December 4, 2023

Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
c/o Dockets Management Staff (HFA–305)
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

RE: Docket No. FDA–2023–N–2177 for "Medical Devices; Laboratory Developed Tests."
RIN: 0910–AI85

Dear Dr. Califf:

I am an attorney with the Competitive Enterprise Institute. The Competitive Enterprise Institute is a non-profit research and advocacy organization that focuses on regulatory policy. On behalf of the Competitive Enterprise Institute, I am pleased to submit to the Food and Drug Administration (FDA) the following comments regarding its proposed rule on Medical Devices; Laboratory Developed Tests, 88 Fed. Reg. 68,006 (proposed Oct. 3, 2023) (to be codified at 21 C.F.R. § 809.3(a)).

FDA proposes to add the phrase "including when the manufacturer of these products is a laboratory" to the last sentence of 21 C.F.R. § 809.3(a) so that the section reads as follows:

> *In vitro diagnostic products* are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h)(1)[1] of the Federal Food, Drug, and Cosmetic Act (the act) and may also be biological products subject to section 351 of the Public Health Service Act, including when the manufacturer of these products is a laboratory.

88 Fed. Reg. at 68,031.

The preamble to the proposed rule refers to *in vitro* diagnostic products manufactured in a laboratory as laboratory developed tests or LDTs. As I shall explain below, the statutory text and context are both incompatible with FDA's proposed amendment to section 809.3(a). In addition,

[1] The proposal unobjectionably changes the citation from section 201(h) to section 201(h)(1).

FDA has not conducted a federalism analysis or properly considered the harms that would result from implementing the proposal.

The Proposal is Incompatible with the Statutory Text.

There are two parts to section 809.3(a), a definition and a declaration. FDA proposes to amend the second part, the declaration. The first part defines *in vitro* diagnostic products. The second part of section 809.3(a) declares that what it has defined as *in vitro* diagnostic products are "devices" as defined in section 201(h) of the Food, Drug, and Cosmetic Act ("the Act"). The proposed amendment to section 809.3(a) adds LDTs to the *in vitro* diagnostic products that are declared to be devices. This addition is contrary to law because it relies upon the inconsistency between the regulatory definition and the statutory definition. Section 809.3(a) defines *in vitro diagnostic* products, a term not found in section 201(h) of the Act, to include "systems," a term also not found in section 201(h) of the Act. As will be discussed below, the extraneous word "systems" is essential to bringing LDTs within the FDA's definition of *in vitro* diagnostic products, but it cannot bring LDTs within the Act's definition of device.

The definition of "device" in the Act, as amended by the Medical Device Amendments of 1976, provides:

> The term "device" (except when used in paragraph (n) of this section and in sections 331(i), 343(f), 352(c), and 362(c) of this title) 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--
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> (A) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
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> (B) 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
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> (C) 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. The term "device" does not include software functions excluded pursuant to section 360j(o) of this title.

21 U.S.C. § 321(h)(1) (section 201(h)(1) of the Act)).

Section 809.3(a) is not a definition of *in vitro* reagent, instrument, or any other term in the statutory definition of device. The term "*in vitro* reagent" does not appear anywhere in part 809 ("in Vitro Diagnostic Products for Human Use"). Section 809.3(a) is a definition of a different term, "*in vitro* diagnostic products." Nonetheless, section 809.3(a) declares that what it defines as *in vitro* diagnostic products "are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act" even though that section does not say that *in vitro* diagnostic products are devices.

The problem with declaring *in vitro* diagnostic products as defined in section 809.3(a) to be devices is that section 809.3(a) defines *in vitro* diagnostic products to include not just reagents and instruments, words found in the statutory definition of device, but also systems, a word not found in the statutory definition of device. Section 809.3(a) states, "*In vitro diagnostic products* are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae." This definition, adopted in 1973,[2] predates by three years the Medical Device Amendments of 1976 and its amended definition of device. Medical Device Amendments of 1976, Pub. L. 94-295, § 3(a)(1)(A), 90 Stat. 539, 575 (1976).

