U.S. FOOD & DRUG ADMINISTRATION

Software Submission Best Practices

AMDM 2023 IVD Hybrid Focus Meeting

Karen Bijwaard, MS, RAC, MB(ASCP), CQA
Senior Policy Advisor, CDRH/OPEQ/OHT7/DMGP

October 19, 2023

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.

FDA Oversight of Software

- FDA applies regulatory oversight to the device software functions that meet the medical device definition and whose functionality could pose a risk to a user's safety if the device were to not function as intended
- Software may exist as Software in a Medical Device (SiMD) or Software as a Medical Device (SaMD) alone or in combination
  - Just because software may not be installed on an instrument, does not mean it is necessarily SaMD.
  - For IVDs, software is reviewed as a test system

Key Points

- FDA applies a least burdensome approach to identify minimum amount of information generally needed to support a premarket submission for a device that uses software.
- Guidance documents describe information typically generated and documented during software development, verification, and design validation.
- FDA may request additional information needed to evaluate the submission during a premarket review.

(Updated) Software References to Help Prepare a Premarket Submission

Guidance Documents

- Content of Premarket Submissions for Device Software Functions
- Multiple Function Device Products: Policy and Considerations
- Off-The-Shelf Software Use in Medical Devices
- Design Considerations and Premarket Submission Recommendations for Interoperable Medical Devices
- General Principles of Software Validation
- Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions
- Post-market Management of Cybersecurity in Medical Devices
- Applying Human Factors and Usability Engineering to Medical Devices
- Deciding When to Submit a 510(k) for a Software Change to an Existing Device

FDA-Recognized Voluntary Consensus Standards*

- ANSI/AAMI/ISO 14971: Medical devices -Applications of risk management to medical devices
- ANSI/AAMI/IEC 62304: Medical Device Software - Software Life Cycle Processes
- ANSI/AAMI SW91: Classification of defects in health software
- ANSI/AAMI/UL 2800-1:2022: Standard for Medical Device Interoperability
  - 2800-1-1:2022 Standard for Risk Concerns for Interoperable Medical Products
  - 2800-1-2:2022: Standard for Interoperable Item Development Life Cycle
  - 2800-1-3:2022 Standard for Interoperable Item Integration Life Cycle

*https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

Considerations for Documentation Level

- Sponsor should consider all known or foreseeable software hazards and hazardous situations associated with device
  - including those resulting from reasonably foreseeable misuse, whether intentional or unintentional, prior to the implementation of risk control measures
- Includes likelihood that device functionality is intentionally or unintentionally compromised by inadequate device cybersecurity
- Sponsor is responsible for proactively and comprehensively considering risks as part of device's risk assessment

Software Documentation Level

- Documentation Level
  - Basic
  - Enhanced
- Level:
  - Reflects the device as a whole
  - Depends on device's risk to a patient, a user of a device, or others in the environment of use.
  - Based on the risks of the device software function(s) in the context of the device's intended use
  - Risks where a failure or flaw of any device software function(s) could present a hazardous situation with a probable risk of death or serious injury, either to a patient, user of the device, or others in the environment of use
    - Serious Injury:
      - is life-threatening; or
      - results in permanent impairment of a body function or permanent damage to a body structure; or
      - requires medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.
- In general, software that was previously classified as:
  - Minor or moderate level of concern (LoC) → maps to Basic
  - Major LoC → map to Basic or Enhanced

Considerations for Documentation Level

- Guidance recommends Enhanced Documentation be provided in a premarket submission for devices intended to:
  - test blood donations for transfusion-transmitted infections;
  - determine blood donor and recipient compatibility;
  - automate blood cell separator devices intended for collection of blood components for transfusion or further manufacturing use;
  - blood establishment computer software (BECS).

