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FDA trial regulation of laboratory developed tests (LDTs): An academic medical center's experience with Mpox in-house testing

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ABSTRACT

The 2022 mpox outbreak presented a familiar challenge to clinical laboratories. Accordingly, our institution was able to swiftly implement in-house mpox testing to meet the imminent diagnostic needs of the public health emergency. While the FDA authorized laboratory-developed tests (LDTs) for lesion specimens, however, it restricted the testing of rectal swabs despite mounting evidence of its clinical utility. Notably, within the short timeframe when rectal testing was available, we identified a high-risk patient without apparent lesions who tested monkeypox-positive only by our in-house rectal swab assay. In order for our institution to continue testing non-lesion samples, The FDA required a separate Emergency Use Authorization (EUA) application that demanded additional resource-costly validation studies despite utilizing the same testing platform as lesion samples. Here, we provide a brief review of the history, current status, and legal scope surrounding LDT validations, with an in-depth comparison of the technical requirements by CLIA, CAP and the FDA. Importantly, we provide our experience with the mpox EUA submission process to serve as context for the challenges that may be imposed by the new FDA regulations. We hope that our experience will offer a valuable perspective that promotes constructive discourse towards addressing the imperative to offer high-quality laboratory diagnostics without compromising on the need of the medical laboratory community to provide effective patient care.

1. Introduction

The emergence of mpox disease (caused by the monkeypox virus) outside its typical regions of endemicity threatened the global community. First reported on May 7, 2022 in the U.K., the mpox outbreak soon spread to 27 countries by the following month, with more than 780 cases identified [1]. The U.S. reported its first case on May 17, 2022 from a lesion swab of a Massachusetts resident, which initiated a national response that included guidance for testing and diagnosis, protocols for medical countermeasures, and distribution of prophylaxis and antivirals [2]. By the end of the month, 9 states had reported 17 patients with confirmed non-variola *Orthopoxvirus* (NVO) infections (which were presumed to be monkeypox virus until otherwise proven), of which 14 had reported international travel to 11 different countries [2].

Monkeypox infections typically present with characteristic deep-seated, vesicular or pustular skin rashes that are readily apparent [2]. Accordingly, testing of lesion samples became the gold standard for mpox diagnosis. The recent mpox outbreak, however, was complicated by its atypical presentation as lesions that frequently appeared in the genital and perianal region, which can be subtle or vague, and occasionally mimicking, or even co-occurring with herpes simplex virus (HSV) infection [2,3]. Therefore, definitive mpox diagnosis relied heavily on laboratory confirmation by molecular diagnostic platforms. Importantly, in infected patients who do not present with visible lesions, rectal swabs can test positive for monkeypox, with or without symptoms such as rectal pain and proctitis [4–8]. One recent study found two-thirds of mpox patients with proctitis had no typical rash upon presentation, and 20% of them had no rash at all [7].

Early in the outbreak, in order to address immediate capacity needs and offer greater access to monkeypox testing, the CDC provided support to five large commercial laboratories to supplement the existing 68 Laboratory Response Network (LRN) laboratories with NVO testing capabilities [9]. Later, the Food & Drug Administration (FDA) issued guidance for clinical and commercial laboratories to adopt CDC-endorsed NVO/monkeypox testing protocols for lesion samples, including conditions under which it "does not intend to object" to allowable deviations [10]. While these provisions expedited the implementation of certain monkeypox testing, the FDA also restricted the acceptable

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sample type exclusively to lesions, and required separate Emergency Use Authorization (EUA) for testing of other specimens.

To satisfy clinical needs, our laboratory pursued the EUA submission process for testing of rectal swabs. The venture, unfortunately, proved to be unsuccessful in meeting the requirements of the FDA. With nearly 3 months of additional validation studies, we recognized that the EUA approval required excessive resources typically outside the capacity of most clinical laboratories, and thus, withdrew from the application process. Notably, the additional validation studies were of minimal benefit as the results did not significantly change the performance characteristics originally established for lesion testing. Herein, we provide our institution's EUA experience on in-house monkeypox test implementation, and the challenges imposed by the newly instituted FDA regulations.

