The LDT Final rule–will you be ready?

MSACL Compliance and Accreditation Committee (CAC)

October 29, 2024 Webinar on Phase 1 Compliance for the FDA Final Rule on LDT

Judy Stone, MT(ASCP), PhD, DABCC
MSACL-CAC

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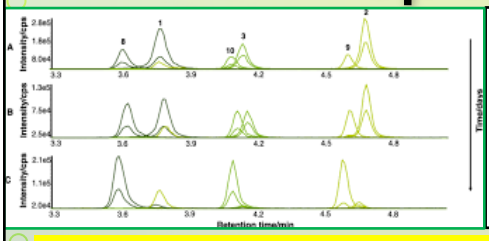
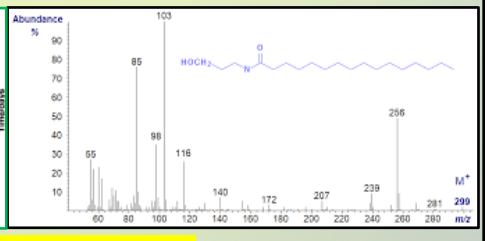
Keep CALM and Mass Spec on





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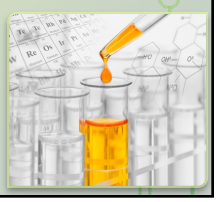

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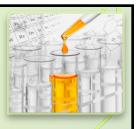
This webinar isn't….



- A broad overview of the LDT Final Rule
- The perfect solution for your 5/6/25 compliance
- Free advice from a $$$ IVD regulatory professional

It is….

1. Focused on LC-MSMS first steps for 5/6/25 compliance
2. Potentially the first of several if 👏
3. "Note these" details from a health system LC-MSMS laboratory colleague after a deep dive into FDA & other guidance on LDT Final Rule

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What is the CAC?

- Established Spring 2024
- Mission: Support clinical LC-MS/MS laboratories worldwide in achieving regulatory compliance and obtaining accreditation
- Initial focus – Compliance of CLIA licensed LC-MSMS laboratories with U.S. FDA Final Rule on Laboratory Developed Tests (LDT)

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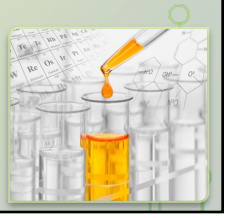
CAC Committee Members

- Jacqueline Hubbard, PhD, DABCC, *Co-Chair CAC*
  Beth Israel Deaconess Medical Center
- Judy Stone, MT(ASCP), PhD, DABCC, *Co-Chair CAC*
  Retired Clinical Chemist
- Dan Wang, PhD, DABCC (CC, TC), *CAC Laboratory Partner*
  Akron Children's Hospital
- Alejandro R. Molinelli, PhD, NRCC-CC, FADLM, *CAC Laboratory Partner*, St. Jude Children's Research Hospital
- Melissa Budelier, PhD, DABCC, *Committee member*
  Tricore Reference Laboratories



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CAC plans related to LDT Final Rule

1. Resources on MSACL-CAC webpage

   Links to:

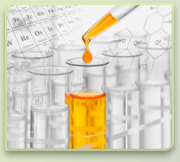
   a. FDA guidance documents

   b. CLSI LDT related documents

   c. Webinars from ADLM, CAP, CLSI, FDA, vendors

   d. CAC templates for SOPs, Forms to adapt for LC-MSMS LDT Final Rule compliance

2. MSACL Webinars & Blogs (next slide)



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Ideas for Webinar/Blog topics

1. With CAC Laboratory Partners
   a. Compliance Planning & Outcomes
   b. Labeling (due 5/6/26) with an example
   c. FDA interactions
   d. De Novo/510K/PMA LC-MSMS LDT submission(s) to FDA
2. Committee perspectives on interpreting CFR language for "devices" as applied to LC-MSMS LDTs
3. Use of a Product Database for materials tracking
4. Promote dialogue with FDA about LC-MSMS LDT specifically (2nd most common LDT technology)

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FDA Final Rule on LDTs Timeline