- Guidance generally recommends Enhanced Documentation be provided for Class III devices and device constituent parts of a combination product; however, a sponsor may determine that an Enhanced Documentation level does not apply in certain cases, for which the sponsor should provide a detailed rationale as to why Basic Documentation is appropriate for the premarket submission.
  - If the review team disagrees or believes additional documentation needed, it can be requested during review

Content of Premarket Submissions for Device Software Functions Guidance (2023)

- Documentation elements are generally similar to the software activities described in the 2005 “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices”

Software (SW) Documentation Elements	Level of Concern (2005 Guidance)		Documentation Level (2023 Guidance)	
	Moderate	Major	Basic	Enhanced
Documentation Level Evaluation	A statement indicating the Level of Concern and a description of the rationale for that level.		A statement indicating the Documentation Level and a description of the rationale for that level.	
Software Description	A summary overview of the features and SW operating environment.		SW description, including overview of significant SW features, functions, analyses, inputs/outputs, and hardware platforms.	
Risk Management File	Tabular description of identified hardware and SW hazards, including severity assessment and mitigations.		Risk management plan, risk assessment demonstrating that risks have been appropriately mitigated, and risk management report.	
Software Requirements Specification (SRS)	Complete SRS document. Describes functional, performance, interface, design, developmental, and other requirements for the SW (e.g., hardware requirements, programing language, identification of off-the-shelf SW, etc.).		SRS documentation, describing the needs or expectations for a system or SW, presented in an organized format, at the SW system level or subsystem level, as appropriate, and with sufficient information to understand the traceability of the information with respect to the other SW documentation elements (e.g., risk management file, SW design specification, system and SW architecture design chart, SW testing).	
Software Design Specification (SDS)	SW design specification document describes the implementation of the requirements for the SW Device. Should provide adequate information to allow for review of the implementation plan for the SW requirements in terms of intended use, functionality, safety, and effectiveness.		FDA is not recommending the SDS as part of the premarket submission. Sponsor should document this information on the design via the DHF for the device. During premarket review, FDA may request additional information, if needed, to evaluate the safety and effectiveness of the device.	SDS documentation, including sufficient information that would allow FDA to understand the technical design details of how the software functions, how the software design completely and correctly implements all the requirements of the SRS, and how the software design traces to the SRS in terms of intended use, functionality, safety, and effectiveness.

Software Documentation Elements	Level of Concern (2005 Guidance)		Documentation Level (2023 Guidance)	
	Moderate	**Major**	**Basic**	**Enhanced**
System and Software Architecture Design	Detailed depiction of functional units and SW modules. May include state diagrams as well as flow charts.		Detailed diagrams of the modules, layers, and interfaces that comprise the device, their relationships, the data inputs/outputs and flow of data, and how users or external products (including information technology (IT) infrastructure and peripherals) interact with the system and SW.	
Traceability	Traceability among requirements, specifications, identified hazards and mitigations, and Verification and Validation testing.		Provided within required documentation.	
Software Development, Configuration Management, and Maintenance Practices	Summary of SW life cycle development plan, including a summary of the configuration management and maintenance activities.	Summary of SW life cycle development plan. Annotated list of control documents generated during development process. Include the configuration management and maintenance plan documents.	A summary of the life cycle development plan and a summary of configuration management and maintenance activities; **OR** A Declaration of Conformity[6] to the FDA-recognized version of IEC 62304, including subclauses 5.1.1-5.1.3, 5.1.6 - 5.1.9, clause 6 (Software maintenance process), and clause 8 (SW configuration management process), among others as applicable.	**Basic Documentation Level, PLUS** complete configuration management and maintenance plan document(s); **OR** A Declaration of Conformity to the FDA-recognized version of IEC 62304, including subclause 5.1 (Software development planning), clause 6 (software maintenance process), and clause 8 (software configuration management process), among others as applicable.

Software Documentation Elements	Level of Concern (2005 Guidance)		Documentation Level (2023 Guidance)	
	Moderate	**Major**	**Basic**	**Enhanced**
Software Testing as Part of Verification and Validation	Description of V&V activities at the unit, integration, and system level. System level test protocol, including pass/fail criteria, and tests results.	Description of V&V activities at the unit, integration, and system level. Unit, integration and system level test protocols, including pass/fail criteria, test report, summary, and tests results.	A summary description of the testing activities at the unit, integration and system levels; **AND** System level test protocol including expected results, observed results, pass/fail determination, and system level test report.	**Basic Documentation Level, PLUS** unit and integration level test protocols including expected results, observed results, pass/fail determination, and unit and integration level test reports.
Software Version History	Revision history log, including release version number and date.		A history of tested SW versions including the date, version number, and a brief description of all changes relative to the previously tested SW version.	
Unresolved Software Anomalies	List of remaining SW anomalies, annotated with an explanation of the impact on safety or effectiveness, including operator usage and human factors.		List of remaining unresolved SW anomalies with an evaluation of the impact of each unresolved SW anomaly on the device's safety and effectiveness.	