1.1. Historical overview of laboratory-developed test (LDT) regulation

The quality of clinical laboratories and the clinical testing process is regulated by the Centers for Medicare and Medicaid Services (CMS) pursuant to the Clinical Laboratory Improvement Amendments (CLIA) of 1988 [11]. Notably, under the predating 1976 Medical Device Amendment to the Food, Drug, and Cosmetic Act, congress deemed that clinical *in vitro* diagnostics (IVDs) are encompassed within the FDA regulation of medical devices intended for use in humans [12–14]. Historically, however, the FDA has exercised certain "enforcement discretion," while CMS has granted the College of American Pathologists (CAP) Laboratory Accreditation Program "deeming authority" to allow it to perform laboratory inspections in lieu of CMS to monitor adherence to federal regulations [13,15].

Prior to the recent decade, LDTs were generally simple clinical tests aimed towards the diagnosis of rare diseases and conditions, and were intended to be used by physicians and pathologists directly engaged in the patient's care within a single institution. In addition, the components of such LDTs were individually regulated by the FDA as analyte-specific reagents (ASR). Accordingly, the validation of LDTs following CAP guidelines has largely been deemed satisfactory of all applicable federal requirements, without further oversight by the FDA [16].

In the current landscape of clinical laboratory diagnostics, however, LDTs are increasingly being utilized as a platform to assess high-risk yet relatively common diseases and conditions. In a review of currently available LDTs, the FDA offered a series of 20 case studies with which it argues the growing necessity for greater oversight in order to address several serious concerns regarding some LDTs, including: lack of evidence supporting the clinical validity of the test, deficient adverse event reporting, lack of premarket review of performance data, and the threat to the scientific integrity of clinical trials, among others [17]. The case series presented problematic LDTs from publicly available information in which faulty tests yielded significant false positive or false negative results, or result in treatment based on disproven scientific concepts [17].

Consistently, the FDA has indicated in 2010 an intent to assume more active regulatory oversight of LDTs [16]. In 2014, the FDA issued a notification in which it elaborated upon its changing stance on LDT reporting according to its "good guidance practices regulation" (21 CFR 10.115) [14]. Contemporaneously, the agency issued a draft guideline utilizing a risk-based framework for LDT validation for industry and clinical laboratories [13]. Both publications, however, stipulated that the guidelines remain tentative, and clinical laboratories need only to notify the FDA of its LDTs for the purposes of facilitating future regulatory activity. For several years following, the FDA withheld issuing final guidance on LDT validation requirements, opting to, instead, maintain an open platform by which stakeholders can comment on any draft guidance for the agency to consider [16]. In 2017, the FDA synthesized all gathered feedback, and published the "Discussion Paper on Laboratory Developed Tests (LDTs)" with the intent to "advance the public discussion" and "spur further dialog" [18]. Importantly, the document was explicit in stating that it does not represent a final, nor enforceable, version of the LDT draft guidelines. To date, the FDA has yet to produce a document establishing its final requirements for the validation of LDTs.

1.2. Timeline of UCLA development/validation of mpox molecular diagnostics

UCLA is a quaternary care health system, and its clinical microbiology laboratory has long been a leader among academic institutions due, in part, to its ability to effectively employ LDTs (which accounts for >30 % of all tests performed) to fulfill the specific diagnostic needs of its patient population. Particularly in the context of public health emergencies, LDTs also serve as the primary mechanism by which UCLA can expeditiously respond to and mitigate the impact of emerging infectious diseases.

