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Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories

FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)

DRAFT GUIDANCE

**This guidance document is being distributed for comment purposes only.
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You should submit comments and suggestions regarding this draft document within 120 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact LDTframework@fda.hhs.gov. For questions regarding this document as applied to devices regulated by CBER, contact the Office of Communication, Outreach and Development in CBER at 1-800-835-4709 or 301-827-1800 or ocod@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of *In Vitro* Diagnostics and Radiological Health

Center for Biologics Evaluation and Research



Preface

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Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories

FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

A. Introduction

This document is intended to describe the process for clinical laboratories to notify the FDA of the laboratory developed tests (LDTs) they manufacture as well as to describe the Medical Device Reporting (MDR) requirements, codified in 21 CFR Part 803, for clinical laboratories manufacturing LDTs. LDTs are those *in vitro* diagnostic devices (IVD) that are intended for clinical use and are designed, manufactured and used within a single laboratory.^{1, 2}

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory

¹ Single laboratory refers to a facility with a single CLIA certificate as described in 42 CFR 493.43(a)-(b). (See also 42 CFR 493.55). LDTs should only be designed, manufactured, and used by laboratories that meet the requirements for high-complexity testing under CLIA as described in 42 CFR 493.17(c)(4) and 493.25.

² The scope of this guidance is consistent with the scope of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs).

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requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

B. Background

LDT Background and Regulatory History

In 1976, Congress enacted the Medical Device Amendments (MDA), which amended the Federal Food, Drug, and Cosmetic Act (the FD&C Act) to create a comprehensive system for the regulation of medical devices intended for use in humans. At that time, the definition of a device was amended to make explicit that it encompasses *in vitro* diagnostic devices (IVDs).³ The definition of device applies equally to *in vitro* diagnostics manufactured by conventional device manufacturers and those manufactured by laboratories. An IVD, therefore, meets the device definition irrespective of where and by whom it is manufactured.

However, since the implementation of the MDA of 1976, FDA has generally exercised enforcement discretion so that the Agency has generally not enforced applicable provisions under the FD&C Act and FDA regulations with respect to LDTs.

Since 1976, when Congress clarified that IVDs were medical devices under the FD&C Act and FDA opted to exercise enforcement discretion with respect to LDTs under this authority, the industry has grown and evolved in significant ways. FDA now finds that in the absence of appropriate oversight of LDTs, there is the potential for increased risk for patients. FDA recognizes that, as with all IVDs, potential risks vary with the wide variety of LDTs. Thus, FDA believes that a risk-based approach to regulatory oversight of LDTs is appropriate and necessary to protect patient safety.

Consistent with the draft guidance entitled “Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)” (LDT Framework Guidance Document) that is being distributed for comment in coordination with this document, FDA intends to enforce certain device requirements for LDTs and device manufacturer requirements for laboratories that manufacture, prepare, propagate, compound, assemble or process

³ Section 201(h) of the FD&C Act provides:

(h) The term "device" (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is--

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

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LDTs.⁴ FDA intends to collect information regarding LDTs currently being offered for clinical use through a notification process. In addition, FDA intends to enforce the requirements under 21 CFR Part 803 for laboratories that are also manufacturers of LDTs for reporting safety issues related to LDTs to provide a mechanism for collecting information on any known or suspected adverse events related to the use of an LDT. The FDA believes that this is the appropriate regulatory approach to adopt to achieve the desired public health goal of assuring that these IVD tests used in the provision of health care, regardless of the manufacturer, provide reasonable assurance of safety and effectiveness.

C. Scope

The goal of this document is to explain to clinical laboratories how they should appropriately notify the FDA of all of the LDTs manufactured, prepared, propagated, compounded, or processed by their laboratories. This guidance also provides information about how to comply with FDA's MDR requirements as they apply to LDTs.

D. Notification to FDA of all LDTs Manufactured by a Laboratory

The notification process described below is intended to collect information on the LDTs being used by laboratories in order to classify LDTs by risk level and assist FDA in determining its priorities in enforcing premarket review requirements for different types of LDTs.

The specific information that should be provided with each LDT notification is described in Appendix A of this document. Information should be submitted on-line through the FDA website. Notification is expected to occur once for each LDT, although if significant changes are made to an LDT, additional notification should be provided.

Completion of this notification does not constitute compliance with registration and listing requirements, nor will the laboratory be considered to be registered and listed with the FDA.

Notification Process for LDTs Currently on the Market and New LDTs on the Market within 6 Months after Publication of the Final LDT Framework Guidance Document:

For all LDTs on the market on the date of publication of the final version of the LDT Framework Guidance Document, and new LDTs that come on the market for the

⁴ See 21 CFR 807.3(d) for definition of these terms. This guidance document uses "manufacture" to encompass all of these terms.

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following 6 months after publication of the document, FDA intends to continue to exercise enforcement discretion with respect to the registration and listing requirements, as described in 21 CFR Part 807, for owners and operators of laboratories⁵ that manufacture, prepare, propagate, compound, assemble, or process⁶ LDTs, provided that these laboratory owners/operators notify the Agency and provide basic information regarding all of the LDTs they manufacture within 6 months of publication of the final LDT Framework Guidance Document.

Notification for New LDTs on the Market after the 6-month Period following Publication of the Final LDT Framework Guidance Document:

Starting 6 months after publication of the final version of the LDT Framework Guidance Document, FDA intends to continue to exercise enforcement discretion with respect to the registration and listing requirements, as described in 21 CFR Part 807, for owners and operators of laboratories⁷ that manufacture, prepare, propagate, compound, assemble, or process⁸ new LDTs, provided that these laboratory owners/operators notify the Agency and provide basic information regarding the new LDTs they manufacture prior to offering these LDTs for clinical use.

