Laboratory-Developed Tests
The FDA's Proposed Rule and Potential Clinical Laboratory Impact

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NOVEMBER 2023

ARUP LABORATORIES
Private Information

Introduction

ARUP Laboratories

ARUP is a nonprofit clinical laboratory enterprise of the University of Utah Department of Pathology

October 3, 2023

FDA Published a **Proposed Rule** to Regulate Laboratory Developed Tests as Medical Devices

Public Announcement

FDA

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FDA NEWS RELEASE

FDA Proposes Rule Aimed at Helping to Ensure Safety and Effectiveness of Laboratory Developed Tests

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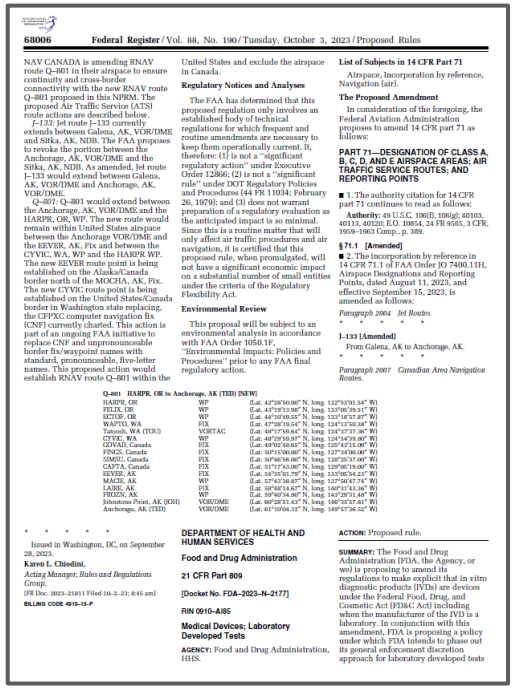
For Immediate Release:

September 29, 2023

Proposed Rule



68006 Federal Register / Vol. 88, No. 190 / Tuesday, October 3, 2023 / Proposed Rules

NAV CANADA is amending RNAV route Q–801 in their airspace to ensure continuity and cross-border connectivity with the new RNAV route Q–801 proposed in this NPRM. The proposed Air Traffic Service (ATS) route actions are described below.

J–133: Jet route J–133 currently extends between Galena, AK, VOR/DME and Sitka, AK, NDB. The FAA proposes to revoke the portion between the Anchorage, AK, VOR/DME and the Sitka, AK, NDB. As amended, Jet route J–133 would extend between Galena, AK, VOR/DME and Anchorage, AK, VOR/DME.

Q–801: Q–801 would extend between the Anchorage, AK, VOR/DME and the HARPR, OR, WP. The new route would remain within United States airspace between the Anchorage VOR/DME and the EEVER, AK, Fix and between the CYVIC, WA, WP and the HARPR WP. The new EEVER route point is being established on the Alaska/Canada border north of the MOCHA, AK, Fix. The new CYVIC route point is being established on the United States/Canada border in Washington state replacing, the CFPXC computer navigation fix (CNF) currently charted. This action is part of an ongoing FAA initiative to replace CNF and unpronounceable border fix/waypoint names with standard, pronounceable, five-letter names. This proposed action would establish RNAV route Q–801 within the United States and exclude the airspace in Canada.

Regulatory Notices and Analyses

The FAA has determined that this proposed regulation only involves an established body of technical regulations for which frequent and routine amendments are necessary to keep them operationally current. It, therefore: (1) is not a "significant regulatory action" under Executive Order 12866; (2) is not a "significant rule" under DOT Regulatory Policies and Procedures (44 FR 11034; February 26, 1979); and (3) does not warrant preparation of a regulatory evaluation as the anticipated impact is so minimal. Since this is a routine matter that will only affect air traffic procedures and air navigation, it is certified that this proposed rule, when promulgated, will not have a significant economic impact on a substantial number of small entities under the criteria of the Regulatory Flexibility Act.

Environmental Review

This proposal will be subject to an environmental analysis in accordance with FAA Order 1050.1F, "Environmental Impacts: Policies and Procedures" prior to any FAA final regulatory action.

