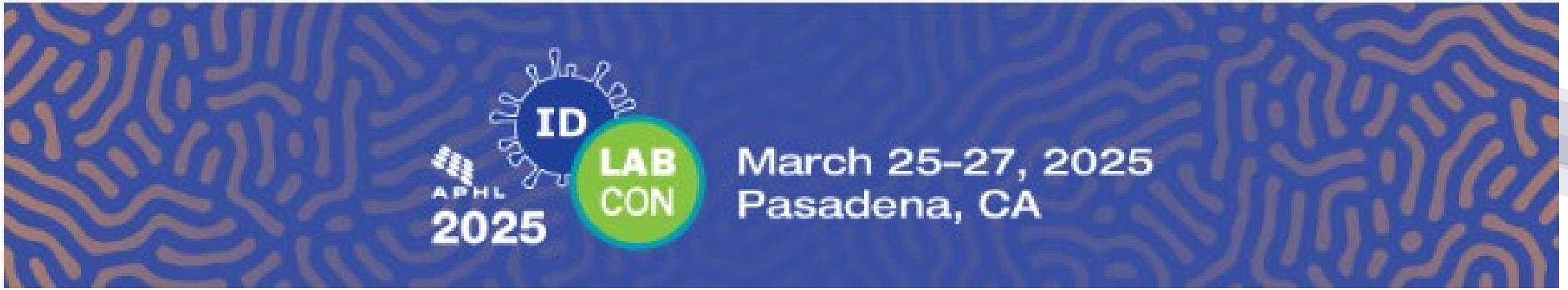


Assuring Regulatory Compliance in an Era of Change: What's a Lab to Do?

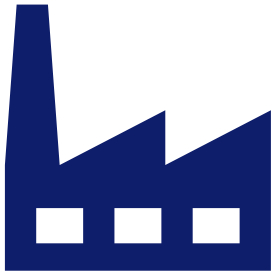
Industry Perspectives

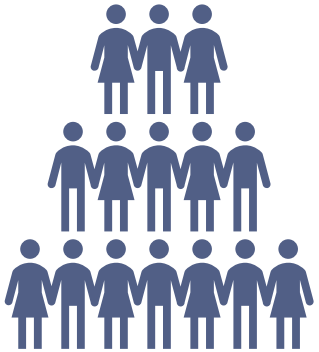
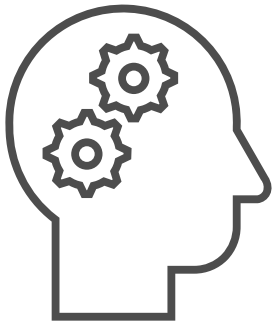
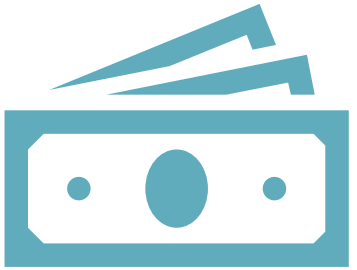
Karen Harrington, PhD HCLD (ABB)
Director Scientific Affairs, Hologic Inc.

Disclaimer: The information within these slides is for informational purposes only and is not intended to be either legal or regulatory advice

LDT FINAL RULE STAGE 1 READINESS

Industry is way ahead of the game....



Bigger isn’t always better…..

Right of Reference Letter

IVD Company authorizes the FDA to reference information in company's 510k, PMA, EUA for purposes of the laboratory's regulatory submission under review by the FDA.

- Analytical performance data
- Clinical performance data
- Stability data

The "new" manufacturer can reference the proprietary data, but does not have direct access to the data.

The FDA can consider the data in the context of the new submission and the "new" manufacturer would generally not have to repeat that validation for their submission to the FDA.

Risk Management

RISK MANAGEMENT FOR MEDICAL DEVICES

ISO 14971:2019

Risk Management is continuous

During design and development of assay

During manufacturing (ordering reagents and supplies, making of master mixes, etc)

During verification/validation of assay

During use – testing (pre-analytical/ analytical)

Post use (post-analytical) – results reporting, results interpretation

Who are appropriate parties to be included in Risk Management activities?

