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Development Of Standards for Showing Analytical and Clinical Validity in Animal-Based Diagnostics

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Abstract:

Pandemic fears fueled by outbreaks of extremely virulent illnesses such as the new Coronavirus disease of 2019 (COVID-19) have heightened interest in non-invasive and quick diagnostic methods. The adoption of animal-based diagnostics, which have the potential to be more accurate and efficient than traditional diagnostics, is one answer. According to one study, trained detection dogs were able to accurately identify C. difficile infections in patients with 97 percent accuracy, which was greater than the reported accuracy of 92.7 percent for real-time PCR diagnostic procedures. While these animal-based diagnostics obviously come within the purview of the FDA's regulatory authority, advancements in diagnostic technology, particularly animal-based diagnostics, have overtaken the Agency's capacity to update its standards for obtaining marketing clearance for these products. As a result, researchers in this field are confronted with a regulatory framework that does not adequately handle the obstacles and hazards associated with using animals to identify illnesses. It is suggested in this article that the Agency will regulate animal-based diagnostics in a manner that is insufficient in comparison to the existing regulatory environment. Finally, by (1) developing guidelines for demonstrating analytical and clinical validity in animal-based diagnostics and (2) adopting the technology certification pathway provisions of the proposed FDA VALID Act of 2020, a reform bill that would streamline how FDA regulates medical diagnostics, it is proposed that the current regulatory regime be modified in order to encourage development of animal-based diagnostics.

Keywords: Pandemic, FDA, real-time PCR, animal-based diagnostics, regulatory authority

I INTRODUCTION

Several years ago, a paper in the British Medical Journal described a dog that had been trained to detect Clostridium difficile infections in patients with remarkable accuracy. Clostridium difficile infection is a common hospital-borne infection that causes toxin-mediated intestinal disease, with symptoms ranging from mild diarrhea to fatal intestinal infections. As a result of the bacteria's

widespread presence in hospitals and in patient groups with impaired immune systems or who have recently been exposed to antibiotics, early diagnosis is critical. 3 C. difficile infections were properly recognized in 97 percent of stool samples and in 95.3 percent of patients by the dog, Cliff, who was two years old at the time of the study. This performance much surpasses that of FDA-approved diagnostic tests usually used to identify the illness. Cliff was also efficient, screening a full ward of patients for Clostridium difficile in less than 10 minutes with no physical contact or the requirement to collect stool samples from the patients. 5 Following the completion of this groundbreaking investigation, it was concluded that dogs may be a helpful detecting tool if properly trained. It was found to be so promising that a Canadian hospital has employed a team of C. difficile detection dogs to identify areas of contamination since 2016, and has reported a reduction in the number of C. difficile outbreaks in its hospital as a result of using dogs to help combat the spread of this bacteria. Similar outcomes have been found for a variety of different animal-based diagnostics by other researchers. As an example, according to a 2019 research, canines were able to detect malaria infections in youngsters who were not showing any symptoms by sniffing their socks. Multiple studies have confirmed that dogs can be trained to detect the odor of prostate cancer in patient samples with accuracy levels ranging from 90 percent to 99 percent. This represents a more reliable alternative to conventional diagnostic methods, which are only 25 percent accurate when screening for prostate cancer. The effectiveness of training detection dogs to identify human illnesses has prompted researchers throughout the globe to investigate whether detection dogs can be taught to detect the unique Coronavirus disease of 2019 (COVID-19) in persons who are not showing any signs or symptoms of the disease. Detection dogs are currently being used at Helsinki's airport as well as in the surrounding areas of Abu Dhabi and Dubai to check for asymptomatic Coronavirus cases after successful research projects in Finland and the United Arab Emirates. Animal-based diagnostics have the potential to become unique, non-invasive methods for diagnosing human illnesses, however the development of such diagnostics faces unknown regulatory obstacles.