List of Subjects in 14 CFR Part 71

Airspace, Incorporation by reference, Navigation (air).

The Proposed Amendment

In consideration of the foregoing, the Federal Aviation Administration proposes to amend 14 CFR part 71 as follows:

PART 71—DESIGNATION OF CLASS A, B, C, D, AND E AIRSPACE AREAS; AIR TRAFFIC SERVICE ROUTES; AND REPORTING POINTS

■ 1. The authority citation for 14 CFR part 71 continues to read as follows:

Authority: 49 U.S.C. 106(f), 106(g); 40103, 40113, 40120; E.O. 10854, 24 FR 9565, 3 CFR, 1959–1963 Comp., p. 389.

§ 71.1 [Amended]

■ 2. The incorporation by reference in 14 CFR 71.1 of FAA Order JO 7400.11H, Airspace Designations and Reporting Points, dated August 11, 2023, and effective September 15, 2023, is amended as follows:

Paragraph 2004 Jet Routes

* * * * *

J–133 [Amended]

From Galena, AK to Anchorage, AK.

* * * * *

Paragraph 2007 Canadian Area Navigation Routes.

Q–801 HARPR, OR to Anchorage, AK (TED) [NEW]

HARPR, OR	WP	(Lat. 42°28'50.06" N, long. 122°55'01.54" W)
FIELS, OR	WP	(Lat. 43°10'13.98" N, long. 123°56'28.51" W)
ECTOF, OR	WP	(Lat. 44°10'49.55" N, long. 123°18'57.87" W)
WAPTO, WA	FIX	(Lat. 47°28'19.54" N, long. 124°13'50.38" W)
Tatoosh, WA (TOU)	VORTAC	(Lat. 48°17'39.64" N, long. 124°37'37.36" W)
CYVIC, WA	WP	(Lat. 48°29'59.97" N, long. 124°54'29.89" W)
GOVAD, Canada	FIX	(Lat. 49°02'48.65" N, long. 125°42'15.09" W)
FINZS, Canada	FIX	(Lat. 50°15'00.00" N, long. 127°54'00.00" W)
SIMSU, Canada	FIX	(Lat. 50°46'56.00" N, long. 128°25'37.00" W)
CAPTA, Canada	FIX	(Lat. 51°17'43.00" N, long. 129°06'19.00" W)
EEVER, AK	FIX	(Lat. 54°35'01.75" N, long. 133°06'54.23" W)
MACIE, AK	WP	(Lat. 57°43'38.07" N, long. 137°56'47.74" W)
LARIE, AK	FIX	(Lat. 58°46'14.67" N, long. 140°31'43.38" W)
FRIZN, AK	WP	(Lat. 59°60'34.96" N, long. 143°20'31.48" W)
Johnstone Point, AK (JOH)	VOR/DME	(Lat. 60°29'31.43" N, long. 146°35'3.91" W)
Anchorage, AK (TED)	VOR/DME	(Lat. 61°10'04.32" N, long. 149°53'36.52" W)

* * * * *

Issued in Washington, DC, on September 28, 2023.

Karen L. Chiodini,

Acting Manager, Rules and Regulations Group.

[FR Doc. 2023–21811 Filed 10–2–23; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 809

[Docket No. FDA–2023–N–2177]

RIN 0910–AI85

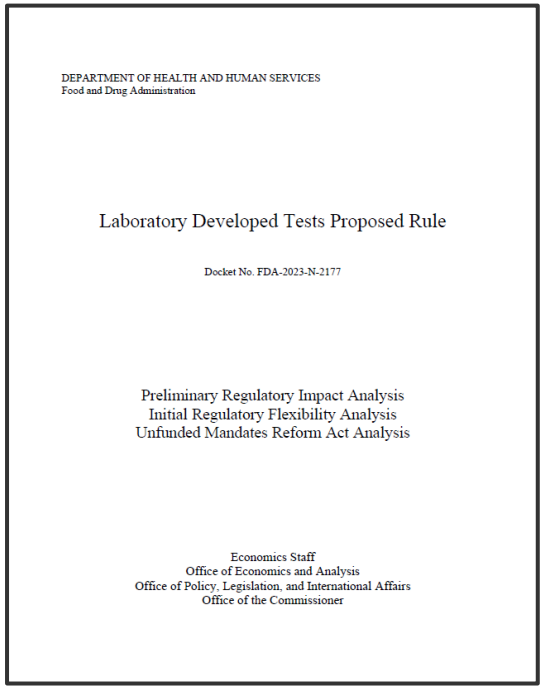
Medical Devices; Laboratory Developed Tests