Evaluating Risk Acceptability

Severity Rating Scale

Rating	Description	Definition
5	Extremely High	Failure directly or indirectly leads to death or severe morbidity to patient – severely impacts patient outcome
4	High	Failure leads to increased morbidity to patient – negatively impacts patient outcome
3	Medium	Failure leads to incorrect answer – may impact diagnosis and patient outcome resulting in additional testing, therapy, cost of care, delayed recovery
2	Low	Failure may affect product performance with minimal or no impact on treatment/patient outcome – causes customer dissatisfaction
1	None	No effect on patient – does not impact treatment and is a minor inconvenience

Tables above are illustrative

Occurrence Rating Scale

Rating	Description	Definition
5	Very High: Always	1 in 10 Likely to occur many times per year
4	High: Repeated	1 in 100 Likely to occur several times per year
3	Medium: Occasional	1 in 1000 Likely to occur less than once per year
2	Low: Infrequent	1 in 100,000 Likely to occur 1X or less in the life of the test
1	Remote: Never	1 in >1,000,000 Extremely unlikely to occur in life of test

Detectability Rating Scale

Rating	Description	Definition
5	Cannot Detect	Failure cannot be detected at the time of occurrence
4	Low probability to detect	Failure unlikely to be detected at the time of occurrence
3	Medium probability to detect	Failure can be detected 50% of time
2	High probability to detect	Failure is likely detected at the time of occurrence
1	Certain to detect	Failure detected 100% of time

Risk Priority Number (RPN)

RPN = Severity x Occurrence x Detectability

RPN	Risk Range	Action Required
1 – 25	Safe, no need for further risk reduction	No action is required. If RPN falls into the low category, risk reduction may be considered by management.
26 – 40	ALARP, may consider risk reduction	No action required. If RPN falls into the ALARP category, risk reduction may be considered as desired by management. These risks are monitored on a regular basis (annually or as necessary)
41 – 125 Or S = 5	Unacceptable, must reduce risk prior to releasing product for use	Risk reduction is required. These risks are monitored closely.

Table above is illustrative

Risk Control and Prevention

FMEA – Failure Mode and Effects Analysis

- Potential failure modes: FP, FN, Invalid
- Potential effects of failure: unnecessary treatment, no treatment
- Potential causes of failure: poor primer design, instrument out of specifications, contamination during manufacture
- Current controls: validation, maintenance and calibration checks, quality control/quality assurance testing
- Recommended mitigation actions: monitor complaints, track mutations