The FDA (United States Food and Drug Administration) has strict regulations on the safety and effectiveness of diagnostic kits used to identify diseases (FDA). To bring their goods to market, the creators of such kits must adhere to tight FDA regulations and procedures. However, if an animal were to take the role of a diagnostic kit, how would the FDA expand its regulatory jurisdiction to control the animal's medical application?

It has become increasingly critical as more animal-based diagnostics are produced and have the potential to be marketed that the answer to this issue be discovered and published. Furthermore, due to outbreaks of extremely virulent illnesses such as COVID-19, where identification is difficult and transmission between infected patients and healthcare workers is high, interest in quick and non-invasive diagnostics is growing.

Developers of animal-based diagnostics, on the other hand, confront an unknown number of regulatory obstacles. In general, the FDA does not control animals used for medical purposes, and it has never regulated animals used expressly as diagnostic equipment in the past. In its present form, the FDA's regulatory system for diagnostic kits does not offer a framework for the assessment and licensing of animal-based diagnostic products. Furthermore, the existing regulatory procedure would most likely require developers to present safety and effectiveness data, which might be expensive and time-consuming to provide on a per-test or per-animal basis, given the current regulatory environment. Due to the uncertainty around how the FDA will govern this new technology and whether or not it will be worth the effort, prospective sponsors may be reluctant to proceed with animal-based diagnostics research and development.

The purpose of this article is to explain uncertainties in the existing legislation and forecast how the FDA will govern animal-based diagnostics in the future, among other things. This Article will demonstrate how the existing regulatory structure falls short of adequately addressing the safety and effectiveness concerns highlighted by the use of animals in diagnostic procedures. (2) adopting the technology certification approval pathway proposed by the VALID Act, a reform bill that would streamline how the Agency regulates medical diagnostics, and applying it to animal-based diagnostics; and (3) adopting the requirements for the validation and approval of animal-based diagnostics.

II FDA REGULATION OF CONVENTIONAL DIAGNOSTIC TESTS

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) is responsible for regulating medical devices, ensuring that devices produced and marketed for medical use in the United States fulfill specified safety and efficacy requirements. Because of the broad definition of "device" under the Federal Food, Drug, and Cosmetic Act (FDCA), the Food and Drug Administration (FDA) has claimed its power to regulate a majority of diagnostic tests as medical devices, and animal-based diagnostics are unlikely to be excluded from regulation. There are two types of traditional diagnostic tests: in vitro diagnostic (IVD) assays and laboratory-developed tests (LDTs). The FDA has historically chosen to regulate IVD assays as medical devices, whereas LDTs have been regulated as laboratory-developed tests. "If [the tests] are conceived or produced entirely or partially outside of the laboratory that sells and utilizes them, [they] cannot be classified as LDTs," according to the practical distinction between the two groups. In this context, it is critical to distinguish between IVDs and LDTs since, under the existing regulatory framework, IVDs and LDTs are treated differently.

This article makes the assumption that animals that perform diagnostic activities similar to those of traditional testing would similarly fall within the regulatory scope of the FDA. However, since technical advancements in diagnostic testing have surpassed the development of regulatory frameworks, it is unclear how the FDA would expressly oversee animals that perform diagnostic

tasks. If an animal-based diagnosis is done by clinical laboratory services as an LDT, it is feasible that developers will be able to manage the environment and testing settings, resulting in more accurate performance. However, it is also likely that the animal-based diagnosis will be packaged and sold as a stand-alone IVD test kit. Following that, we'll go through the regulations that apply to both sorts of diagnostics in more depth.

A Laboratory-Developed Tests are subject to government regulation.

Diagnostic tests that are produced and utilized inside a laboratory service are referred to as "laboratory-developed tests" (LDTs). Regulation of laboratory-developed tests (LDTs) has gained substantial attention in recent years, and this section reviews some of the reform ideas because they show possible techniques for regulating animal-based diagnostics as laboratory-developed tests (LDTs). According to existing legislation, the FDA has the ability to regulate LDTs. FDA, on the other hand, has traditionally chosen not to use this jurisdiction. As a result of the Clinical Laboratory Improvement Amendments of 1988, the Centers for Medicare and Medicaid Services (CMS) has taken over regulation of LDTs in the United States. CMS requires the laboratory provider to establish analytical validity for the LDT in accordance with these Amendments. However, there is no need to demonstrate clinical value or validity.