FDA seeks to use the word "systems" to bring LDTs under the rubric of *in vitro* diagnostic products and from there bring them under the rubric of devices. The second step does not follow from the first. Systems could be deemed to be *in vitro* diagnostic products, but it does not follow from this that systems are *in vitro* reagents or instruments and thus devices. *In vitro* is Latin for "in glass." In a medical context it means "observable in a test tube; in an artificial environment."[3] A reagent is "a substance used to produce a chemical reaction so as to detect, measure, or produce other substances."[4] An LDT, as described by FDA, is more than a reagent or an instrument. For that reason, the word in section 809.3(a) that FDA relies upon is systems. A system, as FDA envisages it with regard to LDTs, is a much broader concept. "Test systems," FDA states, "are sets of IVDs—for example, reagents, instruments, specimen collection devices, software, and other related materials—that function together to produce a test result." 88 Fed. Reg. at 68,017. An earlier draft guidance from FDA gave as an example of an LDT a situation in which "[t]he laboratory uses general purpose reagents and analyte specific reagents combined with general laboratory instruments and develops a testing protocol, that together constitute a test system."[5] The entire system of reagents, instruments, specimen collection devices, software, and testing protocols functioning together within a laboratory is not a reagent (*in vitro* or otherwise), nor an instrument, nor a "similar or related article." The system functioning together is not an article of any kind because it is an intangible concept. It encompasses the services clinical laboratories provide. The word "article" refers to a tangible thing and does not include services. *Wilton Meadow Ltd. Partnership v. Coratolo*, 14 A.3d 982, 987 (Conn. 2011); *Fortin v. Marshall*, 608 F.2d 525, 527-28 (1st Cir. 1979).

Components that are devices within the meaning of the Act can be part of a system that composes an overall article that is also a device, as illustrated by the inapposite case FDA cites, *Shuker v. Smith & Nephew, PLC*, 885 F.3d 760 (3d Cir. 2018). That case concerned the components of a hip replacement, i.e, "a metal head, metal sleeve, and a stem connecting the metal head to the thighbone." *Id.* at 768. The court said the hip replacement was "a system that is itself a 'device,'" *id.*, but that system or device was a tangible article that was surgically implanted in

[2] 88 Fed. Reg. at 68,017; Labeling Requirements and Procedures for Development of Standards for In Vitro Diagnostic Products for Human Use, 38 Fed. Reg. 7,096, 7,098 (Mar. 15, 1973) (to be codified at 21 C.F.R. § 167.1(a)).
[3] Miller-Keane Encyclopedia and Dictionary of Medicine, Nursing, and Allied Health, Seventh Edition. (2003). Retrieved November 28, 2023 from https://medical-dictionary.thefreedictionary.com/in+vitro.
[4] *Id.* from https://medical-dictionary.thefreedictionary.com/reagent.
[5] Food and Drug Administration, Framework for Regulatory Oversight of Laboratory Developed Tests: Draft Guidance at 5 (Oct. 3, 2014), https://www.fda.gov/media/89841/download.

the plaintiff. A surgically implanted hip replacement is not at all analogous to the intangible system of elements and processes that function together to produce test results in a laboratory.

The proposed amendment to section 809.3(a), as explained in the preamble, would provide that the intangible system of elements and processes that function together to produce diagnostic test results in a laboratory are products that "are devices as defined in section 201(h)(1)" of the Act. This proposal expands the definition of device in section 201(h)(1) of the Act beyond recognition. The text of section 201(h)(1) does not allow such a distortion of its plain meaning.

The Proposal is Incompatible with the Act as Whole.

The rest of the Act confirms the conclusion that FDA's proposal rests on an understanding of "device" that is impermissibly broad. Far too many provisions of the Act are simply incompatible with the notion that a device can be the sort of system that encompasses LDTs.