Phase	Due date (YYYY-MM-DD)	Requirements for LDTs	Exempt
1	2025-05-06	Medical device reporting Corrections/removal reporting Quality System complaint files	**Risk management**
2	2026-05-06	Register/list with the FDA Labeling requirements Investigational requirements	**What, where, details of current LDTs?**
3	2027-05-06	Remainder of Quality System requirements (*Records only)	Unmet need*, currently marketed*, minor modification, rare RBC antigen
4	2027-11-06	PMA for high risk (Class III)	Unmet need, currently marketed, minor modification, rare RBC antigen, NY CLEP
5	2028-05-06	Premarket (510k)/de novo for low (Class I)/mod (Class II) risk	Unmet need, currently marketed, minor modification, rare RBC antigen, NY CLEP

Exempt from Final Rule LDTs: 1976 type, HLA for transplant, forensic purposes, or within the VHA or DoD

Exceptions to Enforcement Discretion LDTs: ("marketed before May 6, 2024, without significant changes"; "meeting unmet needs criteria within a healthcare system"; NY State CLEP

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Action Plan A

1. Define details – what needs to be in place for LDT Final Rule compliance by 6 May 2025?
2. Review existing internal systems (LC-MSMS section, Core/Chemistry laboratory, Laboratory Medicine or Pathology department, Quality Assurance/Compliance/Regulatory, Liability Depts., Hospital/Corporate Admin & Leadership) – what can/must be:
   a. *Used as is*
   b. *Adapted/Revised/Amended*
   c. *Retired/Replaced*

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Action Plan B

3. List new/revised systems/processes/entities/documents /training/**FDA IDs, Accounts/dry runs needed**
4. Meet with QA, other Regulatory departments of your organization – ALERT!, **what overlap is/will exist** between those departments & new LDT requirements? **Who has authority** to decide/create/implement?
5. Ensure **open, ongoing lines of communication** between laboratory & organization leadership & quality assurance departments on this issue
6. Write action plan, who does what by hard deadlines

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Implementation

1. Create/modify-SOPs, forms, tracking mechanisms, training materials, checklists, train and document competency/online solutions/obtain ***FDA Accounts/#s/IDs needed for reporting/tracking***
2. Define (name) the designated unit for Complaints review, investigation and reporting (mission statement, SOPs, kickoff meeting)
3. Rehearsal? As for fire, disaster – "mock" serious injury of patient event possibly related to an LC-MSMS LDT result – what follows?

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Monitoring after Go-Live

One, two & 6 (weeks, months) post go-live:

1. Interview frontline staff, LC-MSMS Supervisor, LDT-QA committee – what is working, what isn't
2. Review frequency, patterns, root causes of any recorded Complaints, Nonconforming Products, Corrections, Removals
3. Update SOPs, forms, tracking, online solutions, training as needed
4. Repeat a dry run for MDR reporting, a Correction?

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Compliance due 6 May 2025

1. Complaint files
2. Medical Device Reporting (MDR)
3. Corrections
4. Removals

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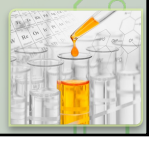
SOPs & Forms on MSACL-CAC page (coming soon)

1. With comments from reviewers
2. For download (MS Word)
   - Complaints SOP
   - Complaints Recording Form
   - Nonconforming Events/Products SOP
   - NCE Reporting Form



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What might compliance look like for Complaints?

Have approved, in use, with formal "go live" date on/before 6 May 2025:

1. SOP/Forms on documenting, evaluating, investigating, records storage for Complaints about LC-MSMS LDTs
2. Unique Device Identifiers (UDI) for LC-MSMS LDTs
3. Tracking (Hx, frequency, trending of Complaints)
4. Staff trained on Complaint Handling (competency)
5. A "formally designated unit" for Complaints review, investigation, action (replies, Corrections, Removals) and reporting [internal & MDR to FDA])

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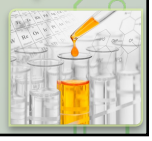
Complaints SOP-"What is old hat"?

Use of existing QS (quality systems)

- Rename/Modify using FDA definitions
- More documentation ("document oral complaints")
- Tracking/Storage – may need new systems, refine existing systems, opt for digital whenever possible



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Complaints SOP- "new to us"?