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing to amend its regulations to make explicit that in vitro diagnostic products (IVDs) are devices under the Federal Food, Drug, and Cosmetic Act (FD&C Act) including when the manufacturer of the IVD is a laboratory. In conjunction with this amendment, FDA is proposing a policy under which FDA intends to phase out its general enforcement discretion approach for laboratory developed tests

Regulatory Impact Analysis



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Laboratory Developed Tests Proposed Rule

Docket No. FDA-2023-N-2177

Preliminary Regulatory Impact Analysis
Initial Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

Economics Staff
Office of Economics and Analysis
Office of Policy, Legislation, and International Affairs
Office of the Commissioner

Laboratory Developed Test (LDT)

"an [in vitro diagnostic] IVD that is intended for clinical use and designed, *manufactured*, and used within a single laboratory"

This is <u>not</u> a legal definition

[e.g. "home brew" test]

Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories. Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs). Food and Drug Administration. Center for Devices and Radiological Health. Rockville, MD. October 3, 2014.

Proposed Amendment

"We are proposing to amend…updating the definition of "in vitro diagnostic products" to make explicit that IVDs are devices under the FD&C Act **including when the *manufacturer* of the IVD is a laboratory**."

26,000 words of explanation and *proposed* role-out

Federal Register / Vol. 88, No. 190 / Tuesday, October 3, 2023, p.68017.

FDA Proposed Rule

- **Exercise enforcement over all essentially all LDTs**
  - » **Continued enforcement discretion over manual tests ("pre-1976 tests"), HLA, forensic (law enforcement), public health**
- **Proposed Stages**

Many more rules and guidance documents would be required.

Stage	Action (Ending Enforcement Discretion Over)	Time after Final Publication
Stage 1	**Medical device reporting (MDR)**, correction, and removal requirements	1 year
Stage 2	**Registration**, **listing**, **labeling**, **investigational use** requirements	2 years
Stage 3	**Quality systems** requirements (e.g., purchasing controls, acceptance activities, CAPA, records requirements)	3 years
Stage 4	Pre-market review of **high-risk IVDs**	3.5 years
Stage 5	Pre-market review of **low and moderate risk IVDs**	4 years

Current User Fees

Application Type	Standard Fee	Small Business Fee†
510(k)‡	$21,760	$5,440
513(g)	$6,528	$3,264
PMA, PDP, PMR, BLA	$483,560	$120,890
De Novo Classification Request	$145,068	$36,267
Panel-track Supplement	$386,848	$96,712
180-Day Supplement	$72,534	$18,134
Real-Time Supplement	$33,849	$8,462
BLA Efficacy Supplement	$483,560	$120,890
30-Day Notice	$7,737	$3,869
Annual Fee for Periodic Reporting on a Class III device (PMAs,PDPs, and PMRs)	$16,925	$4,231

Medium Risk

High Risk

Medium Risk (No Predicate)

And "Change in Intended Use"

Annual Establishment Registration Fee
$7,653

Medical Device Amendments of 1976

"to amend the Federal Food, Drug, and Cosmetic Act […] to provide for the **safety** and **effectiveness** of **medical devices…**"

Official Whitehouse Photo – Public Domain

President Gerald Ford

Law

- Authorized FDA to regulate **in vitro diagnostic devices**
- Established Device Classes (risk based):
  - Class I, General Controls (lowest risk)
  - Class II, Performance Standard (moderate risk)
    - Subject to General and Special Controls
    - Premarket notification (**510k**) "*clearance*"
  - Class III, Premarket Approval (highest risk); **PMA**; "*approval*"

Public Law 94-295-May 28, 1976
Regulation of Clinical Tests: In Vitro Diagnostic (IVC) Devices, Laboratory Developed Tests (LDTs), and Genetic Tests; Congressional Research Service; 7-570 R43438

Medical Device Amendments

Law

(d) the term '**device**'…means an instrument,…in vitro **reagent**, or other similar or related article…., which is:

(2) **intended for use in the diagnosis of disease or other condition**…

In Vitro Reagents Are Devices

LDTs Are Not Discussed

Neither in the law nor in prior Congressional hearings.