With the recent mpox outbreak, its rapid development created an overwhelming demand for monkeypox testing that resulted in an extended turn-around time (TAT) of nearly 7–10 days as a send-out test. To provide the most effective and appropriate care, our institution sought to offer an in-house molecular assay to significantly shorten TAT. Correspondingly, our laboratory pursued NVO/monkeypox test development, referencing the FDA-approved CDC protocols for PCR-based detection of NVO and monkeypox nucleic acids in clinical specimens [19,20].

Beginning early in the outbreak on July 6, our lab completed the test validation on August 4, by the time the U.S. Department of Health and Human Services (DHHS) declared a national public health emergency (Fig. 1) [21]. The test was launched across the health system on September 6 for the testing of lesion swab(s) and/or rectal swab(s) of patients with suspicion of or high-risk for NVO/monkeypox infection. Incidentally, on September 7, the FDA issued an EUA for Medical Devices, including a guidance document describing the agency's review priorities for NVO/monkeypox IVDs, and without prior public comment, required all labs performing clinical NVO/monkeypox testing to notify the agency within 5 days of offering the assay [10]. Importantly, the document also included the restrictive stipulation that the accompanying EUA is limited to lesion swab testing only, and use of other clinical samples require a separate EUA application by the performing laboratory [10,22].

While the current mpox outbreak was initially recognized by its atypical presentation as anogenital lesions, as the outbreak evolved, accumulating data supported the clinical utility of rectal swab testing for patients presenting with consistent symptoms and/or known risk for exposure, but without apparent lesions [4–7]. Despite strong evidence, however, the FDA remained steadfast on its initial guidelines, and consequently notified UCLA on September 14 to terminate its NVO/-monkeypox testing of non-lesion specimens. In order to adhere to current federal guidelines, and yet continue to offer comprehensive care to its patients, UCLA suspended its NVO/monkeypox assay for rectal swabs after September 16, but concomitantly declared intent to submit a EUA application to resume testing. Notably, within the brief period when our lab accepted such specimens, a patient presented to the UCLA emergency department with only rectal pain and without visible lesions, but reported recent high-risk activities for monkeypox exposure. The patient consequently tested monkeypox-positive only by our in-house rectal swab assay. In this case, without the clinical NVO/monkeypox test for rectal swab specimens, the patient would not have received timely diagnosis and appropriate care.

After initial inquiries with the FDA, UCLA submitted its pre-EUA (PEUA) request on September 29, which was approved on Oct 11. Immediately following, our laboratory initiated its secondary validation in accordance with the FDA requirements delineated in the EUA application form. On November 21, UCLA completed its EUA submission, including the supplemental validation documents requested, to be reviewed by the FDA for authorization.

