An Analysis of the COVID Pandemic Emergency Use Authorization (EUA) and Future Regulatory Strategy Considerations

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Abstract

The COVID-19 pandemic has required and benefited from emergency regulatory clearance strategies by the FDA. This paper considers application of these strategies as part of the routine future product review process to modernize and streamline some diagnostic submissions using the COVID-19 Emergency Use Authorization (EUA) experience. This will accelerate the timeliness of FDA activities and serve patient and provider needs with a proven safe and effective regulatory approach.

Early in the pandemic outbreak, the FDA published Guidance that permitted developers of antibody tests to market their devices without obtaining EUA so that prior infection could be documented.[1] Concurrently, the agency focused on evaluating new diagnostic devices for active infection under Emergency Use. The market was flooded with serology tests, some of which performed poorly and many of which were marketed in a manner that were not compliant to FDA policy. With experience, the Emergency Use submission requirements were enhanced and clarified on an ongoing basis. The results of the EUA experience presents clear opportunities to apply this process to many routine diagnostic and device submissions.

Introduction

After more than a year of the public health emergency of the pandemic, COVID-19 has brought rarely used regulatory procedures to the forefront of product authorization. The most commonly seen among these pathways is the FDA EUA authority, the expedited pathway through which at-home tests, point-of-care tests, high volume laboratory tests, personal protective equipment and even the COVID-19 vaccine candidates have been authorized for use. Prior to 2020, a very limited number of medical products have received an FDA EUA, refer to Appendix 1 for a list of these products.

Under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the FDA commissioner has the authority to allow unapproved medical products or unapproved uses of approved medical products to be authorized for use in an emergency. This section of the FD&C Act has been amended[*] on numerous occasions to align with prevailing public health needs. In order to meet immediate, emergent need for specific and highly sensitive tests and in compliance with the Department of Health and Human Services (HHS) determination, the FDA currently does not require traditional premarket notification or emergency authorization for CLIA-validated tests developed by laboratories.[3]

This paper analyzes the FDA's application of emergency use regulatory practices to authorize medical products during the COVID-19 pandemic and examines streamlining the process to modernize future diagnostic and device submissions that would encourage competition while preserving the safety and effectiveness for the claims allowed. In addition, the contents of this essay are intended to encourage FDA's issuance of updated Guidance and promulgate new regulations based on the EUA pathway that will subject future *in vitro* diagnostic products and devices to federal streamlined policies that have been already used and confirm the safety and effectiveness of testing products and devices.

[*] This includes the Health Security and Bioterrorism Preparedness and Response Act of 2002, the Project BioShield Act of 2004, the Pandemic and All-Hazards Preparedness Act (PAHPA) of 2006, the Public Readiness and Emergency Preparedness Act (PREP Act) of 2005, the Pandemic and All-Hazards Preparedness Reauthorization Act Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA) of 2013, 21st Century Cures Act, Public Law 115-92 (H.R. 4374), and the Pandemic and All-Hazards Preparedness and Advancing Innovation Act (PAHPAIA) of 2019.

Discussion

The 3-Systems at CDRH

Several types of premarket submissions can be made to the Center for Devices and Radiological Health (CDRH). In order to legally market a device in the U.S., the most common forms of premarket submissions to FDA are the 510(k) premarket notification submission, the Premarket Approval (PMA) and the de novo classification request. For the purpose of this paper, diagnostics are considered devices per 21 CFR 809.3(a) and will be the focus of this manuscript. Diagnostics for blood transfusion screening submitted to CBER via the Biologics License Applications (BLA) process are intentionally excluded.