→ Law *only* applies to devices "**distributed through interstate commerce**"

Commercial Distribution **Interstate Commerce**

Public Law 94-295-May 28, 1976
https://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapII.htm

1977-1992

- For **16 years** after passage of the Medical Device Amendments, the **FDA did not claim any authority over LDTs**
- Two "pathways" for laboratory testing developed:
  - **Commercially Distributed Pathway** (*regulated by the FDA*)
  - **LDTs** (*regulated by CMS under CLIA*)

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

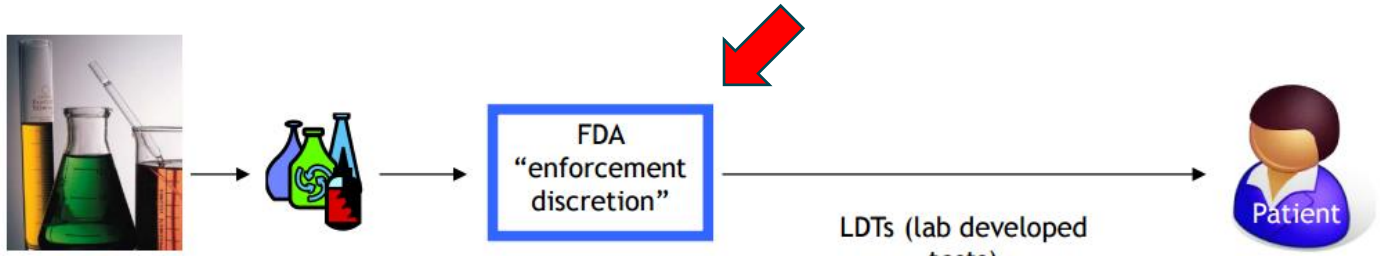
Current Regulatory Reality

1) Commercially Distributed Test Pathway:

"test kit" manufactured for distribution to multiple labs

"Test kits" distributed to patients, hospital, or clinical lab

2) Lab Developed Test (LDT) Pathway:



Test designed, manufactured, and used in a single lab

LDTs (lab developed tests) enter the market without review

Buy Someone Else's Kit

FDA

Validate Your Own Test
Perform In-house Only

CLIA

Oversight of Laboratory Developed Tests
APHL Annual Meeting 2015; Alberto Gutierrez, PhD
http://www.aphl.org/conferences/proceedings/Documents/2015/70Gutierrez.pdf

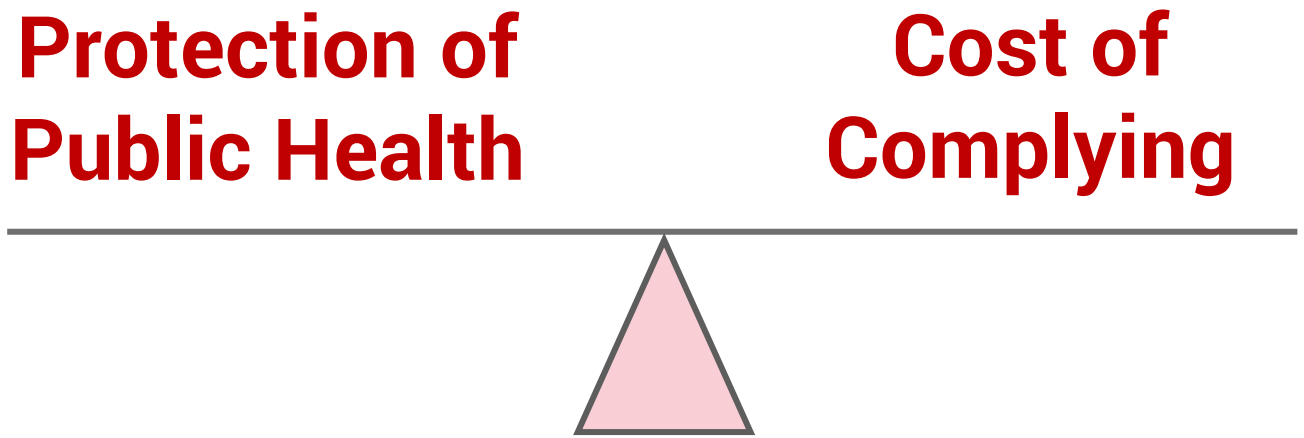
MDA "General Rule"