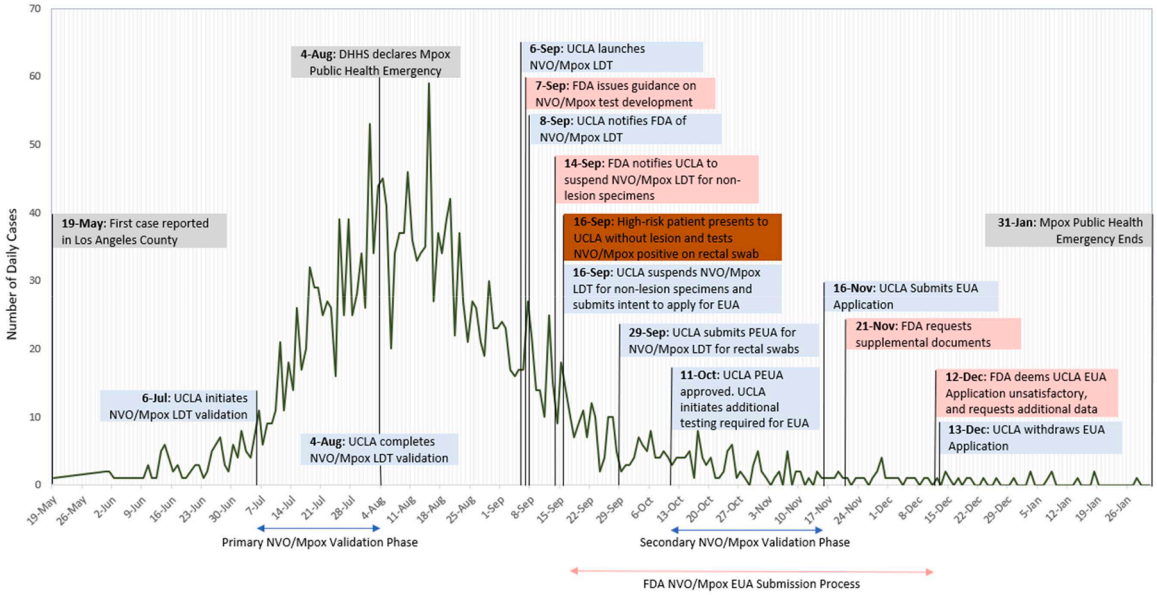

Fig. 1. Timeline of UCLA NVO/Mpox Test Development against Los Angeles County Mpox daily case positivity. Line represents daily case positivity in Los Angeles County from May 19, 2022 to January 31, 2023. Inlaid text represents notable dates in UCLA NVO/monkeypox test development (grey: Public Health Department; Blue: UCLA Clinical Microbiology Lab; Pink: FDA; Dark Orange: UCLA Medical Center).

Nearly three months into the submission process, the FDA communicated on December 12 that it has deemed UCLA's EUA application for NVO/monkeypox testing of rectal swabs unsatisfactory, citing significant deficiencies in its evaluation of test performance and clinical utility. In considering the resources that would be required to fulfill the noted inadequacies in an already costly venture, particularly given the current low positivity rate of mpox in Los Angeles County, UCLA formally withdrew its EUA application on December 13.

1.3. Comparison of LDT validation requirements

The development and evaluation of LDTs have long been successfully regulated by CAP in accordance with the federal codes without significant oversight from the FDA. When the FDA elected to exercise its technical legal right to regulate EUA of LDTs as clinical IVDs, its implementation included guidelines that both aligned with existing CMS/CLIA and CAP LDT regulations for clinical laboratories, but also incorporated comprehensive requirements more consistent with those intended for full FDA approval of commercial and industrial assays.

The requirements for the evaluation of clinical test systems as described in Title 42, Part 493.1253 (42 CFR § 493.1253) of the Code of Federal Regulations (CFR) simply dictates that before reporting patient test results, the performing laboratory must "establish for each test system the performance specifications for the following performance characteristics, as applicable: accuracy, precision, analytical sensitivity, analytical specificity to include interfering substances, reportable range of test results for the test system, reference intervals (normal values), and any other performance characteristic required for test performance" (Table 1) [11]. In direct translation of the terms of the federal codes, specifically with respect to LDTs, CAP requires that prior to clinical use, the laboratory must have performed a validation study and prepared a written assessment of each of the aforementioned test method performance specifications using a sufficient number of characterized samples at the discretion of the laboratory director [23]. Implicitly, CAP grants autonomy to the performing laboratory and its director(s) to establish its own framework for the validation of LDTs, with only the stipulation that the laboratory director(s) record(s) the criteria used in cases where it deviates from standard practices [23]. The FDA, in contrast, prescribes specific requirements to satisfy each test method specification that, while consistent in intent with CMS/CAP guidelines, demand more resource-costly studies (Table 1) [22].

Apart from the requirements common with CMS/CLIA and CAP, the FDA NVO/monkeypox EUA application emphasizes evaluating reagent stability, specimen stability, and clinical utility. Specifically, for establishing initial reagent stability claims, the FDA recommends following the Clinical Laboratory Standards Institute (CLSI) Standard EP25 – "Evaluation of Stability of In Vitro Diagnostic Reagents." The guideline requires testing of a minimum of 3 product lots for shelf life, 1 for in-use life, and 1 for transport simulation [24]. Using these parameters, the FDA requires addressing stability timeframe (including a 10 % allowance for the one to be authorized), stability temperatures, in-use/opened kit stability, freeze-thaw stability, unopened shelf-life stability, unopened shipping stability, and inverted stability, all to be performed in at least 5 replicates [22].