Notification to FDA regarding Significant Changes to LDTs:

When a laboratory makes a significant change to the marketed intended use of an LDT for which they have previously provided notification, the LDT will be considered by the FDA to be a new LDT.⁹ Therefore, a new notification should be provided within 6 months of publication of the final LDT Framework Guidance Document or prior to offering that LDT for clinical use if offered after that 6-month period. This notification is especially important for those changes in marketed intended use that increase the risk of the device. Additionally, FDA urges laboratories that make other significant modifications to LDTs after the initial notification to re-submit notification data to FDA to communicate such changes (see section D.5.(e) of the LDT Framework Guidance Document for additional information on significant device modifications).

Laboratories That Do Not Provide Notification:

Laboratories that do not opt to notify the Agency and provide basic information regarding each of the LDTs manufactured in their laboratory within the abovementioned timeframes or that do not opt to notify the Agency and provide basic information after a significant change is made to the marketed intended use of their LDT will not be within the scope of FDA's enforcement discretion policy with respect to the registration and

⁵ Laboratory refers to a facility with a single CLIA certificate as described in 42 CFR 493.43(a)-(b). (See also 42 CFR 493.55).

⁶ See 21 CFR 807.3(d) for definition of these terms. This guidance document uses "manufacture" to encompass all of these terms.

⁷ See *supra* note 3.

⁸ See *supra* note 4.

⁹ For purposes of this guidance, FDA uses the term "marketed intended use" to refer to the use(s) of a test that a laboratory promotes or includes in any applicable labeling. Although FDA generally considers new devices to include other types of modifications to an existing device (e.g., technological changes), for the purposes of this subsection only, new LDTs do not include other types of modifications to an existing LDT.

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listing requirements codified in 21 CFR Part 807. Such laboratories would fall within the agency's normal enforcement approach with respect to the registration and listing requirements. These requirements include payment of the required registration fee (Section 738(a)(3) of the FD&C Act; 21 U.S.C. 379j(a)(3)), registration of each establishment¹⁰ with the FDA, and listing of the devices manufactured in these facilities (21 CFR 807.20(a)).

Instructions for Establishments That Are Involved in the Manufacture of Other Medical Devices, in Addition to LDTs:

FDA intends to exercise enforcement discretion with respect to registration and listing requirements solely for laboratories that manufacture prepare, propagate, compound, assemble, or process *only* LDTs. Establishments that manufacture, prepare, propagate, compound, assemble, or process other medical devices, in addition to LDTs, must comply with the registration and listing requirements codified in 21 CFR Part 807, including payment of the required registration fee (Section 738(a)(3) of the FD&C Act; 21 U.S.C. 379j(a)(3)), registration of their establishment with the FDA and listing of the devices manufactured in these facilities (21 CFR 807.20(a)), including LDTs. FDA does not believe that enforcement discretion is warranted for such laboratories because FDA is already enforcing registration and listing requirements for such establishments based upon their activities related to other medical device products.

When completing registration and listing with the FDA, owners and operators of these establishments should provide listing information for their LDT by utilizing the LDT product code, "OQS" into the FDA's Unified Registration and Listing System (FURLS). This product code is specific for LDTs that have not received product codes through the FDA clearance or approval process.

Registration and Listing Requirements for LDTs that Seek FDA Clearance or Approval

FDA intends to enforce registration and listing requirements for establishments that manufacture, prepare, propagate, compound, assemble or process an LDT once a laboratory has submitted a premarket submission (e.g., premarket approval application or a premarket notification submission (510(k))) to the Agency for the LDT. A laboratory may seek premarket clearance/approval for its LDT either because FDA has announced its intent to enforce premarket review requirements for that LDT category (see draft LDT Framework Guidance Document) or because the laboratory has chosen to do so.

Manufacturers of LDTs that receive FDA clearance or approval **should not** list these cleared or approved medical device(s) under the "OQS" product code. Rather, the establishment should utilize the product code that FDA assigns to their medical device in the clearance/approval of their premarket submission. These manufacturers should only use the "OQS" code when listing LDTs that are not cleared or approved.

¹⁰ See 21 CFR 807.3(c) for definition of "establishment."

E. Medical Device Reporting for LDTs

Overview of Medical Device Reporting (MDR) Requirements

Medical Device Reporting (MDR) requirements are codified in 21 CFR Part 803. One objective of the MDR regulation is to provide a mechanism for FDA and device manufacturers to identify and monitor significant adverse events involving medical devices so that problems may be detected and corrected in a timely manner. This regulation implements reporting requirements for importers, manufacturers, and user facilities.

Laboratories have always been subject to certain provisions of the MDR regulation in their capacity as device user facilities¹¹ (21 CFR 803.10(a), 803.30, 803.32, and 803.33). User facilities are required to report to the device manufacturer, if known, and to FDA no more than 10 work days after the day they become aware of information from any source that reasonably suggests that a device has caused or may have caused or contributed to the death of a patient of their facility. 21 CFR 803.30(a)(1). User facilities are required to submit a report to the device manufacturer¹² no later than 10 work days after the day they become aware of information from any source that a device has or may have caused or contributed to a serious injury to a patient of their facility. 21 CFR 803.30(a)(2). If the device manufacturer is not known, user facilities must report to FDA. 21 CFR 803.30(a)(2). User facilities are also required to submit annual reports (see 21 CFR 803.33) to FDA that include information for each reportable event that occurred during the annual reporting period.