Law

"shall not impose requirements **unduly burdensome** to a device manufacturer, importer, or distributor taking into account his **cost of complying** with such requirements and the **need for the protection of the public health** and the **implementation of this Act**."

Concerns

- Overestimated Purported Risk of LDTs
- Ignoring Clinical Benefits of LDTs
- Not Factoring Patient Impact from Loss of Testing



Concerns

- Overestimating Financial Benefits to Society
- Underestimating Costs to Patients and Health Systems
- Compliance Costs Prohibitive for Most Clinical Laboratories

Medical Device Amendments of 1976." (PL 94 –295, May 28, 1976) United States Statutes at Large, 90 (1976) pp. 539–83. https://www.gpo.gov/fdsys/pkg/STATUTE-90/pdf/STATUTE-90-Pg539.pdf. Accessed 11/13/2023

LDTs in Clinical Care

2021 Data, University of Utah Health

Study of all test orders in our health system.

	Volume of Tests Ordered	Distinct Assays
FDA Assays	2,831,489 (93.9%)	983 (50.3%)
FDA	2,807,104 (93.0%)	977 (50.0%)
EUA	24,385 (0.8%)	4 (0.2%)
LDT Assays	116,583 (3.9%)	880 (45.0%)
LDT	110,282 (3.7%)	831 (42.5%)
Modified FDA	6,301 (0.2%)	49 (2.5%)
Standard Methods	68,856 (2.3%)	91 (4.7%)
Total	3,016,928	1,954

Leveling the playing field?

Rychert J, Schmidt RL, Genzen JR. Laboratory-Developed Tests Account for a Small Minority of Tests Ordered in an Academic Hospital System. *AJCP*. 2023 Sep 1;160(3):297-302.

LDTs in Clinical Care

2021 Data, University of Utah Health

Laboratory-Developed Tests

Test Name	Specimen	% LDT Volume
Tacrolimus	WB	10.9%
Cytomegalovirus, viral load	P	4.5%
Estradiol	S, P	3.9%
Leukemia/lymph. phenotyping	WB	3.8%
Targeted drug profile	U	2.9%
CD4 lymphocyte subset	WB	2.9%
Vitamin B1	WB	2.8%
Zinc	S, P	2.5%
Copper	S, P	2.3%
Epstein-Barr virus, viral load	S, P	2.2%

Standard Tests

Assay	Specimen	% Standard Volume
Differential cell count (manual)	WB	37.6%
Erythrocyte sedimentation rate	WB	30.8%
Urinalysis	U	10.4%
Cell count	BF, CSF	7.4%
Blood smear with interpretation	WB	3.5%
Gram Stain	BF, CSF	1.9%
Ova and parasite exam	Stool	1.9%
Wet prep, vaginal	G	1.1%

Rychert J, Schmidt RL, Genzen JR. Laboratory-Developed Tests Account for a Small Minority of Tests Ordered in an Academic Hospital System. *AJCP*. 2023 Sep 1;160(3):297-302.

Theranos Paradox

FDA

"**Cleared** a Theranos Test"

"LDTs"

"Running FDA-cleared assays off label with dilutions"

CMS (CLIA) + Investigative Journalism

"**Stopped** Theranos"

Devices@FDA

FDA Home › Medical Devices › Databases

1 records returned meeting your search criteria - ***theranos***

New Search | Export to Excel | Help

Device Name	Company	Date Approved	Device or Consumer Information/Instructions
Theranos Herpes Simplex Virus-1 IgG Assay	THERANOS, INC.	Jul 02, 2015	K143236

We welcome your comments and feedback about Devices@FDA.