Risk Management File

- Should include documentation demonstrating following 3 components:
  1. Risk Management Plan: demonstrates how a manufacturer plans to approach a risk assessment for their device and evaluate the overall residual risk against the benefits of the intended use of the device.
  2. Risk Assessment: documents (e.g., in a tabular format) known or foreseeable hazards and resulting hazardous situations, initial risk evaluation of the hazardous situation, risk control measures, residual risk evaluation after implemented risk control measures and traceability of risk control measures.
  3. Risk Management Report: shows how the risk management plan has been appropriately implemented.
     - Verification that individual risk mitigations and controls were properly implemented
- FDA recommends sponsors refer to FDA-recognized version of ISO 14971 and account for the recommendations provided in the guidance “Multiple Function Device Products: Policy and Considerations”

System and Software Architecture Diagram

- Provide detailed diagrams of the modules, layers, and interfaces that comprise the device, the data inputs, outputs, and flow, and how users or external products (including IT infrastructure and peripherals) interact with the system and software.
- Recommends that sponsors provide the appropriate level of detail to convey information in a manner that facilitates an efficient premarket review.
- Includes visual, language, and reference considerations that can be leveraged when developing the diagrams for a premarket submission.
- Appendix B of the guidance 2023 Software Functions Guidance includes example system and software architecture diagrams.

Unresolved Software Anomalies

- Recommends the following information (e.g., in tabular format) is provided for each unresolved anomaly:
  - A description of problem;
  - Identification of how anomaly was discovered and, where possible, identification of its root cause(s);
  - Evaluation of impact of anomaly on device's safety and effectiveness, including operator usage and human factors considerations;
  - Outcome of evaluation; and
  - Risk-based rationale for not correcting or fixing anomaly in alignment with sponsor's risk management plan or procedure(s).
- Encourages communication of unresolved anomalies to end user(s) as appropriate to assist in proper device operation
- Expectation for resolution of anomaly(ies)
  - If plan to address in 'next software update', clarify when that is expected to be
- Reference to ANSI/AAMI SW91 Classification of defects in health software provided

Other Software Considerations

- Overlap with Other Premarket Submission Documents
  - If the same documentation has been submitted in another pre-market submission, sponsors may provide it again or reference the other submission it was submitted under and where it the submission it can be found
- Use of Artificial Intelligence and Machine Learning (AI/ML)
  - Sponsor should clearly explain how:
    - AI/ML utilized in device
    - Development and function of algorithms
    - If ML is static or dynamic
    - Updates are developed and deployed
- Predetermined Change Control Plans – discuss early with FDA review division through pre-submission process

Device Master Files (MAF)

- Should be used to provide documentation for new or existing instruments especially when a third parties are involved to maintain confidentiality
- Should include needed current instrument hardware, firmware, software, cybersecurity, and EMC/EMI/RFI related documentation
- For IVDs:
  - If an instrument is exempt from 510(k) and is used with a non-exempt assay, the instrument exemption does not negate need for review of instrument and software documentation.
- If an assay manufacturer is utilizing 3rd party instrument, the sponsor should work with instrument manufacturer ASAP to ensure MAF submitted at or prior to regulatory submission
- Can also be used if submission sponsor and instrument manufacturer are the same – facilitates future referencing

Instruments & Software Previously Reviewed

- Clearly identify changes since the last premarket submission
  - Specify the last time the instrument and/or software was submitted and reviewed and associated submission and MAF number/supplement/amendment
  - Clearly identify and describe the changes to the instrument hardware, firmware, and/or software since the last FDA premarket submission
  - Provide tabulated list of modifications to the instrument, functions, and software (include each software version) in including
    - Specify for each operationally significant software feature, if the feature is unchanged, removed, modified, or new from the previous clearance or approval.
    - Dates the modifications were developed, validated, and implemented through the versions used with the current device
- Provide documentation applicable to modifications made since the last time reviewed to version intended to-be-marketed with current device
- New EMC/EMI/RFI only needed if instrument/instrument configuration has been modified since previously submitted in a way that effects previous testing. Testing should follow current recognized standards or provide a gap analysis provided to most appropriate FDA recognized standards.