To assess the stability of sample types other than the CDC-recommended dry swabs, the FDA requires a study demonstrating stability throughout "real-world conditions" in which clinical specimens would be collected and tested. The study requires 50 samples distributed among negative ($n = 10$), 1–2x limit of detection (LoD) ($n = 30$), and 3–5xLoD ($n = 10$). If the test is intended to be performed on clinical samples that may be stored prior to test performance (i.e., refrigerated or frozen for a timeframe proposed in the candidate protocol), the FDA recommends evaluating both fresh and stored samples at each designated time point in an equivalence study [22].

Lastly, the FDA recommends a clinical evaluation of test utility in a prospective, blinded, randomized study of patients suspected of mpox by their healthcare provider. In such studies, the sample used for clinical testing should not be the same as the sample used for investigational purposes, with the standard of care clinical sample being collected first. If prospective or retrospective specimens are not available at the time of validation/submission, a fully contrived clinical evaluation may be acceptable for initial authorization, with the clinical utility study using natural specimens provided as a condition of authorization [22].

Notably, the evaluation of the parameters above are not explicitly required by CMS/CLIA, and while they are mentioned in the CAP All Common Checklist, their guidelines are broad and tentative at the discretion of the director(s) of the performing laboratory [11,23]. Also, it is interesting to note that validation of the precision of the candidate

Table 1
Comparison of the requirements for validation of test performance specifications from CLIA (LDT), CAP (LDT) and FDA (NVO/monkeypox EUA). Comparison of the requirements according to the CFR, CAP All Common Checklist, and the NVO/monkeypox EUA application.

		CLIA (LDT) [11]	CAP (LDT) [23]	FDA (NVO/monkeypox EUA) [22]
Accuracy		Each laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text book procedures), or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable: • Accuracy • Precision • Analytical sensitivity • Analytical specificity to include interfering substances • Reportable range of test results for the test system • Reference intervals (normal values) • Any other performance characteristic required for test performance (42 CFR § 493.1253)	Accuracy is validated by comparing results to a definitive or reference method, or an established comparative method. For qualitative tests, a minimum of 20 samples, including positive, negative, and low-positive samples with concentrations near the lower level of detection should be used. If the laboratory uses fewer samples, the laboratory director must record the criteria used to determine the appropriateness of the sample size (COM.40350)	FDA recommends a clinical agreement study with at least 30 positive and 30 negative samples evaluated by both the candidate test and comparator test. For the study, FDA recommends use of clinical specimens if available, in a prospective, blinded, randomized study of patients suspected of Mpox by their healthcare provider. If no prospective or retrospective specimens are available at the time of submission, a fully contrived clinical evaluation may be acceptable for initial authorization, with additional clinical testing or positive natural clinical specimens provided as a condition of authorization.
Precision			Precision is validated by repeat measurement of samples at varying concentrations or activities within-run and between-run over a period of time (COM.40350)	Not explicitly addressed
Analytical Specificity			The laboratory must understand the analytical interferences for each test, and have an appropriate plan of action when they are present (COM.40500). Analytical specificity refers to the ability of a test or procedure to correctly identify or quantify an entity in the presence of interfering cross-reactive substances that might be expected to be present. Laboratories are encouraged to review the published literature for guidance on analytical specificity (COM.40350)	Cross-reactivity: FDA recommends an *in silico* cross-reactivity data against a prescribed list of organisms. Inclusivity: FDA also encourages including a highly conserved Mpox target or NVO target as part of a multiple target test which may improve performance with new genetic variants. Test developers should also monitor new and emerging viral mutations and variants that could impact molecular test performance on an ongoing basis through a monitoring plan strategy with monitoring access points and a steady monitoring frequency. Microbial Interference Studies: FDA recommends if *in silico* cross-reactivity revealed ≥80% homology Endogenous/Exogenous Interference Substances Studies: If candidate test uses extraction methods not previously reviewed by FDA, FDA recommend testing for potential interferents against a prescribed list of substances.
Analytical Sensitivity			Analytical sensitivity is the lowest concentration or amount of the analyte or substance that can be measured or distinguished from a blank (COM.40350)	FDA recommends the most current version of the CLSI EP17 "*Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures.*" EP17-A2 Vol. 32 No. 8: Section 6.3 Experimental Design for evaluation of LoD has a minimum requirement of 2 reagent lots, 1 instrument system, 3 days, 3 replicates/sample (for each reagent lot, instrument system, and day combination), 4 independent low-level samples of known measurand concentration, and 36 total low level sample replicates/reagent lot (across all low-level samples, instrument systems and days)
Reportable Range			Not applicable to qualitative assays	
Reference Interval			Not applicable to qualitative assays	
Other characteristics required for assessment of test performance	Reagent Stability	Not explicitly addressed	Other performance characteristics required for analytical test performance include specimen stability, reagent stability, linearity, carryover, and cross-contamination, as appropriate and applicable (COM.40350)	Studies generally do not need to be completed prior to authorization; however, FDA recommends that the study design be submitted in the EUA request and that testing begin immediately following authorization, if not before. FDA recommends following CLSI EP25 "*Evaluation of Stability of In Vitro Diagnostic Reagents.*" EP25-A Vol. 29 No. 20 Section 4.4 The Stability Testing Plan requires testing of a minimum of 3 product lots for