In addition to enforcing laboratories' obligations to report adverse events as user facilities, FDA also intends to enforce manufacturer reporting requirements for laboratories that manufacture¹³ LDTs in accordance with 21 CFR Part 803, including 21 CFR 803.10(c), 21 CFR 803.50, and 21 CFR 803.52. The following guidance is intended to assist clinical laboratories in submitting adverse event reports as manufacturers and to meet their other requirements as manufacturers under 21 CFR Part 803, including 21 CFR 803.17, 21 CFR 803.18, 21 CFR 803.53 and 21 CFR 803.56:

1. Manufacturer Reporting Requirements

¹¹ A "device user facility" is defined under 21 CFR Part 803.3 as a "hospital, ambulatory surgical facility, nursing home, outpatient diagnostic facility, or outpatient treatment facility. . ." The focus of this guidance document is laboratories offering LDTs.

¹² Note that, for LDTs, the laboratory is both the user facility and the manufacturer.

¹³ In accordance with 21 CFR 803.3 a manufacturer is "any person who manufactures, prepares, propagates, compounds, assembles, or processes a device by chemical, physical, biological or other procedure." This definition therefore encompasses laboratories that design and manufacture LDTs, or those that significantly modify FDA cleared/approved devices (e.g., modify performance or intended use).

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The MDR regulation requires the manufacturer of a medical device to submit reports to the FDA whenever they become aware¹⁴ of information that reasonably suggests that a device they market may have caused or contributed to¹⁵ a death or serious injury¹⁶, or has malfunctioned and the malfunction would be likely to cause or contribute to a reportable death or serious injury should it recur. 21 CFR 803.50.

Manufacturers (21 CFR 803.3), including foreign manufacturers, of medical devices are required to:

- Submit MDR reportable events involving their medical devices as described in 21 CFR 803.10(c), 21 CFR 803.50, and 21 CFR 803.52;
- Submit 5-day reports as described in 21 CFR 803.53;
- Submit supplemental reports as described in 21 CFR 803.56;
- Conduct an investigation of each event and evaluate the cause of the event as described in 21 CFR 803.50(b)(3);
- Develop, maintain, and implement written MDR procedures described in 21 CFR 803.17; and
- Establish and maintain complete files for all MDR events concerning adverse medical device events as described in 21 CFR 803.18(a) and (e).

When to submit a report

All clinical laboratories manufacturing LDTs for clinical use are required as medical device manufacturers to submit MDR reports to the FDA as follows:

- Submit reports of individual adverse events no later than 30 calendar days after the day that the laboratory becomes aware of information from any source, that reasonably suggests that an LDT they manufacture:
 - May have caused or contributed to a death or serious injury or
 - Has malfunctioned and this device or similar LDT they manufacture would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur. (21 CFR 803.50(a))

¹⁴ A manufacturer has “become aware” of an event when an employee of the entity required to report has acquired information to reasonably suggest a reportable adverse event has occurred. (21 CFR 803.3).

¹⁵ The term “caused or contributed to” means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of failure, malfunction, improper or inadequate design, manufacture, labeling, or user error. (21 CFR 803.3)

¹⁶ “Serious Injury” means an injury or illness that is life-threatening, results in permanent impairment of a body function or permanent damage to a body structure, or necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. (21 CFR 803.3)

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- Submit reports of individual adverse events no later than 5 working days after the day that the laboratory becomes aware of a reportable event that necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health; or a reportable event for which the FDA has made a written request. (21 CFR 803.53)
- Submit supplemental reports within 1 month of the day the laboratory receives reportable information that was not submitted in an initial report. (21 CFR 803.56)

How to submit a report

Laboratories reporting on adverse events related to their LDTs must complete the MedWatch 3500A form available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf> then mail the completed form to FDA.¹⁷

Submit MedWatch 3500A forms to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, MD 20847-3002

These forms can also be submitted electronically. For electronic filing instructions please see Section E, question 14.

Please note: Laboratories that have not registered and listed with the FDA, but that have notified the FDA of their LDTs using the process described in the guidance should utilize their notification confirmation number, instead of a FDA registration number, to create an appropriate “Mfr Report Number” (top right hand corner of MedWatch 3500A form).

Additionally, laboratories should include the term “procode OQS” (unless the LDT has been cleared or approved by FDA, in which case the procode assigned in the clearance/approval process should be used) in the section of the MedWatch 3500A form entitled “D. Suspect Medical Device” subsection D.4 “Other.”

The MDR report (MedWatch 3500A form) must contain all the information described in 21 CFR 803.52 that is known or reasonably known to the clinical laboratory as a manufacturer. Information reasonably known includes any information that:

¹⁷ The MDR regulation in 21 CFR Part 803 was amended on February 14, 2014, to require device manufacturers and importers to submit MDRs (including supplemental reports) to the FDA in electronic format as specified in the amended rule. 79 FR 8832. The amended rule takes effect on August 14, 2015. *Id.* Once the amended rule takes effect, LDT manufacturers must submit MDRs (including supplemental reports) to the FDA in electronic format as specified in the amended rule unless FDA grants an exemption under 21 CFR 803.19. *Id.*

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- Can be obtained by contacting a user facility, importer, or other initial reporter;
- Is in the possession of the manufacturer; or
- Can be obtained by analysis, testing, or other evaluation of the device.