Risk/Benefit

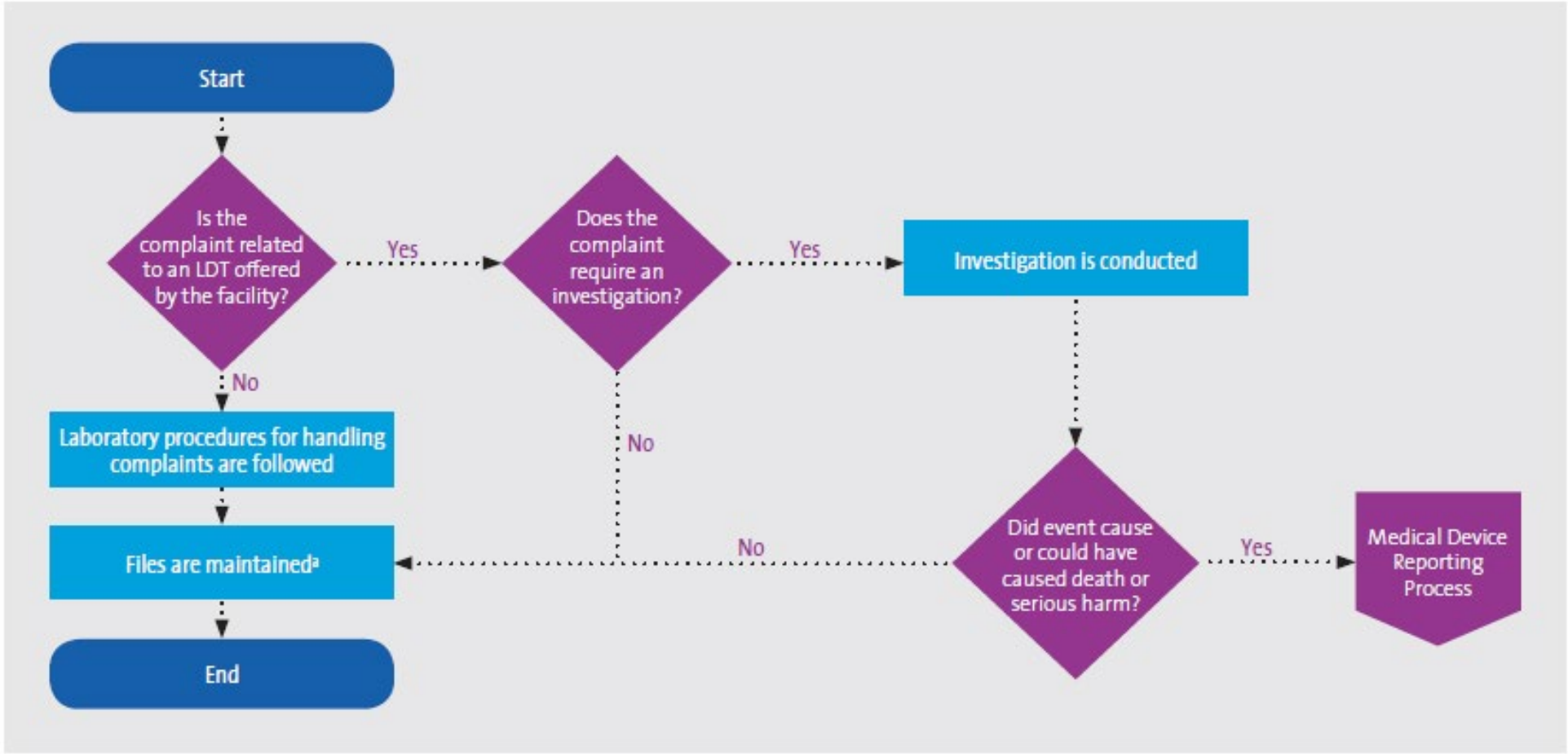
LDT Final Rule Stage 1 Requirements

Medical Device Quality System Requirements, Complaint Files
21 CFR 820.198

Medical Device Reporting Requirements
21 CFR pt. 803

Corrections and Removals Reporting Requirements
21 CFR pt. 806

Complaint Process: 21 CFR 820.198



CLSI. Quality System Regulation for Laboratory Developed Tests: A Practical Guide for the Laboratory. CLSI Document QSRLDT. Wayne, PA. Clinical and Laboratory Standards Institute 2025.

How QSRs compare to CLIA and CAP

CLIA:

493.1233 Standard: Complaint investigations.

The laboratory must have a system in place to ensure that it documents all complaints and problems reported to the laboratory. The laboratory must conduct investigations of complaints, when appropriate.

CAP:

GEN.20208 Identification of Non-conforming Events

There must be a process for recording problems involving the laboratory that are identified internally, as well as those identified through outside sources such as complaints from patients, physicians or nurses.

GEN.20310 Investigation of Non-conforming Events

The QMS requires a root cause analysis (RCA) when a non-conforming event occurs that results in death, permanent harm or severe temporary harm. For nonconforming events that represent a risk to patients, donors, employees, or the health and safety of the general public, but are not sentinel events (eg, near misses), the QMS includes a process to define the scope and extent of the investigation required.

GEN.20318 Corrective and Preventive Action

The QMS includes processes for recording corrective and preventive actions taken for non-conforming events (errors and incidents) and quality indicators that do not meet defined targets, and evaluating the effectiveness of the actions taken.

QSR:

- Procedure and designated group for complaint handling
  - Complaints handled and processed in timely manner
  - Oral complaints documented on receipt
  - Each complaint evaluated for reportable event to FDA
- Evaluate each complaint to determine if investigation is needed
- Any complaint involving possible failure must be investigated unless duplicative
- Any complaint related to an event that caused serious harm or death must be reported to FDA
- Investigation must include sufficient details and report on device related problem(s) directly or indirectly related to adverse event
- Records must be kept requiring specific information and be made accessible

Complaint Investigation

Results of Investigation MUST include:

(1)Whether the device failed to meet specifications;
Did the LDT work as expected??