(*continued on next page*)

Table 1 (*continued*)

	CLIA (LDT) [11]	CAP (LDT) [23]	FDA (NVO/monkeypox EUA) [22]
			shelf life, 1 for in-use life, and 1 for transport simulation.
Sample Stability			Testing should be conducted to demonstrate sample stability throughout the real-world conditions in which they are collected and tested for 50 samples
Clinical Utility		The predictive values for relevant disease(s) or condition(s) must be established by the laboratory unless the clinical validity of the test is documented in peer-reviewed literature or textbooks (COM.40640)	FDA recommends use of clinical specimens if available, in a prospective, blinded, randomized study of patients suspected of Mpox by their healthcare provider. Samples should be tested in a blinded fashion, e.g., positive and negative samples should be presented to the end user in a blinder fashion. The end user should also be blinded to the results of any comparator method testing.

assay is not addressed in the FDA EUA application, overlooking this requirement by CMS/CLIA [11].

1.4. Challenges imposed by FDA requirements on UCLA NVO/monkeypox development

LDTs serve as a significant platform by which diagnostic laboratories can expeditiously respond to unmet clinical needs. The FDA requirements for EUA of NVO/monkeypox testing of non-lesion specimens levied significant challenges to our ability to provide comprehensive care to patients. The additional requirements beyond the performance specifications explicitly listed in the CFR proved to be unfeasibly costly in resources and time.

First, to establish initial reagent stability claims, the FDA-endorsed CLSI guidelines proposed testing of at least 3 separate lots of reagents. While conceptually valid to safeguard against the use of "deteriorated" or "substandard quality" reagents as articulated in 42 CFR § 493.1252 [25], the reality of multi-lot studies are not often practical in resource- and time-restricted scenarios, such as public health emergencies, where reagents and other consumables may be in short supply – a critical realization that was made from past experiences with the COVID-19 pandemic. As such, for the UCLA NVO/monkeypox testing, a single lot of primers, for example, were specifically preferred to avoid lot-to-lot variation, and more importantly, unforeseen delays in production between lots. This condition automatically disqualified our laboratory from being able to satisfy this FDA-required criterion.