21 CFR 803.50(b).

Instructions for completing specific items on the MedWatch 3500A form can be found at: <http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf>.

The coding manual can be found at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm106737.htm>.

2. Requirement for developing, maintaining and implementing written MDR procedures

As is the case with other medical device manufacturers, clinical laboratories manufacturing LDTs for clinical use must develop, maintain, and implement written MDR procedures. 21 CFR 803.17. Specifically, these procedures should include internal systems that provide instructions for: timely and effective identification, communication, and evaluation of events that may be subject to MDR requirements; a standardized review process or procedure that assists in determining when an event meets MDR reporting criteria; and timely transmission of complete MDR reports to the FDA. 21 CFR 803.17(a).

Further, these procedures must include instructions for how the clinical laboratory will address documentation and record keeping requirements for: information that was evaluated to determine if an event was reportable; all medical device reports and information submitted to the FDA; any information that was evaluated for the purpose of preparing the submission of annual reports; and systems that ensure access to information that facilitates timely follow-up and inspection by FDA. 21 CFR 803.17(b).

Laboratories, as manufacturers, are also required to establish and maintain MDR event files, required by 21 CFR 803.18.

For additional guidance on the MDR regulation and the reporting requirements, refer to the document titled “Medical Device Reporting for Manufacturers” at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094529.htm>.

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Reporting Adverse Events as a User Facility and as a Manufacturer

1. What are the basic adverse event reporting obligations for user facilities and manufacturers?

A. Reports of individual adverse events required for user facilities and manufacturers under 21 CFR Part 803:

User facilities and manufacturers report individual adverse events to FDA under a uniform, unified reporting system. Both user facilities and manufacturers report adverse events on the same MedWatch 3500A form, the "Medication and Device Experience Report." 21 CFR 803.11 (You can find a copy of the Mandatory MedWatch report form at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf>).

When a user facility receives information about a reportable adverse event, it must report the event to FDA and/or the manufacturer after it becomes aware of the adverse event. 21 CFR 803.30. The user facility fills out certain parts of the MedWatch 3500A form and forwards copies of the form to both FDA and the manufacturer within ten (10) work days after the day the user facility becomes aware if the adverse event involves a death. If the adverse event involves a serious injury, the user facility is required to report the event to the manufacturer within ten (10) work days after the day the user facility becomes aware of the event. 21 CFR 803.30. If the identity of the manufacturer is unknown, the user facility must report the serious injury to FDA within ten (10) work days after the day the user facility becomes aware of the event. 21 CFR 803.30.

The manufacturer, after becoming aware of the reportable event from the user facility, further investigates the event and provides additional information on the MedWatch 3500A form. 21 CFR 803.50. The manufacturer must submit a completed MedWatch 3500A form to FDA within thirty (30) calendar days after the day it becomes aware of the adverse event. 21 CFR 803.50. A manufacturer also is obligated to submit a MedWatch 3500A form to FDA within five (5) work days after the day it becomes aware of a reportable MDR event that requires remedial action in accordance with 21 CFR 803.53. This requirement is further discussed in question 6D, below. 21 CFR Part 803, Subpart E.

B. Other adverse event reports required for user facilities:

User facilities must complete and submit to FDA an annual report by January 1 of each year. 21 CFR 803.33. Under 21 CFR 803.33, the information in the annual report must include:

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- User facility's Center for Medicare and Medicaid Services (CMS) provider number or the number assigned by FDA for reporting purposes;
- Reporting year;
- Facility name and complete address;
- Total number of reports attached or summarized;
- Date of the annual report and the lowest and highest user facility report number of medical device reports submitted during the report period (for example, 123456790-2001-0001 through 0895);
- Name, position title, and complete address of the user facility contact person responsible for reporting to us and whether that person is a new contact for you; and
- Information for each reportable event that occurred during the annual reporting period (see 21 CFR 803.33 (7) (i-vi) for details).

The annual report information must be submitted to the Agency using FDA form 3419 or its electronic equivalent as approved by FDA under 21 CFR 803.14. 21 CFR 803.33. If no reports are submitted to either FDA or manufacturers during these time periods, no annual report is required. 21 CFR 803.33(c).

C. Other adverse event reports required for manufacturers:

Manufacturers are required to submit Supplemental Reports of required information that was not known or was not available at the time of the initial report. 21 CFR 803.56. This information must be submitted within one (1) month of the day the manufacturer receives the information. 21 CFR 803.56.

2. How does being a manufacturer of a device change my adverse event reporting obligations?

As an entity that is a manufacturer of a device in addition to being a user facility, your clinical laboratory is now also subject to the manufacturer's adverse event reporting requirements. **Accordingly, for adverse events involving LDTs, you must fulfill both the 21 CFR Part 803 reporting requirements of a user facility and a manufacturer.** 21 CFR 803.3. This guidance document is intended to assist you in determining when a clinical laboratory must fulfill both the user facility and the manufacturer reporting requirements of 21 CFR Part 803 and when you only have to fulfill the user facility reporting requirements of 21 CFR Part 803.

3. What are the major differences between the user facility and manufacturer adverse event reporting requirements under 21 CFR Part 803?

There are several significant differences between reporting an adverse event to FDA as a user facility versus as a device manufacturer. Device manufacturers are required to report serious injuries to FDA rather than to the manufacturer; fill out additional sections of MedWatch 3500A form; report certain device malfunctions; and submit

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five (5) day remedial action event reports to the Agency. In addition to filing the MedWatch 3500A form, manufacturers are required to submit Supplemental MDR Reports as appropriate.

