Guidance for FDA Reviewers

Premarket Notification Submissions for Automated Testing Instruments Used in Blood Establishments

DRAFT GUIDANCE

This guidance is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted by the date provided in the *Federal Register* notice announcing the availability of the draft guidance.
Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448. Or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm

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U.S. Department of Health and Human Services
Food and Drug Administration
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TABLE OF CONTENTS

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This guidance document represents the agency's current thinking on the review of premarket notification submissions for automated instruments used for testing in blood establishments. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance is intended to assist FDA's staff in the review of premarket notification submissions for automated instruments intended for use in establishments that manufacture blood and blood components (e.g., in testing for blood borne pathogens, blood grouping/typing, pre-transfusion compatibility, etc.). It was prepared by the Biological Devices Branch, Division of Blood Applications, Office of Blood Research and Review, Center for Biologics Evaluation and Research. Additional information regarding software for such instruments is available in the "Guidance for FDA Reviewers and Industry: Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," final document issued by Office of Device Evaluation, Center for Devices and Radiological Health, May 29, 1998.

II. BACKGROUND

Section 510(k) of the Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 360(k), states that each person who is required to register under that section of the Act and who proposes to begin the introduction or delivery for introduction into interstate commerce for commercial distribution of a device intended for human use shall, at least ninety days before making such introduction or delivery, report to the Secretary (in such form and manner as the Secretary shall by regulation prescribe). Title 21 of the Code of Federal Regulations (CFR) Part 807 identifies the requirements for the content and format of the 510(k) notifications that are to be submitted to the Food and Drug Administration (FDA). The purpose of a 510(k) is to demonstrate that the medical device to be marketed is substantially equivalent to a device that is already legally marketed.

This guidance presents an overview of the type of information FDA reviewers should expect to be included in premarket notifications submitted for such devices and the approach FDA reviewers normally should take in reviewing premarket submissions for automated instruments used for testing in blood establishments. The detailed requirements for premarket notifications in 21 CFR Part 807 should also be consulted.

III. RECOMMENDATIONS FOR REVIEWERS

Part 807 identifies the following as information to be included in a 510(k) submission:

A. The device name, including trade or proprietary name, and common or usual name

This information should include the product name, model, and software version number.

B. Establishment Registration number

This information should include the establishment registration number.

C. Device class determination

This information should include the product code with the device classification.

D. Performance Standards

There are no FDA performance standards promulgated for these devices.

E. Proposed labels, labeling, and advertisements sufficient to describe the device, the intended use, and the directions for use.

The requirements for labeling in vitro diagnostic products are identified in 21 CFR 809.10. The intended use should be specific to the device and reflect the claimed indications. The labeling should include, but is not necessarily limited to:

1. User's manual or other operating instructions;

2. Installation procedures;

3. A list that identifies any reagent(s)/kit(s) or device(s), recommended but not provided, and claimed to be compatible with the instrument; and

4. Specifications sufficient to describe the device's operating characteristics, precautions, limitations which should include the user controlled functional requirements as identified in the hazard analysis, and calibration maintenance information.

F. A statement of substantial equivalence

1. Pursuant to 21 CFR 807.92(a)(3), the submission must contain a statement that the device to be marketed is substantially equivalent to a legally marketed device that was or is on the U.S. market. Substantial equivalence may be claimed to:

    a. A legally marketed pre-amendments device (one which was marketed prior to May 28, 1976). For purposes of documenting pre-amendment status in regard to intended use and commercial distribution, information provided must be adequate to document that the pre-amendment firm's device was labeled, promoted, and distributed in interstate commerce for the same intended use to which the submitter of the premarket notification (510(k)) is claiming substantial equivalence. This may be accomplished by providing copies of the firm's advertisements, catalogue pages or other promotional material dated prior to May 28, 1976 and shipping documents such as invoices, bills of lading, receipts, etc. showing the interstate transit of the device dated prior to May 28, 1976; or

    b. A device that has been cleared by the FDA as substantially equivalent to a pre-amendment device for the same intended use(s).

2. Pursuant to 21 CFR 807.92(a)(3), the statement must identify the predicate device. Information about the predicate device should include manufacturer, common name, trade name including model, version, and/or release numbers and any reference number assigned by the FDA.

3. The statement should include a comparison of the intended use(s) of the device to the intended use(s) of the predicate device to which substantial equivalence is claimed.

