the inspection
  - Have registrations and listings updated
  - Coordinate easy retrieval and documents and records
  - Coordinate staff to assist with the inspection
  - Close any open CAPAs, file any required MDRs

Enforcement and Compliance: FDA Inspection

- Inspection
  - Inspector will present credentials and Form 482 (the Notice of Inspection)
  - Top management official greets/meets with inspector
  - Opening meeting
  - Walk-through of facility
  - Inspector reviews documents and records
    - **Inspector will issue “483s” for any violations**

Enforcement and Compliance: FDA Enforcement Options

- Untitled Letter
  - For a violation of the FD&C Act that does not necessitate a Warning Letter, FDA may send an Untitled Letter
  - Untitled Letters do not include a statement that warns the individual or firm that failure to promptly correct the violation may result in enforcement action
  - It gives parties an opportunity to take voluntary and prompt action to correct the violation before FDA initiates enforcement action

Enforcement and Compliance: FDA Enforcement Actions

- Warning Letter
  - Warning Letters identify a violation of the FD&C Act, such as poor manufacturing practices, problems with claims, or incorrect directions for use
  - The letter makes clear that the company must correct the violation
  - In Warning Letters, FDA provides directions and a timeframe for the company to inform FDA of its plans for correction
  - FDA follows up

Enforcement and Compliance: FDA Enforcement Options

- Seizure = An action brought against an FDA-regulated product because it is adulterated and/or misbranded. The purpose of such an action is to remove specific violative goods from commerce.
- Injunction = An order by a court that requires an individual or corporation to do or refrain from doing a specific act. FDA may seek injunctions against individuals and/or corporations to prevent them from violating or causing violations of the FD&C Act.
- Criminal prosecution = May be recommended in appropriate cases for violation of 21 U.S.C. § 331.
  - Misdemeanor convictions, which do not require proof of intent to violate the FD&C Act, can result in fines and/or imprisonment up to one year.
  - Felony convictions, which apply to second violations or the intent to defraud or mislead, can result in fines and/or imprisonment up to three years.

Thank You!

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