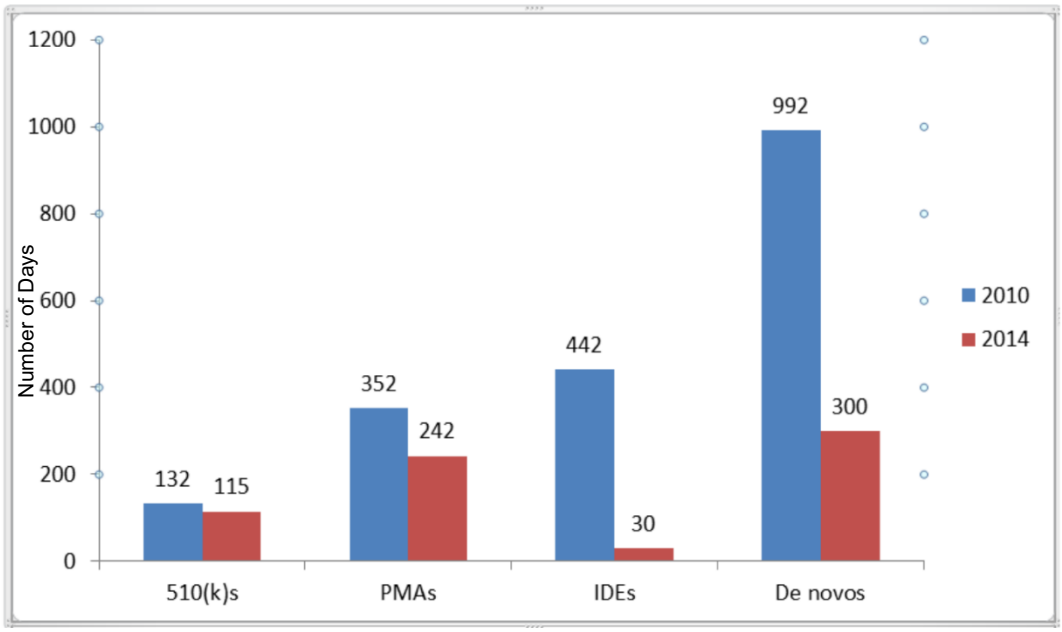
Each of these CDRH submission types result in a determination by FDA that clears [510(k)], approves [PMA], or grants [de novo] marketing rights to the successful submitter. The latter process establishes a predicate for future 510(k) submissions. Devices that require 510(k)-level review can be class I, II or III. A few Pre-Amendment Class III products allow for a 510(k), but most are class II (which have a moderate risk when the results are used for medical decision-making). 510(k) submissions for IVDs usually include preclinical, analytical and clinical data from patient samples. The volume and statistical basis for the clinical data depends upon how much is already known about the characteristics of the device/analyte combination. A device that is found to be substantially equivalent and cleared exhibits similar performance characteristics to the cleared marketed product to which it has been compared for the same intended use. A device that is found to be not substantially equivalent usually has different performance or technological characteristics, different risks or a different intended use. When there is no marketed device to which a new device can be found substantially equivalent, a de novo review process or PMA is indicated. The targeted average time between receipt of a 510(k) by the FDA and final decision is just over 3 months for a certain percentage of submissions[4], based on the FDA's User Fee Agreement with Industry, the Medical Device User Fee Act (MDUFA).

PMA applications reflect analytical evaluation by the manufacturer and evaluation of clinical performance, and generally demonstrates that the device can accurately and reproducibly measure the analyte under controlled conditions. The analytical testing also covers areas such as limit of detection, interfering substances and shelf-life/open container/shipping stability. The clinical section must show that the device provides the expected result in defined patient populations that reflect the intended use of a device. To be approved, a device should have clear clinical validity and effectiveness. When appropriate, the FDA will seek the advice of

outside experts who have been appointed to one of the agency's Medical Device Advisory Committees to provide decision-making advice. The average time between receipt of an original PMA by the FDA and a final decision is around 8 months[4] but can often be longer. The target for the percentage of completed reviews is also covered in the FDA/Industry User Fee agreement. However, when FDA responds to an application, the review clock stops, so published statistics of "FDA review times," such as the 8-month figure, can be misleading.