(2) Whether the device was being used for treatment or diagnosis; and

(3) The relationship, if any, of the device to the reported incident or adverse event. – directly or indirectly

COMPLAINT INVESTIGATION RECORD

Name of the device:_____
Date complaint received:_____
Unique device identifier (UDI):_____

Complainant info:
Name/Address/Phone

Details of complaint:

Reply to complainant:

Investigation:
☐ No _____*Signature of responsible individual*
☐ Yes
Dates and results of investigation

Corrective Action:

Determining if an Adverse Event

Caused or contributed:

- Failure
- Malfunction
- Improper or inadequate design
- Manufacture
- Labeling
- User error

Serious injury or illness

- Life threatening
- Results in permanent impairment or damage to body function or structure
- Requires medical or surgical intervention to preclude permanent impairment or damage to body function or structure

Resource: https://www.fda.gov/medical-devices/medical-devices-news-and-events/webinar-in-vitro-diagnostic-products-ivds-mdr-requirements-correction-and-removal-reporting

Filing a MedWatch Report (MDR)

1. FEI (FDA Establishment Number)
2. Establish Product Codes for your LDTs

APHL Guide to the LDT Final Rule. March 2025.
https://www.aphl.org/policy/Advocacy_Documents/APHL%20Guide%20to%20Meeting%20the%20LDT%20Final%20Rule%20Stage%201%20Requirements.pdf

LDT Product Code Classification

LDT Product Code	Description
SCE	**IVD offered as LDT, first marketed before May 6, 2024, not modified beyond scope described in preamble to LDT Final Rule** Currently marketed IVD products offered as LDTs that were first marketed before May 6, 2024, and not modified following that date or not modified beyond the scope described in section V.B.3 of the preamble to the LDT Final Rule (89 FR 37286).
SCF	**LDT, unmet need within an integrated health care system** LDTs manufactured and performed by a laboratory integrated within a health care system to meet an unmet need of patients receiving care within the same health care system as described in section V.B.3 of the preamble to the LDT Final Rule (89 FR 37286).
SCG	**Modified version of another manufacturer's FDA-authorized test within scope described in preamble to LDT Final Rule** When a laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and meeting CLIA's regulatory requirements to perform high-complexity testing modifies another manufacturer's 510(k) cleared or De Novo authorized test, and in compliance as described in section V.C.3 of the preamble to the LDT Final Rule, in a manner that could not significantly affect the safety or effectiveness of the test and does not constitute a major change or modification in intended use, and where the modified test is performed only in the laboratory making the modification as described in sections V.C.4 and V.C.5 of the preamble to the LDT Final Rule (89 FR 37286).
SCH	**LDT, approved by NYS CLEP** LDTs that are approved by the NYS CLEP described in section V.B.2 of the preamble to the LDT Final Rule (89 FR 37286).
SCI	**IVD offered as LDT, not an LDT or under a targeted enforcement discretion policy described in preamble to LDT Final Rule** IVDs offered as LDTs that are not designed, manufactured, and used within a single laboratory, are within the scope of the phase out policy and are not subject to a targeted enforcement discretion policy described in the preamble to the LDT Final Rule (89 FR 37286).
SCJ	**LDT, not under a targeted enforcement discretion policy described in preamble to LDT Final Rule** LDTs within the scope of the phase out policy and not subject to a targeted enforcement discretion policy described in section V.B of the preamble to the LDT Final Rule (89 FR 37286).
SCK	**LDT, Non-molecular antisera for RBC antigens when there is no alternative IVD** Non-molecular antisera LDTs for rare RBC antigens when manufactured and performed by blood establishments, including transfusion services and immunohematology laboratories, and when there is no alternative IVD product available to meet the patient's need for a compatible blood transfusion within the scope described in Section V.B.3 of the preamble to the Final LDT Rule (89 FR 37286).