The Act refers to characteristics of devices that LDTs cannot possess. Devices move: they have "movement in interstate commerce." 21 U.S.C. § 373(a). They can be imported or exported. *Id.* § 381. Devices can be packed, stored, and installed. *Id.* §§ 351(h), 360b, 360h(b)(1)(A)(iii), 360j(f)(1). A device can be replaced with an equivalent device that is in conformity with the Act. *Id.* § 360h(b)(2)(A). Another remedy available under the Act is an order "[t]o refund the purchase price of the device (less a reasonable allowance for use if such device has been in the possession of the device user for one year or more . . .)." *Id.* § 360h(b)(2)(C). An LDT does not have a purchase price and it is not in the possession of the device user.

Devices are supposed to be labeled. If the label is false or misleading or does not bear adequate instructions, the device is misbranded. *Id.* § 352(a), (f). It is unclear how the system that constitutes an LDT could be labeled with adequate instructions. Without a label, it would be misbranded unless the secretary of health and human services promulgates regulations exempting it under § 352(f). The proposal does not contain such an exemption.

An important characteristic of devices is that they are for commercial distribution. Commercial distribution is an element of requirements, prohibitions, remedies, exemptions, and classifications with respect to devices. *Id.* §§ 360(j); 360(k); 360c(c), (f); 360e(b), (i); 360h(a)(1), (b)(1)(A)(i); 360j(b)(1)(C), (g)(2)(C); 360bbb-3(a)(2). Of these, the preamble acknowledges only § 360(k) (section 510(k) of the Act) and ignores the rest. It then argues that "LDTs are for commercial distribution, so the presence of the phrase does not change the operation of those provisions with respect to these IVDs." 88 Fed. Reg. at 68,021. The preamble's authority for that statement is that "the legislative history, FDA's near contemporaneous regulation, and at least one judicial decision reflect that the phrase 'commercial distribution' means 'on the market.'" *Id.*

None of those provide much support for that gloss on commercial distribution. The cited legislative history is a statement in one committee report. An isolated statement in a committee report does not represent an authoritative interpretation of a congressional enactment. *N.L.R.B. v. Health Care & Retirement Corp. of Am.*, 511 U.S. 571, 582 (1994). The preamble cites just one district court decision in support of "our longstanding, judicially endorsed interpretation," *United States v. An Article of Device Consisting of 1,217 Cardboard Boxes*, 607 F. Supp. 990 (W.D. Mich. 1985), and that case deferred to an FDA letter citing the committee report in the course of improperly deciding a genuine issue of material fact on summary judgment. *See id.* at 994–97.

Lastly, "FDA's near contemporaneous regulation" refutes the position FDA takes in the preamble. The regulation states,

> *Commercial distribution* means any distribution of a device intended for human use which is held or offered for sale but does not include the following:
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> (1) Internal or interplant transfer of a device between establishments within the same parent, subsidiary, and/or affiliate company. . . .

21 C.F.R. § 807.3(b). This definition quite reasonably begins with an element of commercial distribution that should be obvious—distribution—and then states an exception that excludes LDTs, which the definition already excludes because they lack the element of distribution. Any movement of LDTs is interplant transfer, not distribution. LDTs are not transferred or distributed outside of laboratories "because they are the entities that generally perform the tests." 88 Fed. Reg. at 68,018. LDTs, the preamble states, "are often used in laboratories outside of the patient's healthcare setting." *Id.* at 68,009.