1. Establish a "formally designated unit" for review
2. If no investigation – document rationale and "name of the individual responsible for the decision not to investigate"
3. Document Complaints about "Labeling"
4. "Unique Device Identifiers (UDI)" required
5. Document complainant address (as well as name, phone #) and the reply to complainant
6. FDA reporting (MDR, Corrections, Removals)

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Complaints SOP- "new to us"?

1. Establish a "formally designated unit" for review
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3. Document Complaints as "Labeling"
4. "Unique Device Identifiers (UDI) required
5. Document complainant address (as well as name, phone #) and the reply to complainant
6. FDA reporting (MDR, Corrections, Removals)

See also CFR 820.198 (f) & (g) regarding Records Storage

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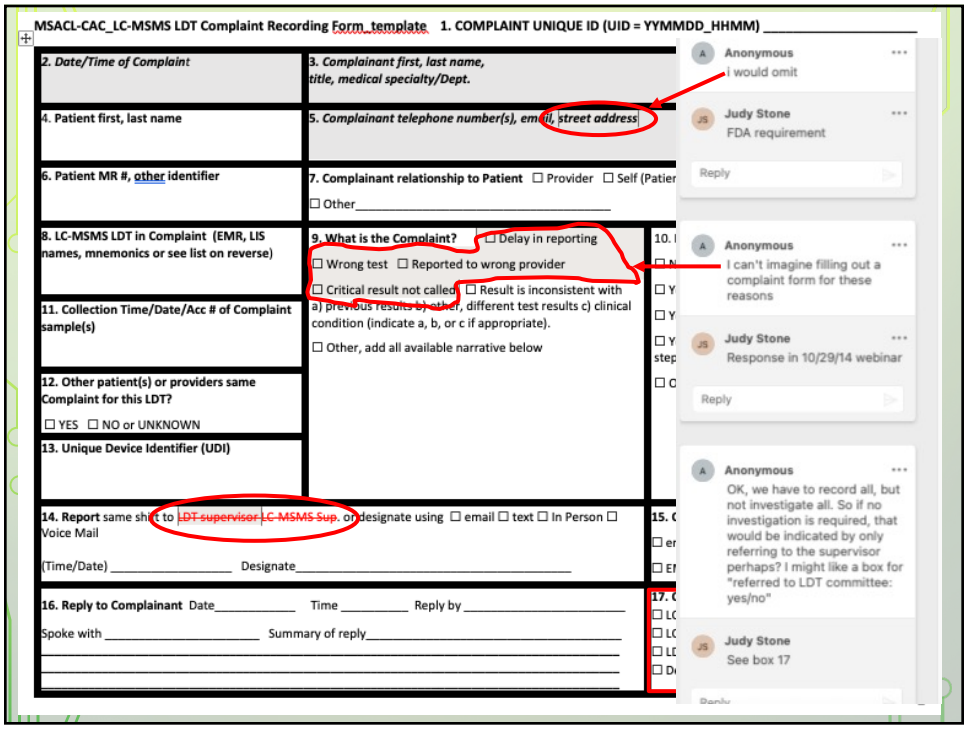