Filing a MedWatch Report (MDR)

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3. Download FDA software applications: eSubmitter and WebTrader programs and set up accounts
4. Establish Electronic Systems Gateway Account
5. Download Adverse Event Code lists

APHL Guide to the LDT Final Rule. March 2025.
https://www.aphl.org/policy/Advocacy_Documents/APHL%20Guide%20to%20Meeting%20the%20LDT%20Final%20Rule%20Stage%201%20Requirements.pdf

Adverse Event Codes

Code Type	Hierarchy
Medical Device Problem	Annex A
Medical Device Component	Annex G
Cause Investigation – Type of Investigation	Annex B
Cause Investigation - Investigation Findings	Annex C
Cause Investigation - Investigation Conclusion	Annex D
Health Effects - Clinical Signs and Symptoms or Conditions	Annex E
Health Effects - Health Impact	Annex F

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6. Complete MedWatch Form 3500A

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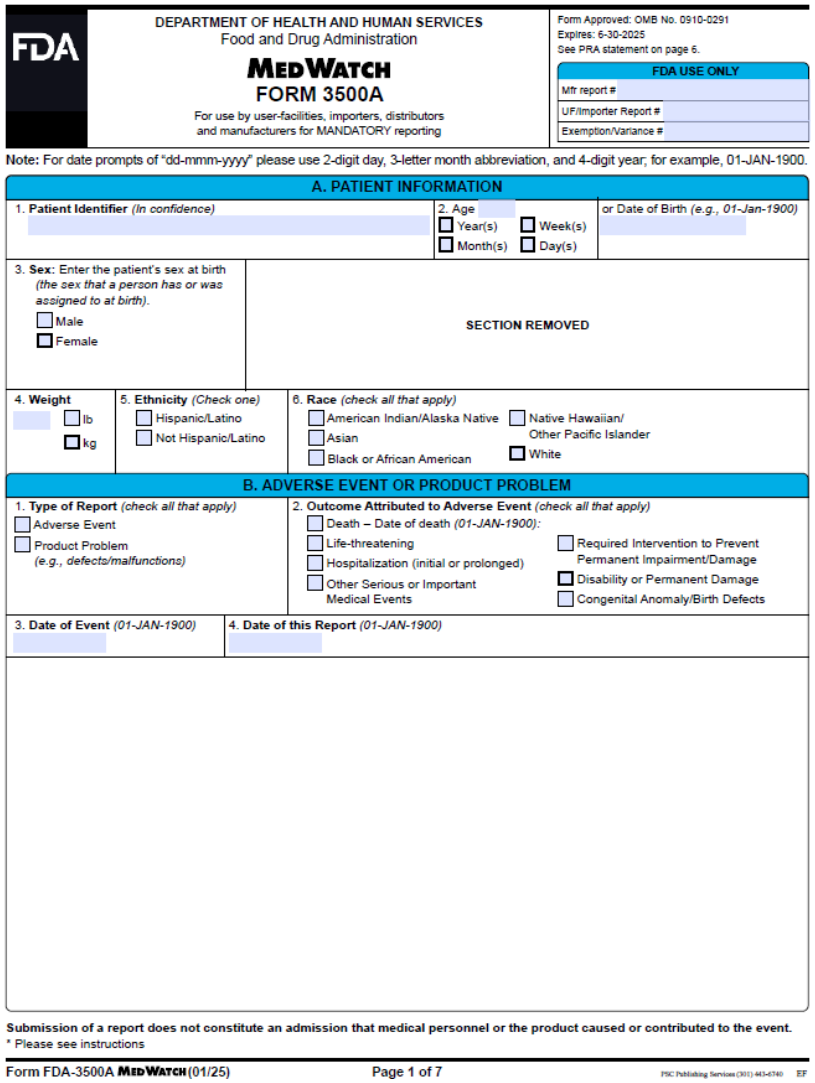
MedWatch Form 3500A



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

MEDWATCH
FORM 3500A

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Form Approved: OMB No. 0910-0291
Expires: 6-30-2025
See PRA statement on page 6.

FDA USE ONLY
Mfr report #
UF/Importer Report #
Exemption/Variance #

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-JAN-1900.