Since the advent of current technical breakthroughs and the quick evolution of business models, LDTs have grown in complexity and prevalence across the sector, and they now pose more dangers than LDTs in use before to the amendment. Following this, a number of modifications have been recommended to assure the safety and effectiveness of the drugs.

In 2010, the FDA said that it intends to vigorously enforce rules to ensure that the clinical validity of moderate- to high-risk LDTs is compatible with the FDCA and that the FDCA is not being violated. FDA produced a draft guideline paper in 2014, after many years of anticipation, outlining the agency's risk-based, phased-in strategy to implementing premarket review requirements for LDTs posing a moderate-to-high risk. According to the proposed advice, device sponsors would be required to show both analytical validity and clinical validity for their devices. It was also stated in the draft guideline that FDA will apply the same risk-based classification system as other devices (such as IVDs classified as Class I, II, or III) and the appropriate premarket review process—510(k), PMA, or de novo—for each LDT classification.

The House Appropriations Committee responded by ordering FDA to "suspend further efforts to finalize the [draft] Guidance" because it "put[] forth a proposed regulatory framework that represents a significant shift in the way LDTs are regulated" and "circumvents the normal rulemaking process." This occurred before FDA finalized its 2014 draft guidance.

The FDA produced a discussion paper in 2017 in response to Congress's clear restriction on the agency's ability to issue further advice. The report offered reform recommendations that scaled

down the majority of the provisions in the 2014 draft guidance, but it did not eliminate them entirely. The discussion paper maintained the risk-based, phased-in approach to enforcement, but it would have exempted traditional LDTs and those currently on the market from the need to register and get regulatory clearance for their use. The 2017 discussion paper also recommended a supplementary supervision structure that would link the more lax analytical validity criteria of CMS with the more stringent clinical validity requirements of the Food and Drug Administration.

III PROPOSED REFORM OF DIAGNOSTIC TEST REGULATION

Following FDA Commissioner Scott Gottlieb's appeal for comprehensive legislation in this field, a bipartisan group of Senators and Representatives produced the Verifying Accurate, Leading-edge IVCT Development (VALID) Act of 2020, which is now before the Senate and House of Representatives. According to the VALID Act, a comprehensive revamp of diagnostic test regulation is proposed, including the creation of a new class of medical devices known as in vitro clinical tests (IVCTs), which would include both standard IVDs and long-term diagnostic tests. The Centers for Disease Control and Prevention (CDRH) would most certainly continue to regulate this new class of tests.

As defined by the proposed legislation, an IVCT is "a test intended to be employed in the collection of specimens obtained from or produced from the human body, as well as in their preparation, analysis, or in vitro clinical assessment." The IVCTs would be further divided into two categories: high-risk IVCTs and low-risk IVCTs, with high-risk IVCTs subject to premarket clearance unless they are excluded from premarket approval under another section of the Act. Those IVCTs that pose a low risk of infection would be excluded from the premarket approval procedure, but they would be subject to registration requirements and certain post-market requirements. Intensive care units (ICUs) are classified as high-risk if a "undetected erroneous result offers a possible unacceptable risk of significant or permanent injury to a patient or patients, or may otherwise cause substantial harm to public health." As a result of the categorization method, an IVCT that would normally be considered high risk might be classified as low risk if mitigation steps can be implemented to minimize or eliminate the inherent hazards of a misdiagnosis. Additionally, a full-fledged PMA procedure will continue to be accessible to IVCT sponsors in addition to the additional approval paths that would be made available to them under the VALID Act. In a press release issued in December 2018, the FDA claimed that the VALID Act would most likely exclude 90 percent of IVCTs from premarket approval under current regulations.