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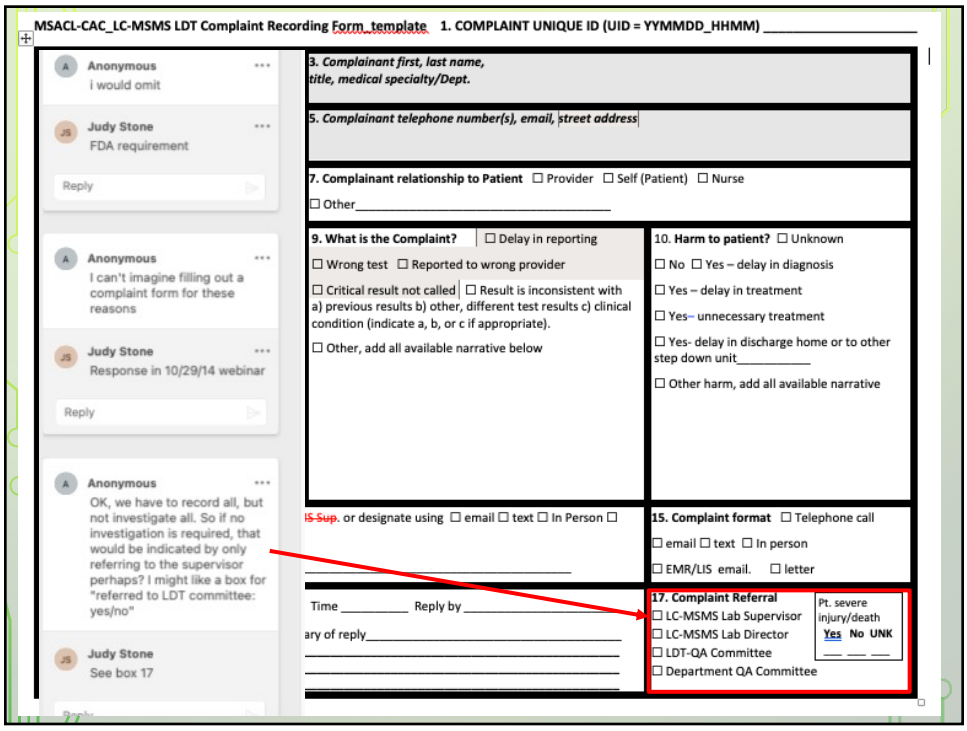
MSACL-CAC_LC-MSMS LDT Complaint Recording Form_template 1. COMPLAINT UNIQUE ID (UID = YYMMDD_HHMM) _____
Anonymous
i would omit
Judy Stone
FDA requirement
Reply
Anonymous
I can't imagine filling out a complaint form for these reasons
Judy Stone
Response in 10/29/14 webinar
Reply
Anonymous
OK, we have to record all, but not investigate all. So if no investigation is required, that would be indicated by only referring to the supervisor perhaps? I might like a box for "referred to LDT committee: yes/no"
Judy Stone
See box 17
3. Complainant first, last name, title, medical specialty/Dept.
5. Complainant telephone number(s), email, street address
7. Complainant relationship to Patient ☐ Provider ☐ Self (Patient) ☐ Nurse
☐ Other_____
9. What is the Complaint? ☐ Delay in reporting
☐ Wrong test ☐ Reported to wrong provider
☐ Critical result not called ☐ Result is inconsistent with a) previous results b) other, different test results c) clinical condition (indicate a, b, or c if appropriate).
☐ Other, add all available narrative below
10. Harm to patient? ☐ Unknown
☐ No ☐ Yes – delay in diagnosis
☐ Yes – delay in treatment
☐ Yes– unnecessary treatment
☐ Yes- delay in discharge home or to other step down unit_____
☐ Other harm, add all available narrative
IS Sup. or designate using ☐ email ☐ text ☐ In Person ☐
15. Complaint format ☐ Telephone call
☐ email ☐ text ☐ In person
☐ EMR/LIS email. ☐ letter
Time _____ Reply by _____
ary of reply_____
17. Complaint Referral
☐ LC-MSMS Lab Supervisor
☐ LC-MSMS Lab Director
☐ LDT-QA Committee
☐ Department QA Committee
Pt. severe injury/death
Yes No UNK