A. PATIENT INFORMATION

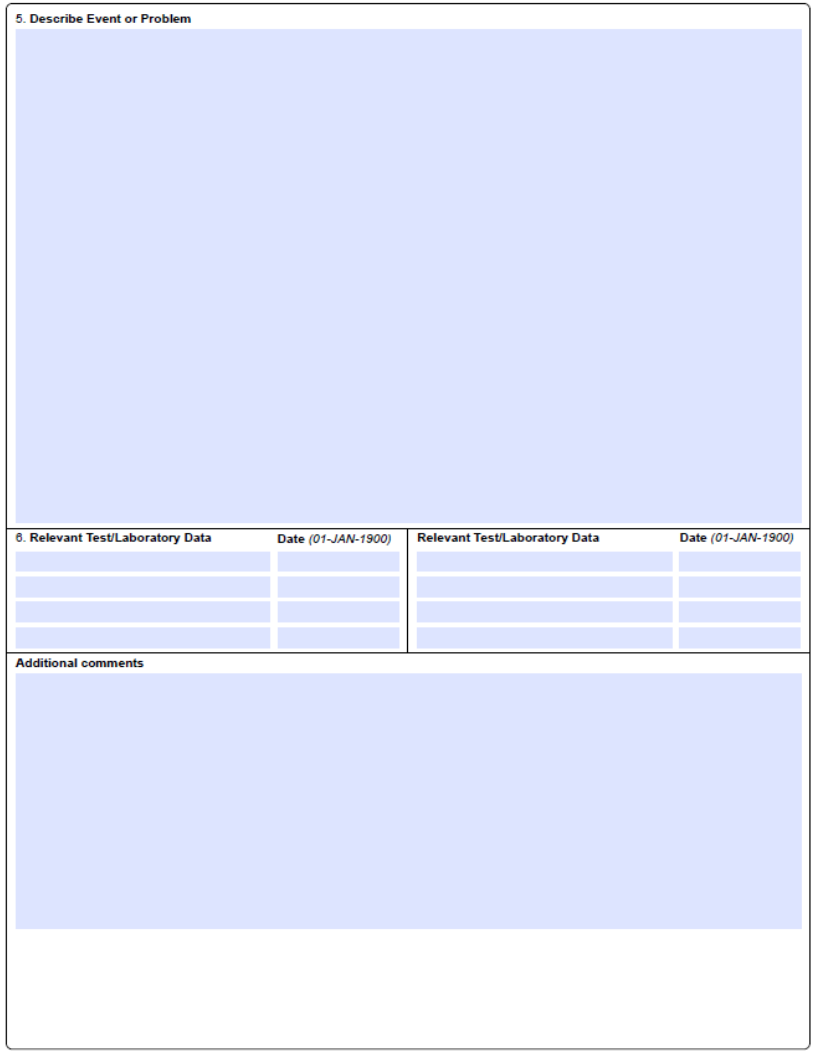
1. **Patient Identifier** *(In confidence)*
2. Age ☐ Year(s) ☐ Week(s) ☐ Month(s) ☐ Day(s)
or Date of Birth *(e.g., 01-Jan-1900)*
3. **Sex:** Enter the patient's sex at birth *(the sex that a person has or was assigned to at birth).* ☐ Male ☐ Female
SECTION REMOVED
4. **Weight** ☐ lb ☐ kg
5. **Ethnicity** *(Check one)* ☐ Hispanic/Latino ☐ Not Hispanic/Latino
6. **Race** *(check all that apply)* ☐ American Indian/Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian/Other Pacific Islander ☐ White

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. **Type of Report** *(check all that apply)* ☐ Adverse Event ☐ Product Problem *(e.g., defects/malfunctions)*
2. **Outcome Attributed to Adverse Event** *(check all that apply)* ☐ Death – Date of death *(01-JAN-1900)*: ☐ Life-threatening ☐ Hospitalization (initial or prolonged) ☐ Other Serious or Important Medical Events ☐ Required Intervention to Prevent Permanent Impairment/Damage ☐ Disability or Permanent Damage ☐ Congenital Anomaly/Birth Defects
3. **Date of Event** *(01-JAN-1900)*
4. **Date of this Report** *(01-JAN-1900)*