To avoid the need of filing a PMA application, sponsors of qualified IVCTs would be allowed to take use of a new technology certification scheme instead. Technology certification orders are granted by the FDA to sponsors under this program, and each order covers just a particular technology or test procedure. The issued order would exclude all IVCTs within its scope from premarket review for a period of up to four years, with the possibility of extending the exemption

for an additional four years provided there are no significant changes to the underlying application information during that time. VALID Act requires that, in order to take use of the technology certification route provided by the Act, a sponsor choose one of the most challenging representative tests among those that would be subject to a proposed scope of the technology certification order. A description of how the representative test is a sufficient representation of the methods contained in the technology certification application must also be provided by the sponsor. To qualify as a representative test for technology certification orders, the sponsor must give much of the same information that is necessary for the PMA procedure. A PMA application may thus be used to qualify as a representative test for technology certification orders. To be considered for technology certification, the sponsor must not only provide specific evidence demonstrating analytical and clinical validity for the representative test, but they must also provide procedures for assuring analytical and clinical validity for all IVCTs that fall within the proposed scope of the technology certification order. All IVCTs that fall under the scope of the order are exempt from premarket review if the technology certification order is granted and the sponsor complies with the validation procedures outlined in the order. As a result, sponsors are able to market these tests without having to submit additional data to the FDA. The technology certification route also specifies which tests are excluded for this accelerated kind of assessment, as well as which tests are allowed. One of the categories that are disqualified is for IVCTs that are "one-of-a-kind." A diagnostic that varies from a previously authorized diagnostic may be included in this category at the FDA's exclusive discretion, in essence. It is anticipated that if diagnostics are omitted from the technology certification process, sponsors will be required to submit a PMA application for each diagnostic.

The VALID Act, on the other hand, establishes a special premarket approval pathway for eligible IVCTs, including first-of-a-kind devices, under which sponsors are not required to submit raw data demonstrating analytical validity or quality requirement information, in a manner similar to exempt IVCTs under a technology certification order, in order to obtain premarket approval. As an additional feature of VALID, the Act establishes a petition process through which sponsors can argue that new information has become available regarding the IVCT's risks and mitigating measures and that the IVCT should be eligible for technology certification or otherwise exempt from premarket review. This new regulatory approach might save diagnostic test sponsors time and money that would otherwise be spent obtaining data for FDA clearance of each new device if the VALID Act is signed into law in its entirety. Furthermore, the VALID Act seems to include the regulation and licensing of animal-based diagnostics, based on the broad definition of IVCTs that it contains. Although the issue of whether its adoption would have an impact on the licensing of animal-based diagnostic procedures remains.

IV FDA REGULATION OF ANIMALS AS DIAGNOSTIC DEVICES

As previously mentioned, animal-based diagnostics obviously come within the regulatory competence of the Food and Drug Administration. In the Federal Diagnostic and Classification Act, the term "device" is defined broadly and is intended to include all in vitro diagnostic tests. The FDA has also proved its readiness to control animals used as medicinal devices by approving the use of maggots and leeches for therapeutic purposes. To that end, being familiar with the requirements of both conventional diagnostics (such as diagnostic kits) and animal-based therapeutics (such as frogs and leeches) can help sponsors of animal-based diagnostics determine the best premarket application strategy while also preparing for what may be unfamiliar and unexpected regulatory requirements in the future.

At the time of this writing, we are not aware of any animal-based diagnostics products that have gained FDA marketing approval or that have ever applied for FDA marketing clearance. As a result, it is unclear how the Food and Drug Administration will govern animal-based diagnostics. However, based on the present legal framework, it is conceivable to foresee the Agency's approach. This research considers that an animal-based diagnostic will be regulated in a manner comparable to that of conventional diagnostics, but that the presence of different characteristics unique to animals will need a change in the regulatory route leading to marketing authorization. When it comes to diagnostic accuracy, one of the most distinguishing characteristics of animal-based methods is the inherent diversity from animal to animal, and even across testing cycles using the same species. As a result of this animal-related variation, repeatability concerns might arise, making it difficult for animal-based diagnostics developers to demonstrate analytical and clinical validity, as required by the FDCA.