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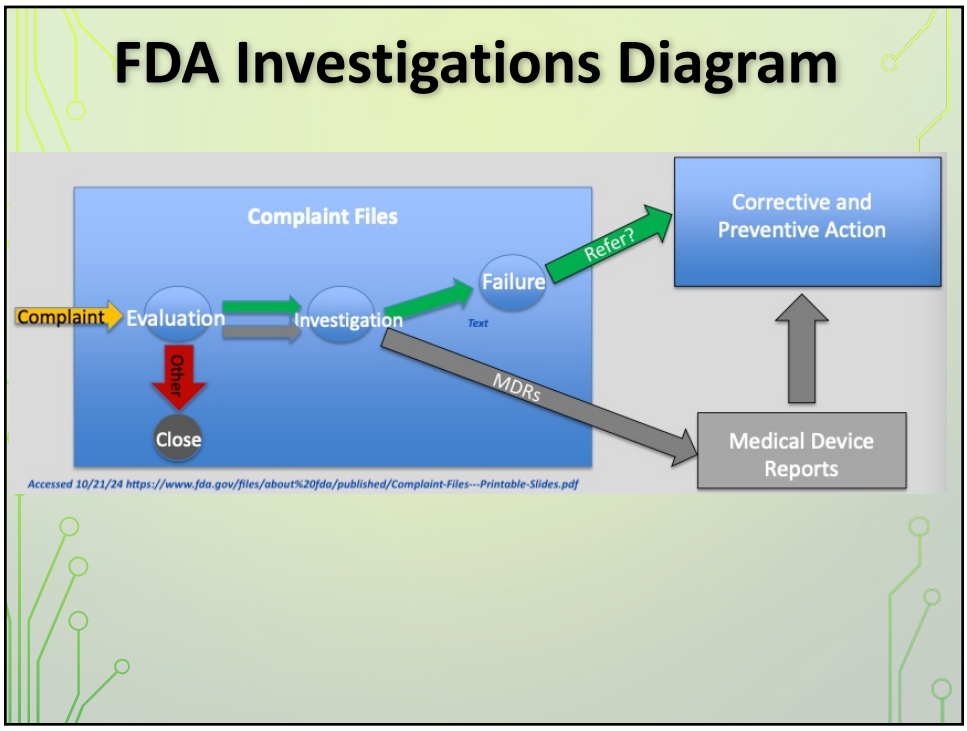
FDA Investigations Diagram
Complaint Files
Complaint
Evaluation
Investigation
Failure
Text
Refer?
Other
Close
MDRs
Corrective and Preventive Action
Medical Device Reports
Accessed 10/21/24 https://www.fda.gov/files/about%20fda/published/Complaint-Files---Printable-Slides.pdf

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1. Do all Complaints need documentation?

Any written, electronic, or oral communication that alleges deficiencies related to the ***identity, quality, durability, reliability, safety, effectiveness, or performance*** of a device after it is released for distribution. (21 CFR 820.3(b))

Sources:
FDA https://www.fda.gov/files/about%20fda/published/Complaint-Files---Printable-Slides.pdf
CLSI QSRLDT https://clsi.org/standards/products/method-evaluation/documents/qsrldt/

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Record Every LC-MSMS LDT related Complaint? If not – who triages?

- Any laboratory person answering the phone or speaking to an in-person complainant?
- Any MLS?
- Any supervisor or designate?
- Any MLS, Supervisor, Designate competent for the LC-MSMS LDT in question?
- Exclude by category (not LDT specific)?
  - Delayed TAT
  - Reported to wrong provider
  - Wrong test performed

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2. "Formally Designated Unit"

- Include an individual who does not report to the LC-MSMS Lab Director/Supervisor

3. "Labeling" related to Complaints?

- Test information visible to potential complainants

(EMR, "My Chart", LIS, Online Test Catalog)

4. "Unique Device Identifier (UDI)"

- **Not designed for LDTs!!!!!!!!!!!** Next slides

Source:

- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/unique-device-identification-system-small-entity-compliance-guide

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FDA UDI Guidance-1

CFR 803.52

Manufacturers ***must include the UDI*** *on the device label or on the device package* in individual ***adverse event report submissions***.

CFR 806.10

The manufacturer *or importer* ***must include on reports of corrections and removals: the UDI*** *that appears on the device label or on the device package*, or the device identifier, *universal product code (UPC), model, catalog, or code number of the device and* the manufacturing lot or serial number of the device or other identification number. (see FDA 8/22/24 webinar on

CFR 806.20

Records of ***corrections and removals not required to be reported to FDA shall contain the UDI***, or the device identifier, *UPC, model, catalog, or code number of the device and* the manufacturing lot or serial number of the device or other identification number.

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FDA UDI Guidance-2

Unique Device Identifier (UDI) = Device Identifier (DI) + Production Identifier (PI)

Production Identifier (PI) includes (" added)

- The lot or batch within which a "device" was manufactured;
- (b) The serial number of a specific "device";
- (c) The expiration date of a specific "device";
- (d) The date a specific "device" was manufactured
- **A mandatory, fixed portion of a UDI that identifies the specific version** or model of a device and the labeler of that device. 21 CFR 801.3.