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.
* Please see instructions

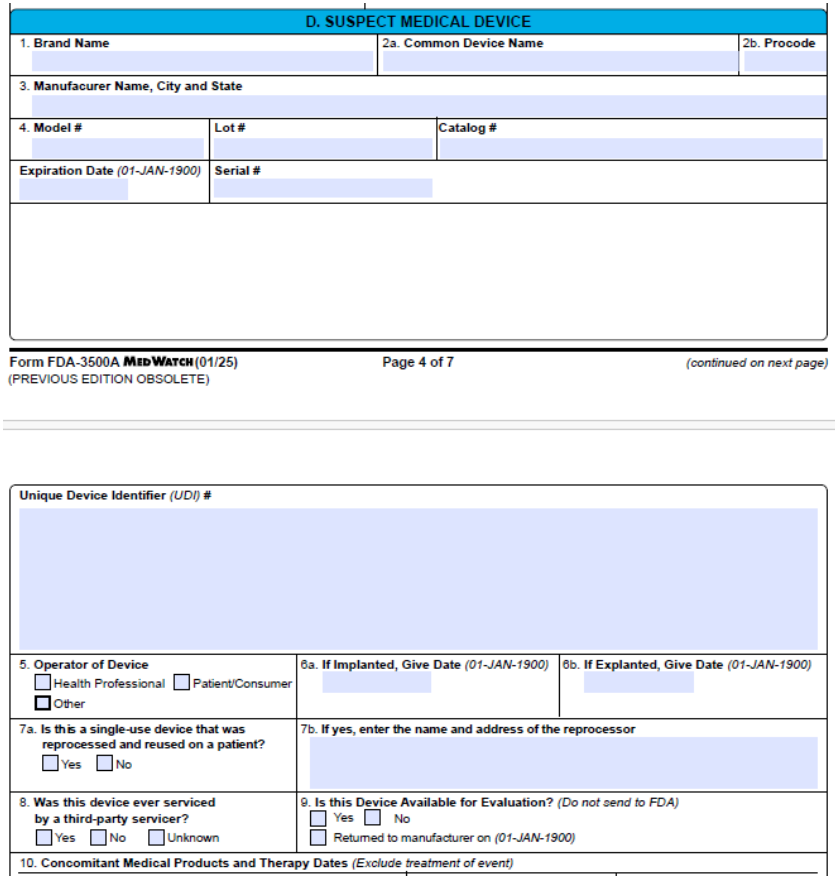
PSC Publishing Services (301) 443-6740 EF



5. **Describe Event or Problem**

6. Relevant Test/Laboratory Data	Date *(01-JAN-1900)*	Relevant Test/Laboratory Data	Date *(01-JAN-1900)*

Additional comments



D. SUSPECT MEDICAL DEVICE

1. **Brand Name**
2a. **Common Device Name**
2b. **Procode**
3. **Manufacturer Name, City and State**
4. **Model #**
Lot #
Catalog #
Expiration Date *(01-JAN-1900)*
Serial #

(PREVIOUS EDITION OBSOLETE)

Unique Device Identifier *(UDI) #*

5. **Operator of Device** ☐ Health Professional ☐ Patient/Consumer ☐ Other
6a. **If Implanted, Give Date** *(01-JAN-1900)*
6b. **If Explanted, Give Date** *(01-JAN-1900)*
7a. **Is this a single-use device that was reprocessed and reused on a patient?** ☐ Yes ☐ No
7b. **If yes, enter the name and address of the reprocessor**
8. **Was this device ever serviced by a third-party servicer?** ☐ Yes ☐ No ☐ Unknown
9. **Is this Device Available for Evaluation?** *(Do not send to FDA)* ☐ Yes ☐ No ☐ Returned to manufacturer on *(01-JAN-1900)*
10. **Concomitant Medical Products and Therapy Dates** *(Exclude treatment of event)*

E. INITIAL REPORTER

1. **Name and Address**

Last Name	First Name

Address

City	State/Province/Region	ZIP/Postal Code	Country
			--

Phone # | Email

2. **Health Professional?**	3. **Occupation** *(Select from list)*	4. *Initial reporter also sent report to FDA*
☐ Yes ☐ No	--	☐ Yes ☐ No ☐ Unknown

G. ALL MANUFACTURERS

1. **Contact Office** *(and Manufacturing Site for Devices)* **or Compounding Outsourcing Facility**