G. Safety and effectiveness of the device

Pursuant to 21 CFR 807.92(b)(2), a 510(k) summary or statement must be included. If a 510(k) statement is included, then the following statement should be submitted on a separate page of the premarket notification submission, clearly identified as the "510(k) statement," signed and dated by the certifier:

> "I certify that, in my capacity as (the position held in company by person required to submit the premarket notification, preferably the official correspondent in the firm), of (company name), I will make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person if the device described in the premarket notification submission is determined to be substantially equivalent. The information I agree to make available will be a duplicate of the premarket notification submission, including any adverse safety and effectiveness

information, but excluding all patient identifiers, and trade secret and confidential commercial information, as defined in 21 CFR 20.61."

A 510(k) summary should be sufficient to provide an understanding of the basis for a determination of substantial equivalence. It must contain the elements discussed in 21 CFR 807.92.

H. A truth and accuracy statement

The following statement must be included in the 510(k) submission and be signed and dated by the certifier:

"To the best of my knowledge, the data and information submitted in this premarket notification are truthful and accurate, and no material fact has been omitted."

The following additional items should be included in the submission in order to make the substantial equivalence determination:

I. Financial Certification or Disclosure

A financial certification or disclosure statement or both must be included in the submission as required by 21 CFR Part 54.

The following additional items should be included in the submission in order to make the substantial equivalence determination:

J. Functional requirements

The functional requirements should include the hardware and software functional requirements and identify the following:

1. Any activities, processes, procedural steps of the test, etc. that are performed by the instrument (e.g., pipetting samples and/or reagents, diluting, incubation time and/or temperature control, washing, sealing of reaction chambers, the calibration of equipment, calculating, etc.);

2. The functions that are controlled by the software;

3. Any limitations of the test (procedure and/or any activities, processes, etc.) normally associated with any function(s) that will not be performed by the instrument (e.g., manual entry of duplicate samples, etc.). Any method of control that is specified as user controlled is considered to be a limitation and should also be included in this document and in the labeling provided the user;

4. The safety critical requirement(s) implemented to ensure the safety, quality, identity, potency, and purity of blood/blood products (e.g., positive sample identification, equipment calibrations, dilution of reagents and/or samples, pipetting volumes, incubation times and/or temperatures, wavelengths, etc.);

5. Any instrument design safeguard (e.g., algorithms, truth tables, error checking, door locking while the instrument is in use, sampling error alarm, warning, or message, liquid level sensing/dispensing, device operation suspended upon error, etc.), to ensure that the safety critical requirement(s) is met; and

6. A matrix of cross-references that traces each functional requirement to the appropriate detailed design specification(s).

K. Design and development

The design and development documentation should include the following:

1. A description of the design and development process, related Standard Operating Procedures (SOPs), and applicable industry standards (e.g., AABB, ANSI, ASA, ASME, ASTM, FDA, IEEE, ISA, ISO, NEC, NEMA, NRC, OSHA, UL, etc.) used during development;

2. A description of all of the hardware components in the instrument, their performance characteristics, and specifications;

3. Diagrams and descriptions of the instrument that demonstrate the relationship of the major components, including the software;

4. Explanation of the procedure for calculations, such as, cutoffs, controls and test samples, examples of calculations, and the number of significant digits appropriate for the answer;

5. Instrument printouts that are indelibly recorded and sequentially numbered for the life of the machine, including all of the following items, as applicable: the run date, time of printout, software and test release/version number, raw signal value, blank value, results (positive, negative, reactive, nonreactive), instrument and test title, sample number, flag on reactives/abnormals, positive/negative control values, cutoff value, control acceptability criteria and outcome, run valid/invalid statement, test kit lot number, wavelength read, calculation for cutoff, and differentiation between the original read and rereads;

6. An audit trail that automatically records all instrument/test run modifications and/or changes;

7. Test methodology, principles of operations, calibration procedures, specimen requirements, etc.; and

8. Detailed design specifications which implement the functional requirements and provide the technical definition of all the software requirements (e.g., data requirements for inputs, performance requirements, interfaces, data flow, etc.) and include the following:

    a. A description of all of the software components, such as, operating system, databases, etc.;

    b. A diagram and description of the software that includes a list and definition of all interfaces that are part of the computerized system;

    c. A list of any specific performance requirements that the instrument or the computerized system must meet (e.g., transactions per second, a transmission rate, maximum number of users, etc.); and

    d. The current plan as to how the instrument will conform to the conversion to the ISBT 128 barcode standard.

L. Hazard analysis

1. The analytical process used to identify the hazardous elements related to blood product safety should be described (e.g., Failure Modes and Effects Analysis, Failure Modes and Effects Criticality Analysis, Fault Tree Analysis, etc.).