Global Unique Device Identification Database (GUDID)

https://accessgudid.nlm.nih.gov

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FDA UDI Rules

- **Required dates format** is: the year, using four digits: followed by the month, using two digits; followed by the day, using two digits; each separated by hyphens. For example, January 2, 2014, must be presented as **2014-01-02**

- You are **required to use a UDI system operated by a FDA-accredited issuing agency (IA)**. In vitro diagnostic products must comply with both UDI label requirements and the label requirements in 21 CFR 809.10

- **FDA has accredited three organizations as UDI issuing agencies:**
  - GS1,
  - Health Industry Business Communications Council (HIBCC), and
  - International Council for Commonality in Blood Banking Automation (ICCBBA)

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Enough with the UDI already!

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UDI Questions

-multiple instruments – same LDT method, BUT different LC-MSMS or ALH:
different UDIs or same UDI?

-changing lots of reagents, internal standards, mobile phases, consumables – same LDT method, same materials,
BUT different lots:
different UDIs or same UDI?

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A global UDI per LC-MSMS LDT?

-AND internally append a Batch UDI denoting

LC-MSMS serial#, ALH serial#, batch unique identifier with reference to MP lot#; I.S. lot#; ext. reagents, media, container(s) lot#s; QC lot#s; LC column/guard lot#s

UDI = Device ID + Product ID

-A single DI per LC-MSMS method vs a DI per each instrument – **feasible but unnecessary (batch ID)**

-A Product ID change with every materials lot - ***unrealistic***

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Thoughts on FDA UDI Guidance

-UDI needed for Labels and Data Submission

-*Label* an LC-MSMS LDT – in SOPs? in Batch records? on Instruments? on Consumables? online test information visible to providers/pts?

-*Data Submission* - trackable across reportable event

Less concern w Labeling

More weight on Data submission

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Done with UDI

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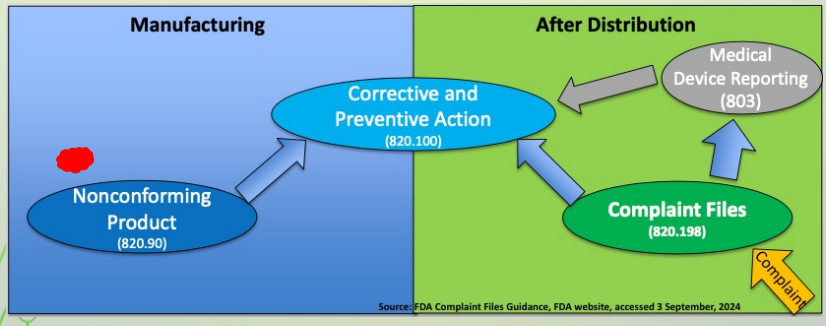
Parts of CAPA Subsystem	Regulation Number (21 CFR)	General Applicability
Nonconforming Product	**820.90**	**Manufacturing**
Corrective and Preventive Action	829.100	Manufacturing and After Distribution
Complaint Files	820.198	After Distribution

FDA Nonconforming Product Printable Slides, FDA website, accessed 9/23/24



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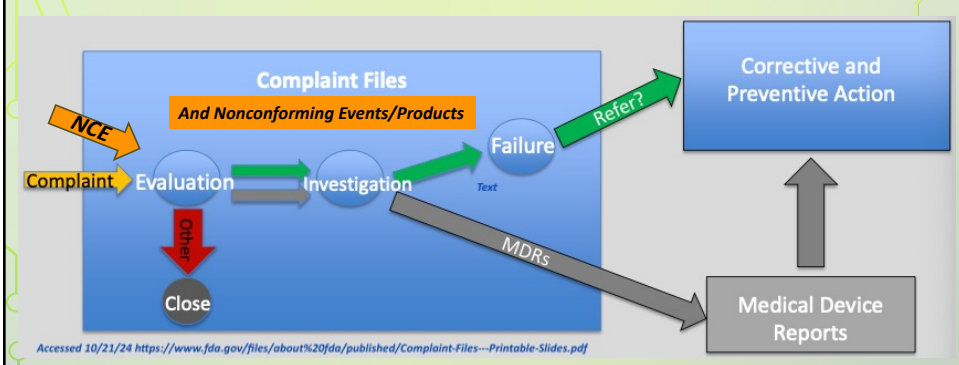
FDA Investigations Diagram