4. How do I know if I am required to report as a manufacturer or a user facility?

Whether you are required to fulfill the user facility adverse event reporting requirements only, or the manufacturer reporting requirements and the user facility requirements depends on whether the adverse event involved an LDT. The answer to whether you report solely as a user facility or whether you also must report as a manufacturer depends on your answer to the following questions:

A. Does the reportable event involve an LDT that was manufactured by your laboratory?

If the reportable event involved an LDT that your facility manufactured, even if the LDT in question contained critical components, such as Analyte specific reagents (ASRs), that were not manufactured by your laboratory (e.g. FDA cleared/approved devices that have been modified by your laboratory in a way that affects intended use or IVD performance), then you have to fulfill the reporting requirements of a manufacturer and a user facility. 21 CFR 803.3.

B. Does the reportable event involve an IVD or other medical device that was not an LDT manufactured by your laboratory?

If the reportable event involved an IVD or other medical device that was not an LDT that you manufactured, you only have to fulfill the reporting requirements of a user facility. 21 CFR 803.3.

5. What types of adverse events must I report when the event *is not related to an LDT manufactured by my clinical laboratory*?

You are required to fulfill user facility adverse event reporting requirements for:

A. Deaths:

As a user facility, you are obligated to report adverse events to FDA, and to the manufacturer, if known, within ten (10) work days after the day you become aware of information that reasonably suggests that a device has or may have caused or contributed to the death of a patient of your facility. 21 CFR 803.30(a)(1).

B. Serious Injuries:

As a user facility, you are obligated to report adverse events to the manufacturer, or to FDA if the identity of the manufacturer is not known, within ten (10) work days after the day you become aware of information that reasonably suggests that a device has or may have caused or contributed to a serious injury to a patient of your facility.

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21 CFR 803.30(a)(2).

6. What types of events must I report as a manufacturer when the event is related to an LDT manufactured by my clinical laboratory?

LDTs are medical devices under the FD&C Act (Section 201(h) of the FD&C Act; 21 U.S.C. 321(h)); therefore, a clinical laboratory that manufactures and offers an LDT for clinical use is considered to be a manufacturer of a medical device. As such, the clinical laboratory must fulfill the manufacturer reporting requirements under 21 CFR 803:

A. Deaths:

As the LDT manufacturer, you are obligated to report adverse events to FDA within thirty (30) calendar days after the day you become aware of information that reasonably suggests that an LDT manufactured by your clinical laboratory has or may have caused or contributed to the death. 21 CFR 803.50(a)(1).

B. Serious Injuries:

As an LDT manufacturer, you are obligated to report adverse events to FDA within thirty (30) calendar days after the day you become aware of information that reasonably suggests that an LDT manufactured by your clinical laboratory has or may have caused or contributed to a serious injury. 21 CFR 803.50(a)(1).

C. Malfunctions:

As an LDT manufacturer, you are obligated to report adverse events to FDA within thirty (30) calendar days after the day you become aware of information that reasonably suggests that the LDT manufactured by your clinical laboratory has malfunctioned and such device (LDT) or similar device (LDT) also manufactured by your clinical laboratory would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur. 21 CFR 803.50(a)(2).

D. Remedial actions; requests:

As an LDT manufacturer, you are obligated to report adverse events to FDA within five (5) work days after the day you become aware of:

1. a reportable event(s) that necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health, or
2. a reportable event(s) for which FDA has made a written request.

21 CFR 803.53(a) and (b).

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- 7. As an LDT manufacturer, I am obligated to report deaths to FDA within 30 calendar days (see question 6A, above). However, as a user facility, I am obligated to report deaths to FDA within 10 work days (See question 5A, above). Do I complete two separate MedWatch 3500A forms in order to meet the different reporting obligations for the same event?**

To avoid filing the same event twice when the event involves a reportable death, you may complete all medical device sections (skip section C) of the MedWatch 3500A form and submit the completed form to the Agency within ten (10) work days.

As the user facility, you must complete sections A – F (skip section C) of the MedWatch 3500A form. 21 CFR 803.32. As the LDT manufacturer, you must complete sections A, B, D, E, G, and H of the MedWatch 3500A form. 21 CFR 803.52. Thus, as both, you must complete sections A, B, and D-H of the MedWatch 3500A form. 21 CFR 803.32 and 21 CFR 803.52.

- 8. What is the definition of "Serious Injury"?**

"Serious injury" is defined as an injury or illness that:

- is life-threatening;
- results in permanent impairment of a body function or permanent damage to body structure; or
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. 21 CFR 803.3.

- 9. What is the definition of "Malfunction"?**

"Malfunction" is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. 21 CFR 803.3. Performance specifications include all claims made in the labeling for the device. 21 CFR 803.3. The intended performance of a device refers to the intended use for which the device is labeled or marketed. 21 CFR 801.4 and 21 CFR 803.3.

- 10. As a user facility, which sections of the MedWatch 3500A form must I complete for a reportable adverse event?**

- A. On the upper right-hand corner on the front page of the MedWatch 3500A form, enter your user facility number under *UF/Dist report #*. The UF # is a combination of your organization's CMS number (or a number FDA assigned to your organization), the 4-digit calendar year in which the report is submitted, and a 4-digit sequence number of the report submitted during the year (e.g., 1234567890-2011-0001, 1234567890-2011-0002, etc.).