Next, defining the parameters of sample stability required the testing of 50 samples at each time and temperature conditions claimed in the candidate test protocol that have to be conducted in "real-world" settings. In an attempt to satisfy this requirement, our laboratory not only had to prepare a significant number of contrived testing samples, but also had to coordinate with laboratory processing and courier services to mock specimen transport and storage for the purposes of the validation. Again, while the requirements of this study may seem conceptually simple to integrate into routine workflow, reality dictated that the need for comprehensive documentation for the validation report (i.e., sample transport tracking and storage records) required a dedicated effort to avoid potentially interfering with and compromising standard workflow. As such, a separate STAT courier had to be deployed, and specific laboratory processing personnel had to be instructed to intercept the specimens as not to cause unnecessary confusion and interrupt on-going clinical functions.

Lastly, the most prohibitive requirement of the FDA EUA application was the validation of clinical utility through a prospective, blinded, randomized study. Specifically in the context of a rapidly evolving infectious disease outbreak, implementing a randomized controlled clinical trial is impractical. As noted in the agency's own documents, "studies involving clinical samples (human specimens) conducted in support of an EUA request are subject to applicable requirements for Institutional Review Board (IRB) review and approval and informed consent" [22]. Establishing an IRB protocol is a time-consuming and laborious commitment that is unlikely to be feasible under the demands of an actively developing epidemic. To recruit and conduct a clinical study would guarantee costly delays to any response effort by a medical institution.

Despite these added challenges, however, UCLA remained resolved in providing science- and data-driven medicine, and attempted to satisfy, in full faith, the requirements of the FDA for EUA of NVO/monkeypox testing of rectal swabs. Yet despite the substantial resources invested balanced with the ample published data to support the claims our laboratory was unable to substantiate directly through in-house studies, the FDA ultimately deemed the UCLA EUA application incomplete and unsatisfactory. Ironically, given the data gathered from the extensive additional testing, the performance of the UCLA NVO/monkeypox assay for rectal swabs did not improve, nor were concerning deficiencies identified.

2. Discussion

The change in the FDA's stance away from its "enforcement discretion" is rooted in the agency's well-founded intent to regulate increasingly complex test systems, specifically the growing field of direct-to-consumer LDTs, in order to minimize the associated increased risks to patients [13,17]. The unintended consequence, however, is an imposing over-regulation of clinical laboratories that utilize LDTs in the "traditional" manner described in the agency's own reporting [13]. The LDTs we have instituted are largely utilizing components that are either legally marketed and produced for clinical use (i.e., "For IVD Use"), or have been extensively validated by the manufacturers and published in peer-reviewed journals. Additionally, many of the problematic LDT examples provided by the FDA pertain to issues with test interpretation, or testing of high-volume routine sample types (e.g., cervical swab collected in SurePath medium for HPV screening) not initially included in the FDA-approved package insert, and are not related to the analytical performance or clinical utility of the LDTs [26]. Most importantly, prior to reporting, the results produced by the UCLA LDTs are interpreted and reviewed by the physicians, pathologists, and trained laboratorians directly responsible for the patients' care. Under these conditions, the LDTs UCLA has produced remain within the context under which the FDA has historically exercised "enforcement discretion."

While the authors of this article do not contend the FDA's legal right to regulate LDTs, nor its imperative need to do so effectively, a critical discrimination must be made between well-established LDTs employed by academic medical centers to respond to specific clinical needs from those by commercial reference laboratories. Whether in routine use or public health emergencies, LDTs offered by clinical laboratories like the

UCLA Clinical Microbiology Laboratory are intended to fulfill a critical gap in the diagnostic space in an effort to offer comprehensive patient care, as well as mitigate the impact of infectious disease outbreaks through timely diagnoses – something that the FDA should not compromise simply to satisfy technical requirements. Here, we provide our experience on the consequences of the FDA's provisions for EUA using the recent mpox outbreak response effort as an example to underscore its potential burden on the ability of clinical laboratories to effectively perform its duties.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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