Name	Email Address	Phone Number

Address

Compounding Outsourcing Facility 503B? ☐ Check box if applicable	Outsourcing Facility

2. **Report Source** *(check all that apply)*

☐ Foreign ☐ Literature ☐ Health Professional ☐ Company Representative
☐ Study ☐ Consumer ☐ Use Faciltiy ☐ Distributor/Importer ☐ Other *(Please list)*

3. **Date Received by Manufacturer** *(01-JAN-1900)*

4. **NDA #**	**ANDA #**	**IND #**	**BLA #**	**PMA/510***(k)* **#**

Check all that apply:

☐ Combination product ☐ Pre-ANDA ☐ Pre-1938 ☐ OTC ☐ Compounded Product

5. **If IND/Pre-ANDA, Give Protocol #**	6. **Type of Report** *(Check all that apply)*
	☐ 5-day ☐ 15-day ☐ Periodic ☐ Follow-up # ☐ 7-day ☐ 30-day ☐ Initial

7. **Adverse Event Term***(s)*	8. **Manufacturer Report Number**

H. DEVICE MANUFACTURERS ONLY

1. **Type of Reportable Event** *(check all that apply.)*	2. **If Follow-up, What Type?**	3. **Device Evaluated by Manufacturer?**
☐ Death ☐ Malfunction ☐ Serious Injury ☐ Summary Report No. of events summarized	☐ Correction ☐ Additional Information ☐ Response to FDA Request ☐ Device Evaluation	☐ Yes ☐ No

4. **Device Manufacture Date** *(01-JAN-1900)*	5. **Labeled for Single Use?**
	☐ Yes ☐ No

6. **Adverse Event Problem** *(Refer to coding manual)*

Health Effect – Clinical Code	Health Effect – Impact Code	Medical Device Problem Code	Component Code

Type of Investigation	Investigation Findings	Investigation Conclusions

7. **If Remedial Action Initiated, Check Type**			8. **Usage of Device**
☐ Recall	☐ Relabeling	☐ Patient Monitoring	☐ Initial Use of Device
☐ Repair	☐ Notification	☐ Modification/Adjustment	☐ Reuse
☐ Replace	☐ Inspection	☐ Other:	☐ Unknown

9. **If action reported to FDA under 21 USC 360i(g), list correction/ removal reporting number:**	10. **Related Report Number**

11. **Additional Manufacturer Narrative**

MedWatch Form 3500A

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4. Establish Electronic Systems Gateway Account
5. Download Adverse Event Code lists
6. Complete MedWatch Form 3500A
7. Follow through on Investigation
8. Determine Correction or Removal and complete notifications and reporting requirements

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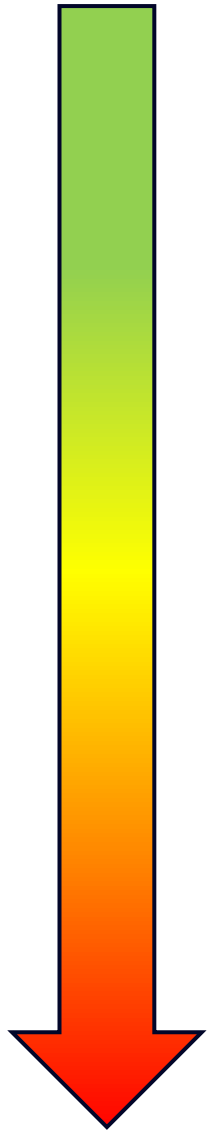
https://www.aphl.org/policy/Advocacy_Documents/APHL%20Guide%20to%20Meeting%20the%20LDT%20Final%20Rule%20Stage%201%20Requirements.pdf

Correction and Removal Requirements



Correction – No Recall

- Actions taken solely to improve performance, quality – unrelated to health risk or compliance issue

Class III Recall

- Unlikely to cause harm, but violates FDA regs

Class II Recall Must be reported to FDA

- May cause temp or medically reversible harm, but risk of serious injury is low

Class I Recall Must be reported to FDA

- May cause serious injury or death

Time to Practice!

#IDLabCon

Adverse Event Activity