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- B. Complete all items in section A. *Patient information*.
- C. Complete all items in section B. *Adverse event or product problem*.

(Note: skip section C. *Suspect medication(s)*.)

- D. Complete all items in section D. *Suspect medical device*. Note that specific device identification information should be entered exactly as it appears on the device or on the device labeling.
- E. Complete all items in section E. *Initial reporter*. The initial reporter is the person who provided the information about the adverse event to the user facility.
- F. Complete all items in section F. *For use by user facility/distributor- devices only*.

21 CFR 803.20 and 21 CFR 803.32.

11. As the manufacturer, which sections of the MedWatch 3500A form must I complete for a reportable adverse event that *involves an LDT that my clinical laboratory manufactured?*

- A. On the upper right-hand corner on the front page of the MedWatch 3500A form, enter your *Mfr. report #*. The *mfr. report #* is composed of either the registration number that FDA assigned to your laboratory when you registered and listed with the Agency as a manufacturer, or the notification confirmation number that you were assigned upon notifying the Agency of your LDTs, the 4-digit calendar year in which the report is submitted, and the 5-digit sequence number for each report submitted during the year (e.g., 9876543210-2011-00001, 9876543210-2011-00002, etc.). You also must enter your user facility report number under *UF/Dist report #* of the MedWatch 3500A form (see 10A above).

- B. Complete all items in section A. *Patient information*.
- C. Complete all items in section B. *Adverse event or product problem*.

(Note: skip section C. *Suspect medications(s)*.)

- D. Complete all items in section D. *Suspect medical device*. For item D.3. *Manufacturer name and address*, enter the name and address of the laboratory that manufactures the LDT. For item D.4 *Other #* enter "Procode OQS" if your LDT is not approved or cleared by the FDA. If your LDT is approved or cleared by the FDA, please enter "Procode" and then the product-specific procode that was assigned to your device.

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- E. Complete all items in section *E. Initial reporter*. The initial reporter is the person who provided the information about the adverse event to the user facility or manufacturer.
- F. Section *F. For use by user facility/distributor-devices only*. If you are considered to be both the user facility and the manufacturer for the event, then you should fill out this section as the user facility. For malfunction events not submitted by the user facility, the manufacturer's submission should not include section F of the MedWatch 3500A form. Corrected or missing information for Section F, including relevant patient problem and device problem codes, should be included in the Section H.11 (*Corrected Data*) section of the MedWatch 3500A form provided by the manufacturer.
1. *F.13. Report sent to manufacturer?* The term "manufacturer" in this block refers to the LDT manufacturer.
 2. *F.14: Manufacturer name/address*. The term "manufacturer" in this block refers to the LDT manufacturer. Because this information should also be entered in section G.1 *Contact office – name/address (& manufacturing site for devices)*, you may enter in section F.14 *Manufacturer name/address*, "see G.1."
- G. Complete all items in section *G. All manufacturers*.
1. *G.1: Contact office – name/address (& manufacturing site for devices)*. Information in this block refers to the LDT manufacturer; therefore, enter the contact office, name, and address of the laboratory that is submitting the report of the LDT event.
 2. *G.4: Date received by manufacturer (mo/day/yyyy)*. This is the date that the laboratory became aware of the adverse event.
 3. *G.5, 6, and 8*. These blocks are not applicable to medical devices.
 4. *G.7: Type of report*. Only three (3) report types are applicable to LDT manufacturers: *5-day*, *Initial (i.e., 30-day reports)*, and *Follow-up*. Select the report type that is applicable to the event that you are reporting.
 5. *G9: Manufacturer Report Number*. G9 should match the manufacturer report number that you assigned to the event in the upper right hand corner of your MedWatch 3500A form, and should appear on any additional pages you might attach to the MedWatch 3500A form.
- H. Complete all blocks in section *H. Device manufacturers only*. As the LDT manufacturer, you must complete all sections regardless of where the device analysis was performed.
1. *H.4: Device manufacturing date (mo/yyyy)*. For the purpose of this block, the manufacturing date is the date that the LDT was manufactured by your clinical laboratory. Note: in cases where components of the LDT were

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manufactured on different dates, FDA considers the “device manufacturing date” to be the date the last component of the LDT was manufactured by the laboratory and/or qualified as suitable for use.

2. *H.7: If remedial action initiated, check type.* Select the most appropriate remedial action(s) that apply. Under the MDR regulation a “remedial action” is any action, other than routine maintenance or servicing of a device, necessary to prevent recurrence of an MDR reportable event. 21 CFR 803.3. FDA does not consider an action taken to correct only a single device involved in a specific MDR reportable event to be a remedial action.
21 CFR 803.20, 21 CFR 803.32, and 21 CFR 803.52.

12. When do I have to file reports of corrections and removals?

Under 21 CFR Part 806, you are required to submit a written report to FDA within ten (10) work days of initiating a correction or removal action that was taken:

- to reduce a risk to health posed by the device; or
- to remedy a device problem which may present a risk to health

The Reports of Correction and Removal regulation, 21 CFR Part 806, specifies the information that must be included in this report, as well as the format the firm should follow when assigning the correction/removal reporting number. This number consists of the registration number for the responsible firm, the date of the report using MM/DD/YY format, a 3 digit sequential number for each report made on that date (i.e., 001, 002, 003, etc.), and the report type designation (i.e., “C” for a report of correction or “R” for a report of removal). 21 CFR 806.10.