To argue that it is sufficient that some, although not all, provisions of the Act can be applied to LDTs is no answer to the disjunction between the Act and the proposal. After acknowledging that section 510(k) of the Act requires "commercial distribution," FDA argues that "the presence of this phrase in that provision and certain other specific device provisions does not bear on the Agency's overall jurisdiction." 88 Fed. Reg. at 68,021. It most certainly does bear on the jurisdiction FDA claims. Statutes must be read as a whole. *Territory of Guam v. United States*, 141 S. Ct. 1608, 1613 (2021). A statute's language has meaning only in context. *Graham Cnty. Soil & Water Conservation Dist. v. United States ex rel. Wilson*, 545 U.S. 409, 415 (2005). Consequently, the words of a statute must be read in their context and with a view to their place in the overall statutory scheme. *Sturgeon v. Frost*, 577 U.S. 424, 438 (2016). A consideration of the context and of the statutory scheme, in particular the number and extent of the incongruities between "device" as governed by Act and "device" as imagined by FDA, compels the conclusion that FDA does not have jurisdiction to regulate LDTs because they are not devices.

FDA Must Conduct a Federalism Analysis.

FDA failed to conduct the federalism analysis required of it by Executive Order No. 13,132, 3 C.F.R. 206 (2000). FDA states that it determined "that this proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government." 88 Fed. Reg. at 68,028. That determination is erroneous.

Exercising their reserved powers, states regulate clinical laboratories that conduct diagnostic tests. *E.g.*, Cal. Bus. & Prof. Code div. 2, ch. 3; Fla. Stat. tit. XXXII, ch. 483, pt. 1; 20 Ill. Comp. Stat. 2310/2310-10, 2310-575; Mass. Gen. Laws ch. 111D; N.Y. Pub. Health Law ch. 45, art. 5, tit. V.

The Medical Device Amendments of 1976 contain an express preemption provision. 21 U.S.C. § 360k. FDA regulations of devices preempt state or local requirements. 21 C.F.R. § 808.1(d). As a result, the proposed regulation has federalism implications through its effects "on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government," Executive Order No. 13,132 § 1(a),

and would preempt state law. Because the proposed regulation has federalism implications and would preempt state law, FDA must comply with all of the requirements of sections 6(c) and 8(a) of Executive Order 13,132.

FDA Has Not Considered the Harms that Would Result from Implementing the Proposal.

FDA estimates that the annualized cost to laboratories of its proposal ranges from $2.52 billion to $19.45 billion at a 7 percent discount rate and that the annualized cost to FDA—more accurately the annualized cost to the taxpayers—ranges from $265 million to $1.06 billion. Annualized benefits over 20 years are estimated to range from $2.67 billion to $86.01 billion at a 7 percent discount rate. 88 Fed. Reg. at 68,008. The wide ranges in FDA's estimates correctly reflect the uncertainty involved in them. Within those ranges the costs of the proposal could exceed its benefits.

The costs surely will exceed the benefits if costs that FDA does not account for are included. FDA estimates some of the costs laboratories will bear. It does not, however, discuss the cost of preparing a diversity action plan for clinical studies, which sponsors of devices must now prepare and submit to FDA. 21 U.S.C. § 360j(g) as amended by § 3601(b) of the Food and Drug Omnibus Reform Act of 2022. More significantly, no estimate is made of the economic cost of laboratories going out of business because they cannot bear all of the costs of compliance.

The FDA does not estimate any costs to consumers or patients or consider health opportunity costs in its preliminary regulatory impact analysis.[6] Indeed, FDA shrugs them off. FDA acknowledges that some *in vitro* diagnostic products may have to come off the market either because they cannot meet applicable requirements or because "the laboratory chooses not to invest resources to meet those requirements." 88 Fed. Reg. at 68,014. A laboratory may be forced to make that choice due to the exorbitant amount of resources that would be needed. FDA estimates the recurring cost of premarket approval applications to be $1.983 billion and the recurring cost of 510(k) submissions or de novo classification requests to be $1.497 billion dollars.[7]