2. The hazard analysis should address (1) the intended use hazards (functional requirements that if not achieved may result in testing errors), and (2) the hazards that may result from the implementation of the functional requirements in the instrument (mechanical failure), and the software environment [e.g., user interfaces (operator), external system interfaces (interfaced to a computer system), internal hardware/software interfaces (compatibility), incorrect sequencing/timing, algorithm/truth table errors, data loss/corruption, alarm/error message malfunction, duplicate records, etc.].

3. The hazard analysis, preferably in a table format, should include:

    a. A description of the hazard;

    b. The cause(s) of the hazard;

    c. The level of concern based on a qualitative estimate, including the definition of terms used;

d. The likelihood of occurrence:

    1. The failure rate for mechanical hazards should be expressed as a ratio of the number of challenges, cycles, etc.; and

    2. The occurrence of software hazards should be based on a qualitative estimate, including the definition of terms used;

5. The method(s) of control used to eliminate or mitigate the hazard (e.g., change in design specification, alarms, warning and/or error messages, manual process/workaround, etc.); and

6. A trace of the method of control to the safety critical design specification and the appropriate verification, validation, and testing.

The following provides an example of a possible format and content for a hazard analysis table:

Hazard	Cause	Level of Concern	Likelihood / Failure Rate	Method of Control	Trace
Incorrect volume aspirated	Clot, plunger stuck, etc. (Hardware)	High	1:X	***Hardware Controlled*** Install sensor, level detector, etc.	Design Specification # VV&T test plan #
		High	Low	***Software Controlled*** Algorithm, e.g., If level or volume is not reached within "x" amount of time then perform an action (alarm, shut down, etc.)	Design Specification # VV&T test plan #
Incorrect incubation time/ temperature	Incorrect thermostat setting, faulty thermostat (Hardware)	High	1:X	***Hardware Controlled*** Redundant sensors, resistance temperature devices, thermocouples, etc.	Design Specification # VV&T test plan #
		High	Low	***Software Controlled*** Algorithm, e.g., If difference between temperature readings is "x" then perform action (alarm, shut down, etc.)	Design Specification # VV&T test plan #
		High	Moderate	***User Controlled*** Visual inspection of temperature	Limitation(s) in the User Manual

M. Validation

Verification, validation, and testing should be submitted to substantiate labeling claims for test kit/reagent compatibility for all of the different instrument(s) and/or computer hardware/software configurations and should include:

1. Test Plan

   The unit level test plan should include structural testing (e.g., branch, path, and statement testing) and functional testing (e.g., normal, boundary, stress, etc.).

   The integration test plan should include internal interface testing (e.g., module to module, etc.) and external interfaces (e.g., peripheral devices, other application software, and network communications, etc.).

   The system level test plan should ensure that all safety critical intended use functions have been included in the system level testing performed in both the developer's (alpha) and the user's (beta) environments and should include evaluating the results of this testing prior to the final distribution of the instrument. These test plans should identify the input, the expected result, and an evaluation of the acceptability based on the comparison of the actual results to the expected results.

2. Populated Decision Tables

   User defined, safety critical, decision tables, populated with results, utilized during the verification, validation, and testing, should be provided.

3. Alpha testing (Developer's environment)

   The test plan and results summary of all in-house mechanical and software verification, validation, and testing performed at the unit/integration/system levels and representative data generated during testing that includes validation of the functional requirements and verification of the design specifications for both the hardware (mechanical) and software.

4. Beta testing (Clinical field trials)

   The test plan, results summary of clinical data, representative instrument printouts, and all data generated during the clinical field trials.

5. All safety critical anomalies ("bugs") or anything observed in the documentation or operation of the instrument or the software that deviates from expectations based on performance, previously verified software products, or reference documents should be identified. Include a description of the corrective action, regression testing, and the summary of results.

N. Configuration management and change control

The 510(k) submission should include:

1. The procedure(s) for approving, implementing, and recording proposed changes;
2. The procedure(s) for maintaining and identifying model/versions; and
3. The procedure(s) for the maintenance of the device history and the device master record.

O. Submission format

The 510(k) submission should be:

1. Bound into a volume(s);
2. Submitted in duplicate on standard size paper, including the original and one copy;
3. Submitted separately for each product the manufacturer intends to market;
4. Designated "510(k) Notification" in the cover letter; and
5. Submitted to:

    FDA/CBER
    Document Control Center
    Suite 200 North, HFM-99
    1401 Rockville Pike
    Rockville, Maryland 20852-1448