You are reminded that a report of correction or removal should be reported to the appropriate FDA district office within 10 working days of initiating such correction or removal, and should contain the information required under 21 CFR 806.10.

13. If I file an adverse event report on the MedWatch 3500A form for an adverse event related to an LDT that I manufactured, do I have to file a corrections and removals report too?

The MedWatch 3500A form does not include all of the data elements required by 21 CFR Part 806 and therefore cannot replace the corrections and removals report. However, you may attach your 21 CFR Part 806 report to the MedWatch 3500A form.

Otherwise, the 21 CFR Part 806 report should be sent to the appropriate FDA District Office, and the MedWatch 3500A form should be submitted to FDA Headquarters.

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14. Can I submit my reports electronically?

Yes, you can file your initial and supplemental reports with FDA in an electronic format. Information on sending initial and supplemental reports electronically is available at <http://www.fda.gov/ForIndustry/FDAeSubmitter/default.htm>. Instructions for electronic reporting are available at the electronic Medical Device Reporting (eMDR) home page at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/eMDR%E2%80%93ElectronicMedicalDeviceReporting/default.htm>.

15. What are the supplemental reports that I must submit as an LDT manufacturer?

As an LDT manufacturer, you are obligated to file a supplemental report, using the MedWatch 3500A form, with FDA within one month of receiving additional or updated information on an adverse event that was not available or known at the time you submitted the initial MedWatch 3500A form. 21 CFR 803.56. You should report the supplemental information by providing the same user facility report number and manufacturer report number that was entered on the original submission by completing blocks *G.7 (Type of report)* and *G.9 (Mfr. report number)* and check the appropriate code in section *H.2*. Only new, changed, or corrected information should be entered on the MedWatch 3500A form. Information that was previously submitted should not be repeated. A detailed description of supplemental reporting requirements is provided in 21 CFR 803.56.

16. Are there additional MDR requirements that apply to user facilities that manufacture LDTs?

Yes. You need to amend your current MDR procedures to comply with your MDR reporting obligations as both an LDT manufacturer and user facility. 21 CFR 803.17.

User facilities and manufacturers are required to establish and maintain MDR event files. 21 CFR 803.18. For adverse events involving LDTs manufactured by your clinical laboratory, you need to incorporate the additional requirements for manufacturers under 21 CFR 803.18(e).

17. How may I request exemptions or alternative reporting options as an LDT manufacturer?

Under 21 CFR 803.19(b) and (c), you may, as an LDT manufacturer, request an exemption from any or all of the reporting requirements of 21 CFR Part 803. FDA may, at its discretion, grant an exemption or alternative form of reporting adverse

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events. When the Agency grants an exemption or alternative form of reporting, it may impose other reporting requirements to ensure the protection of public health.

For information, contact the MDR Policy Branch at MDRPolicy@fda.hhs.gov

18. Where can I get additional information on user facility or manufacturer MDR reporting requirements?

Resources:

Find reporting information at:

- MedWatch: The FDA Safety Information and Adverse Event Reporting Program (<http://www.fda.gov/Safety/MedWatch/default.htm>)
- How to Report a Problem (Medical Devices) (<http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm>)
- MedWatch Coding Tools/Resource Files (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/EventProblemCodes/default.htm>)
- Medical Device Reporting (MDR) modules on the Center for Devices and Radiological Health (CDRH) Learn page available at: (<http://www.fda.gov/training/cdrhlearn/default.htm>).

You may also submit questions on MDR reporting to the MDR Policy Branch (MPB) at: MDRPolicy@fda.hhs.gov; or you may refer to the web site <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm>.

APPENDIX A: FDA Notification Data Elements

To appropriately notify the FDA of all LDTs manufactured at an establishment, the owner/operator should provide information on the following data elements for *each* LDT manufactured at their establishment. Notification information should be submitted on-line through the FDA website.

1. **Laboratory Name**

Indicate the legal name for your laboratory as you wish it to appear in FDA's records.

2. **Laboratory Contact Email Address**

Indicate the contact email address for your laboratory as you wish it to appear in FDA's records.

3. **Test Name**

Indicate the name of the test you are describing. Please note that the name can include a trade name or a general descriptor used by the laboratory to refer to the test.

4. **Monthly Test Volume**

Indicate the number of clinical tests the laboratory conducts using this IVD per month.

5. **Intended Use**

Provide a brief statement describing how your test is intended to be used. Please include a general description of the disease or condition that the test will provide information for diagnosis, treatment, prevention, cure or mitigation. Please note that a single test can have multiple intended uses.

Example 1: The X urine test is an **immunoassay** designed for the **qualitative determination** of human chorionic gonadotropin (hCG) in **urine for the early detection of pregnancy**.

Example 2: Test Y is a qualitative in vitro diagnostic test service, performed in a single laboratory, using the **gene expression profile** of fresh frozen breast cancer tissue samples to assess a patient's risk for distant metastasis. The test is performed for **breast cancer patients** who are less than 61 years old, with Stage I or Stage II disease, with tumor size ≤ 5.0 cm and who are lymph node negative. The result of Test Y is indicated for use **by physicians** as a **prognostic marker only, along with other clinicopathological factors**.

6. **Clinical Use of Test**

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Indicate which of the following categories demonstrate how the information generated by your test is intended to be used clinically. Please indicate all of the terms below that apply to how the information generated by your LDT is intended to be used. If the “other” category is chosen, please specify the type of clinical use intended for the test.