Annotation added (js)

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Nonconforming Events (Product) (NCE)

Why NCE now? Not required for 5/6/25 compliance

- Think of NCE as the "within laboratory" partner to Complaint Files
- Look back at FDA Diagrams/Table – similar handling of NCE & Complaints
- MDR – necessary for NCE & Complaints
- Consider implementing the two together

CLSI_QSRLDTEd2E pg.12: "It might be helpful to group particular elements together, such as nonconforming product and complaint files,…."

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Definitions for NCE (FDA slide-21 CFR 820.3)

- **Specification**

any requirement with which a product, process, service, or other activity must conform [21 CFR 820.3(y)]

- **Product (Events)**

components, manufacturing materials, in-process devices, finished devices, and returned devices [21 CFR 820.3(r)]

(SST; lot to lot testing of reagents, LC columns, mobile phases & internal standards; data review exceptions; EQA/PT; instrument service; ???)

- **Nonconformity**

the nonfulfillment of a specified requirement [21 CFR 820.3(q)]

Sources:

FDA https://www.fda.gov/files/about%20fda/published/Nonconforming-Product---Printable-Slides.pdf

CLSI QSRLDT https://clsi.org/standards/products/method-evaluation/documents/qsrldt/

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What might compliance look like for NCE?

Have approved, in use, with formal "go live" date on/before 6 May 2025:

1. SOP/Forms for *identification, documentation, evaluation, segregation, control, & disposition* of NCE
2. Evaluation→Investigation needed? Signatures
3. Tracking (Hx, frequency, trending of NCE)
4. Staff trained on NCE Handling (competency)
5. "Formally designated unit" for NCE (and Complaints) review, investigation, action (replies, Corrections, Removals) and reporting [internal & MDR to FDA])

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Note before hyperventilating…..

- Not every "failure" = an investigation, evaluate to determine if an investigation is warranted
- Specifications, and therefore failures, are user defined – "When an SST mean peak area is <target, repeat after checking daily maintenance, materials. A failed SST = two consecutive SSTs with mean peak areas ≤80% of threshold."
- Workflow is: 1.ID 2.Document 3.Evaluate. 4.Segregate, Control 5.Dispose

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Disposition

- SOP defines who has responsibility/authority for disposition & documentation of NCE

1. Discard, make new product, retest
2. Return to vendor with request for replacement, retest
3. Retest/Revalidate as is product (FDA rework?)
4. Use as is with justification (data, see #3)

- When to investigate, refer to LDT-QA Committee (FDA term is CAPA) vs "handle within NCE protocols"

$64,000 question

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Handling within NCE (FDA slide)

Examples of Nonconformances Handled under 820.90

- Easy/specific correction
- Isolated
- Minor
- Not a Design issue
- Not a Manufacturing issue

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Refer to CAPA 21 CFR 820.100 (FDA slide)

- No easy/specific correction
- Recurring (based on valid analytical method)
- Severe
- Design issue
- Manufacturing issue

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FDA Investigations Language
(Complaints & NCE)

1. Why no specifics in FDA guidance?
2. Many variables
3. Regulation is flexible, design your own process
4. Define your own details

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Additional CAC templates for 2025?

1. LDT-QA Committee (required for Complaints)
2. Medical Device Reporting
3. Corrections
4. Removals

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Immediate Feedback

- Would additional CAC LDT Final Rule document templates be useful? YES NO
- Future CAC webinars?
  1. CAC Lab partners – Final Rule compliance experience to date? YES NO
  2. Labeling recommendations from an LC-MSMS LDT vendor. YES NO
  3. An LC-MSMS Product Tracking Database is within your reach – Getting Started YES NO

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Thanks for attending!

- Remaining webinar time for Q&A
- Email if not addressed in Q&A

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