A The Regulation of Animal-Based Diagnostics Compared toIVDs and LDTs

Patient safety would most likely be compromised if animal-based diagnostics were designated as either Class II or Class III devices, owing to the inherent hazards associated with faulty or erroneous animal-based diagnostics, which might result in moderate to severe dangers to people. In certain cases, sponsors will be able to use the 510(k) method to get clearance if they can identify the predicate devices. Animal-based diagnostics may also be provided as a clinical laboratory service, with the associated regulatory criteria being less stringent than those for an LDT. This is a possibility. Although it is possible that no such predicate will be identified, at least for the initial sponsors of animal-based diagnostics, the more likely scenario is that the Agency will require the sponsors to conduct clinical trials in order to demonstrate safety and efficacy prior to submitting a PMA application. Understanding the PMA process as well as the limitations of animal-based diagnostics, on the other hand, is critical to the wider deployment of animal-based diagnostics in clinical settings in the future. The following sections go into further depth about each of these possibilities.

It is possible that animal-based diagnostics developers may produce, offer, and execute the tests in their own labs, which would result in the tests falling outside of the IVD category and being classified as a laboratory diagnostic test (LDT). FDA has always retained its jurisdiction to regulate LDTs as medical devices, as noted in Part II.B, supra, but has generally reserved that authority and permitted CMS to oversee labs that manufacture LDTs. It is anticipated that regulatory approval as an LDT rather than an IVD will be a less onerous procedure for animal-based diagnostic developers since CMS only wants proof that LDTs are analytically valid; no demonstration of clinical value or validity is needed.

Although it is probable that showing analytical validity of an animal-based diagnosis would be challenging, this is especially true in light of recent research that has shown substantial variance in some of the present animal-based diagnostic applications. In contrast, since LDTs are designed to be performed only inside a developer's own laboratories, developers may maintain tight control over the setting and testing circumstances of their animal-based lab delivered tests, reducing the possibility of variance due to external influences. To guarantee that the most accurate findings are obtained, they should be able to verify that the proper training and testing protocols are followed, as well as adjust the testing processes as necessary. Clinical Laboratory Improvement Amendments (CLIA) for example, require that analytical validation be demonstrated through the development of verified performance characteristics on a range of metrics including accuracy, precision and range; analytical sensitivity and specificity; reference intervals; and reference interval accuracy. Having established the necessary performance standards in accordance with CLIA, a developer may next focus on developing testing methods that are solely applicable to the unique environment, testing equipment, laboratory personnel, and patients of a particular laboratory. Consequently, these performance standards must be repeated and maintained for every test application, and they must be updated if changes occur in the laboratory setting. Providing that an animal-based diagnostic developer can address the analytical validity of its test, the LDT pathway offers a shorter and less expensive route to market because it does not require the development of clinical studies to demonstrate clinical validity or the accuracy of the animal-based diagnostic in diagnosing patients.

In light of the recently proposed reforms to LDT regulation in the VALID Act of 2020, as well as the FDA's stated intention to reclaim control over LDT regulation, any benefit from animal-based diagnostic developers' self-selection into regulation as an LDT is likely to be short-lived, if it ever occurs. The C. difficile detection dog team at Vancouver Coastal Health, illustrates the likely reality that at least some of these animal-based diagnostics will be subject to FDA regulation as IVDs because the testing will be conducted outside of the facility that trains and validates the animals as diagnostics.