Options:

- *Diagnosis*
- *Prognosis*
- *Monitoring*
- *Assessment of Risk*
- *Screening*
- *Organism Identification*
- *Therapy Selection/Monitoring*
- *Other*

7. What is measured or detected (i.e. analyte, measurand, etc.)

Indicate any analytes that are measured or organisms that are detected by the test.

8. Disease/Condition for which the diagnostic device is indicated

Indicate the type of disease or condition for which the test is used (i.e. cardiovascular disease, diabetes, breast cancer, etc.)

9. Patient Population

Provide a brief description of the patient population in which the test is intended to be used.

Example: Patients at high risk for developing type II diabetes.

10. Does the patient population include pediatric patients? (<21 years old)

Indicate whether the LDT is intended to be used on patients under 21 years old.

11. Sample Type

Indicate all of the sample types used for the test. Please note that a single test can utilize multiple sample types. If choosing “other” please specify the sample type used for the test.

Options:

- Serum
- Plasma
- Urine
- Whole Blood
- Cerebral Spinal Fluid (CSF)
- Bone Marrow

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- Tissue
- Organism Growth
- Other

12. Test Method

Indicate all test methods used for the test. Please note that a single test can utilize multiple test methods. If choosing the “other” category, please specify the additional test methods used for this IVD.

Options:

- Serology
- Flow Cytometry
- Fluorescence In Situ Hybridization (FISH)
- Genotyping/Nucleic Acid Detection (human)
- Immunohistochemistry (IHC)
- Immunoassay
- Mass Spectrometry
- Microarray (i.e. genotyping, proteomics, Array-CGH or array comparative genome hybridization, etc.)
- Nuclear Acid Amplification Test (NAAT) for microbial testing
- High Performance Liquid Chromatography (HPLC)
- Polymerase Chain Reaction (PCR)
- DNA Sequencing
- Other

13. Is the test a modification of an FDA cleared/approved test?

Please indicate whether the IVD represents an FDA cleared or approved in vitro diagnostic test that has been modified in some way so as to affect device performance or intended use.

14. If the test is a modification of an FDA cleared/approved test, what modifications were made?

If the IVD represents an FDA cleared or approved in vitro diagnostic test that has been modified in some way so as to affect device performance or intended use, please indicate what types of modifications were made to the FDA cleared/approved test. Please indicate all options that apply. If choosing “other”, please provide a brief description of the modification.

Options:

- Intended Use Change
- Instrument Change
- Procedure Change
- Software Modification
- Sample/Specimen Type Change

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- Change in results interpretation reporting
- Critical Assay Component Change
- Other

APPENDIX B: ADVERSE EVENT REPORTING REQUIREMENTS

	What types of device-related adverse events must be reported?	Who should receive a copy of the report?	What is the time frame for reporting the adverse event?	Which sections of the MedWatch 3500A form must be completed?
1. An LDT that your clinical laboratory manufactured, that is, you are reporting as a device manufacturer of the LDT	<ul style="list-style-type: none"> Deaths (21 CFR 803.50) 	<ul style="list-style-type: none"> FDA 	<ul style="list-style-type: none"> Within 30 calendar days after the day you become aware of the event. 	For all reports: <ul style="list-style-type: none"> A. Patient information; B. Adverse event or product problem; (Skip section C) D. Suspect medical device; E. Initial reporter; G. All manufacturers; and H. Device manufacturers only.
	<ul style="list-style-type: none"> Serious Injuries (21 CFR 803.50) 	<ul style="list-style-type: none"> FDA 	<ul style="list-style-type: none"> Within 30 calendar days after the day you become aware of the event. 	
	<ul style="list-style-type: none"> Malfunctions (21 CFR 803.50) 	<ul style="list-style-type: none"> FDA 	<ul style="list-style-type: none"> Within 30 calendar days after the day you become aware of the event. 	
	<ul style="list-style-type: none"> Remedial actions that were taken to prevent an unreasonable risk of substantial harm to the public <i>or</i> as requested by FDA. (21 CFR 803.53) 	<ul style="list-style-type: none"> FDA 	<ul style="list-style-type: none"> Within 5 work days after the day you become aware of the need for remedial action from any information, including any trend analysis, or have received a notification from FDA requesting 5-day reports 	
2. A device that is not an LDT manufactured by your clinical laboratory, that is, you are only reporting as a user facility. If you are reporting as user facility and manufacturer, you must	<ul style="list-style-type: none"> Deaths (21 CFR 803.30) 	<ul style="list-style-type: none"> FDA <p style="text-align: center;"><i>And</i></p> <ul style="list-style-type: none"> Device Manufacturer 	<ul style="list-style-type: none"> Within 10 work days after the day you become aware of the event. 	For all reports: <ul style="list-style-type: none"> A. Patient information; B. Adverse event or product problem; (Skip section C) D. Suspect medical device; E. Initial reporter; and F. For use by user facility/distributor-devices only.
	<ul style="list-style-type: none"> Serious Injuries (21 CFR 803.30) 	<ul style="list-style-type: none"> Device Manufacturer <p style="text-align: center;"><i>Or</i></p> <ul style="list-style-type: none"> FDA when the device manufacturer is unknown 	<ul style="list-style-type: none"> Within 10 work days after the day you become aware of the event. 	

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fulfill the reporting requirements of this section and those listed in section 1 above in this chart.

- May voluntarily report malfunctions

- FDA

Or

- Device Manufacturer

- Not required. Voluntary reports may be submitted at any time.
- Link to 3500 voluntary report form
<https://www.accessdata.fda.gov/scripts/medwatch/>