To the prospect of *in vitro* diagnostic products disappearing from the market, FDA offers two unsatisfactory responses. The first is merely an unsupported conclusion or "determination": "To the extent that withdrawal from the market of these IVDs implicates any reliance interests, FDA has made a preliminary determination that the public-health benefits associated with the reasonable assurance of safety and effectiveness of IVDs offered as LDTs outweigh any such interests." 88 Fed. Reg. at 68,014. "In addition," FDA asserts in its second unsatisfactory response, "in the long run, it is possible that any reduction in the number of current IVDs offered as LDTs may be offset by the market entry of IVDs from other manufacturers who will have benefitted from a more consistent oversight approach and increased stability spurring innovation." *Id.* But in the short run, tests become unavailable. In the long run, after patients have been denied *in vitro* diagnostic products they need, new companies might enter the market and introduce other ones that FDA might eventually approve, but FDA gives no reasons to believe that consistent oversight

[6] On the importance of considering the health opportunity costs of policies, see James Broughel & W. Kip Viscusi, *The Mortality Cost of Expenditures*, 39 Contemp. Econ. Pol'y 156 (2021).
[7] Food and Drug Administration, *Laboratory Developed Tests Proposed Rule* 85 (Sept. 28, 2023), https://www.fda.gov/media/172557/download?attachment.

will result in market entry or that its expanded power will increase stability and that this stability will spur innovation.

A reduction in laboratories developing diagnostics, whether in the short or long run, affects the ability of the market to adapt to changes in supply because it reduces the number of laboratories looking for adaptations. Supplies for a test can run out. When that happens, the test needs to be adapted quickly.[8]

FDA's interference with the development of tests for COVID-19 presents a case study of the results of FDA's regulation of diagnostic tests. At first, FDA gave an emergency use authorization (EUA) for a COVID-19 test only to the Centers for Disease Control. This monopoly prevented other laboratories from refining tests and slowed innovation at a critical time.[9] The Government Accountability Office defended FDA's subsequent performance, but one of its findings foreshadows the delays that can be expected if the proposal is adopted. The GAO found that by September 30, 2021, FDA had granted emergency use authorizations for 412 COVID-19 tests, but "there were 370 tests—285 LDTs and 85 tests developed by commercial manufacturers—for which FDA had received EUA requests but had not yet reviewed to make an EUA determination as of September 30, 2021."[10]

Conclusion and Recommendations

The proposed amendment to section 809.3(a) is not merely bad policy. It is unlawful. This is because section 809.3(a) first defines *in vitro* diagnostic products to include systems. Then section 809.3(a) as amended would declare that *in vitro* diagnostic products as so defined "including when the manufacturer of these products is a laboratory" are devices as defined by section 201(h) the Act. The text and context of section 201(h) of the Act, however, conclusively dispose of the mistaken notion that systems developed in a laboratory for use in diagnosis are devices.

FDA should instead make an effort to conform section 809.3(a) to the Act by inserting "*in vitro*" before the word "reagent" and deleting the word "systems." FDA should consider defining *in vitro* reagent. Neither definition should become a quest for jurisdiction over laboratory developed tests. That is a matter to be addressed to Congress.

Cordially yours,

David S. McFadden
Attorney, Competitive Enterprise Institute
David.McFadden@cei.org

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[8] Nikhil S. Sahajpal, *Making a Difference: Adaptation of the Clinical Laboratory in Response to the Rapidly Evolving COVID-19 Pandemic*, 8 Academic Psychology 1 (Jan.-Dec. 2021), https://pubmed.ncbi.nlm.nih.gov/34263025/ .

[9] Barbara J. Evans & Ellen Wright Clayton, *Deadly Delay: The FDA's Role in America's COVID-Testing Debacle*, 130 Yale L.J. Forum 78 (July 29, 2020), https://www.yalelawjournal.org/pdf/EvansClayton_xhi6t72w.pdf; Brian H. Shirts, *We'll See More Shortages of Diagnostic Tests if the FDA Has its Way*, STAT (Apr. 15, 2020), https://www.statnews.com/2020/04/15/diagnostic-tests-shortages-fda-decision/.

[10] Government Accountability Office, *COVID-19: FDA Took Steps to Help Make Tests Available; Policy for Future Public Health Emergencies Needed* 21 (May 2021), https://www.regulations.gov/document/FDA-2023-N-2177-0111.