V SUGGESTIONS FOR REGULATING ANIMAL-BASEDDIAGNOSTICS

Uncertain restrictions, variations in training and findings, and other issues are among the most difficult problems faced by sponsors of animal-based diagnostics seeking FDA clearance for commercialization. Unfortunately, the Agency's regulatory framework is ill-suited to this novel technology. As a consequence, while attempting to have their products authorized under the present laws, producers of animal-based diagnostics will encounter obstacles and setbacks. The FDA's ambiguous regulatory approach to animal-based diagnostics would also likely result in unnecessarily long delays and high costs for sponsors of animal-based diagnostics. In order to address these issues, we suggest the following recommendations.

A FDA Guidance on Animal-Based Diagnostic Validation

The FDA's clearance of animal-based diagnostics is likely to be the most difficult obstacle to overcome. A guidance sheet on this topic would need to address what is likely to be one of the most difficult components of the PMA process for sponsors—demonstrating analytical and clinical validity in the context of animal-related variation. Because of the possibility of animal-related variation, the FDA must clarify what proof a sponsor would be required to produce to demonstrate that their diagnosis is safe and effective. It is necessary for FDA to ensure that animal-based diagnostics are "manufactured" in a manner that ensures their accuracy and reproducibility, similar to the Agency's current Good Manufacturing Practices regulations for conventional medical devices, in order to establish a standardized review process. For example, the FDA currently recognizes third-party quality assurance and manufacturing standards for conventional medical devices, including standards published by organizations such as the Clinical and Laboratory Standards Institute (CLSI) and the American Society for Testing and Materials (ASTM) and standards published by organizations such as the American Society for Testing and Materials (ASTM) (now known as ASTM International). Conformance with third-party metrics, such as the CLSI's Verification and Validation of Multiplex Nucleic Acid Assays, may be used to establish that a nucleic acid assay-based diagnosis is both safe and effective in patients. A comparable set of guidelines for training and testing animals for diagnostic purposes may be endorsed by the FDA, which would be beneficial to those who develop animal-based diagnostics.

First and foremost, the Food and Drug Administration should examine the training procedures used to verify that animals performing diagnostic roles generate reliable findings. Indeed, some animals may be able to deliver more accurate findings than existing diagnostic instruments; but, animals are not fully error-free, and it is inevitable that some animals may provide false-positive and false-negative results. Therefore, the FDA should establish training criteria that effectively calibrate the diagnostic capabilities of the animals so that they can be relied upon to reliably identify people. A few organizations have published guidelines for training dogs in other critical contexts, such as drug detection, explosive detection, missing person detection, pest detection, and

agricultural substance detection, which the FDA could adopt directly or use as a starting point for developing its own guidelines for training animals in the medical diagnostics context. FDA could adopt these guidelines directly or use them as a starting point for developing its own guidelines for training animals in the medical diagnostics context.

VI CONCLUSION

A new generation of animal-based diagnostics has the potential to transform medical diagnostics by giving quicker and more accurate results. This technology may be especially valuable in the fight against extremely virulent illnesses such as COVID-19. These animal-based technologies may give a novel approach for detecting the scents of illnesses that do not presently have a good diagnostic tool available to them. Animal-based diagnostics have the potential to be more accurate, less wasteful, and perhaps less costly than their electrochemical gadget equivalents, as well. While animal-based diagnostics have the potential to improve accuracy and reduce costs, there have been reports of repeatability concerns, which might have a negative impact on their diagnostic accuracy.

Consider the concerns expressed by some detractors of detection dogs, who believe that because of the wide variation in attention span and olfactory ability across dog breeds and even during a single dog's lifespan, detection dogs would never be a suitable replacement for present diagnostic tools. Sponsors of animal-based diagnostics, however, have not been deterred from modifying training techniques and undertaking more research studies in order to uncover and eliminate any hazards associated with the use of animals as detection devices. It is not in doubt that the FDA has the jurisdiction to regulate the animals since the animals are being used "in the diagnosis of sickness or other conditions," as outlined in the FDCA's definition of a medical device. What is up for question, however, is how the FDA will exercise its power and apply the FDCA regulation of medical devices to the approval process for these devices in the first place.

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