Other Functions/Features

- Clearly delineate “Device Functions/Features” from “Other Functions/Features”
  - Not all software or software functions/features may be regulated
  - Clearly separate device functions/features from other functions through design and implementation (e.g., logical separation, architectural separation, code, and data partitioning).
    - Multiple Function Device Products: Policy and Considerations (2020) *https://www.fda.gov/media/112671/download*
    - Molecular Diagnostic Instruments with Combined Functions (2014) *https://www.fda.gov/media/85513/download*

Most best practices are relatively straightforward

General Best Practices

- Consider recommendations from all relevant guidance documents and standards
- Submit a clear software narrative that describes each software documentation element, including the documents associated with each documentation element.
  - Make sure documents referred to in narrative match file names in submission
  - Preferably use understandable/clear file names
- Provide all relevant software documentation for each element based on documentation level
  - Provide copies of referenced documents that are important or will provide clarity
- Documents should be valid (e.g., signed) and include version and implementation date
- If using an alternative approach or providing different documentation to meet satisfy pre-market submission requirements, provide a clear explanation for how the approach and/or documentation satisfies the pre-market submission requirements.
- If declaring conformity to a standard, provide a clear and detailed explanation or acceptable justification for how the validation performed meets the standard (as a whole or relevant parts).
- Use clear language in protocols and test reports

General Best Practices (con't)

- For IVD devices, if different software versions used during analytical and/or clinical validation studies, provide documentation for regression testing or bridging between software versions used to the final to-be-marketed software version.
  - If multiple software versions have been used, clearly describe the differences between the versions and the date the version was developed and deployed.
    - Provide V&V testing documentation for version changes + other affected software documents
  - Rule of thumb for type of validation needed between multiple versions. If the modified software is used:
    - Before data acquisition – typically requires wet bench testing + analysis
    - After data acquisition – typically requires regression testing using existing data (*in silico*)

General Best Practices (con't)

- Include a list of definitions, abbreviations, and acronyms
- Make sure documentation is:
  - In English
  - Optically characterized and searchable before adding headers/footers.
  - If combining multiple documents into a single PDF, please include bookmarks for each document.
- For complex instruments, software, or workflows, inclusion of flowcharts, wire diagrams, pictures, and videos in the submission or pre-submission discussions can help the FDA reviewer team better understand device and software
- When in doubt – ask
  - A few simple questions may be able to be addressed interactively
  - Several or more detailed questions can be addressed in a pre-submission.
- Create documentation as the device software is developed and update it appropriately as the device software evolves.

Conclusion:

- A submission that is complete, clear, well-written, and organized goes a long way to help facilitate the review process.

Other Resources

- CDRH Webinars - https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/medical-device-webinars-and-stakeholder-calls
- CDRH Learn - multi-media educational resource https://www.fda.gov/training-and-continuing-education/cdrh-learn
- Digital Health Policy Navigator - A tool to help in determining whether your product's software functions are potentially the focus of the FDA's oversight https://www.fda.gov/medical-devices/digital-health-center-excellence/digital-health-policy-navigator

Recently Published Software Guidance Documents

- Content of Premarket Submissions for Device Software Functions: Guidance for Industry and Food and Drug Administration Staff (6/14/23) *https://www.fda.gov/media/153781/download*
- Off-The-Shelf Software Use in Medical Devices: Guidance for Industry and Food and Drug Administration Staff (8/11/23) *https://www.fda.gov/media/71794/download*
- Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions: Guidance for Industry and Food and Drug Administration Staff (9/27/23) *https://www.fda.gov/media/119933/download*
- Clinical Decision Support Software: Guidance for Industry and Food and Drug Administration Staff (9/28/22) *https://www.fda.gov/media/109618/download*
- Electromagnetic Compatibility (EMC) of Medical Devices: Guidance for Industry and Food and Drug Administration Staff (6/6/22) *https://www.fda.gov/media/94758/download*
- Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions: Draft Guidance for Industry and Food and Drug Administration Staff (4/3/2023) *https://www.fda.gov/media/166704/download*