FDA's substantial equivalence decision is *still* in effect!

Supreme Court Cases

2022

West Virginia v. Environmental Protection Agency
Issue: **Major Questions Doctrine**

"Courts presume that Congress does not delegate to administration issues of major political or economic significance"

Next Year

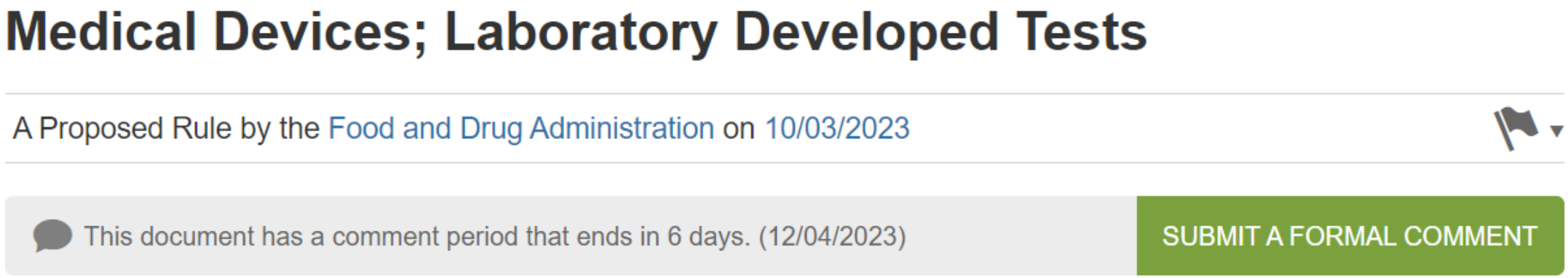
Loper Bright Enterprises et al. v. Raimondo
Issue: Challenge to **Chevron Deference**

"Courts should defer to the agencies' interpretations of a law if it is ambiguous"

https://en.wikipedia.org/wiki/West_Virginia_v._EPA#:~:text=West%20Virginia%20v.%20Environmental%20Protection,emissions%20related%20to%20climate%20change.
https://rollcall.com/2023/05/01/supreme-court-to-decide-major-case-on-federal-rulemaking-power/

Public Comments

Deadline – December 4, 2023



https://www.federalregister.gov/documents/2023/10/03/2023-21662/medical-devices-laboratory-developed-tests

Google 3 Words: "Federal Register LDT"

Submitting Your Own Comments

- We **encourage** you to submit a public comment
- Your voice is incredibly important – you are the experts

Remember: These are public, anyone can read them!

Guidance

- Share your personal opinions and experiences with laboratory testing and LDTs
- Share your opinion on the impact of the proposed rule to patient care
- Be professional

VERY IMPORTANT

Please do **NOT**:

- Submit your comment "on behalf" of your organization
- Share any proprietary information (test volumes, financials, or test details)
- Share any PHI or otherwise sensitive information

ARUP Public Comment

Statutory Authority Over LDTs
- LDTs are Not Devices
- Labs are Not Manufacturers
- Interstate Commerce
- Commercial Distribution
- States are Not Persons
- Violation of MDA General Rule

Regulatory Impact Analysis
- Flawed Calculations
- Overestimated Benefits
- Underestimated Costs

General Concerns
- Patient Safety
- Practice of Medicine
- Logistical Challenges
- Test Modifications
- Academic Medical Centers
- Grandfathering

Public Comment Period Ends December 4th!

https://www.federalregister.gov/documents/2023/10/03/2023-21662/medical-devices-laboratory-developed-tests

Google 3 Words: "Federal Register LDT"

Questions and Discussion

jonathan.genzen@aruplab.com

Public Comment Period Ends December 4th!

https://www.federalregister.gov/documents/2023/10/03/2023-21662/medical-devices-laboratory-developed-tests

Google 3 Words: "Federal Register LDT"

For more information go to:

aruplab.com/fda-ldt

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