FDA has been committed to significant improvements for 510(k), PMA and first-time de novo products total review time goals with each MDUFA reauthorization. As Figure 2 shows, 510(k) and PMA review times has decreased by 13% and 31%, respectively, between 2010 to 2014, while de novo reviews decreased from more than three years in 2010 to 10 months in 2014.[5] Regarding the significantly shortened de novo review timeframes, that decrease may be explained by FDA's "allowing manufacturers to submit de novo device applications directly without first having to go through a 510(k) review and obtaining Not Substantially Equivalent (NSE) decisions."[5]

Figure 2: Review Times in Number of Days for FYE 2010 and 2014 (source: Emergo)



Through the EUA process described in Section 564 of the FDCA†, the FDA may grant expedited market access for unapproved indications of approved products. For example, a

† 21 U.S.C. 360bbb-3 - Authorization for medical products for use in emergencies.

diagnostic product may be approved for screening, a different indication and typically a different population. The statutory criteria are as follows:

1) an emergency must be declared by HHS, 2) the agent specified for the declaration of the emergency can cause a serious or life-threatening disease/condition, 3) it is reasonable to believe the medical product is effective in treating, diagnosing, or preventing that disease/condition based on scientific evidence, 4) the known potential benefits outweigh the known potential risks, and 5) there is no adequate, approved, alternate treatment available.

This last category is somewhat vague as seen with the ongoing EUAs for many COVID-19 products. In fact, one of the FDA COVID-19 conference calls[6] stated that they will continue the EUA process until the declared emergency is terminated. In summary, the agency will grant an EUA where sufficient evidence suggests that it is "reasonable to believe" that the product "may be effective" via an emergency declaration by the Secretary of the Department of HHS.

The FDA has worked diligently to develop a standardized review process that is based on state-of-the-art evaluation techniques and is grounded in the Food and Drug Administration Modernization Act of 1997 (FDAMA) mandate to provide least burdensome premarket reviews. Having said that, the process and guidance issued by CDRH has been updated and enhanced chronically during the emergency. Under an EUA, the FDA makes a product available to the public based on the best available evidence, without waiting for all the same types and amounts of evidence that would be historically needed for FDA approval or clearance. This does not mean that the EUA process is any less stringent or that the products are unsafe. The FDA balances the potential risks and benefits of the products based on the data currently available, just as with the 510(k) and PMA pathway, and is made based on sound scientific data. EUAs are effective until the emergency declaration ends and can be revised or revoked by the FDA at any time as the agency continues to evaluate the available data and patient needs during the public health emergency.

In a fast-evolving industry of testing where medical intervention or significant life decisions may be made, careful analysis and the potential of the FDA submission system are important to allow vigilant health care advancements.

Historical Attempts to Enhance Submission Processes and the LDT Process

Laboratory-developed tests (LDTs) are assays that are assembled, validated, and performed within a clinical laboratory, and the results of which are provided for clinical care. The assays are not sold to other users. Laboratory-developed assays may incorporate analyte-

specific reagents (ASRs) sold by component manufacturers or use reagents produced entirely by the laboratory. Laboratories that make and perform LDTs (with or without using ASRs) are not required to submit data on the test for FDA review. Instead, laboratories that develop their own clinical diagnostic tests must follow the regulations of the Clinical Laboratory Improvement Amendments (CLIA) of 1988.[7] ASRs are considered active ingredients used in diagnostic tests for identification and/or quantification of a chemical substance, ligand, or biological target in patient specimens, generally a single reagent, such as an antibody or nucleic acid probe, that can be used by laboratories in developing a functional clinical assay[‡]. Companies that sell ASRs must register their establishments, list their reagent(s) with the FDA and manufacture them under FDA's Quality System Regulation as appropriate. The user assembles the clinical assay using the ASR, and then is required to validate the performance of the new assay in the intended population. With past experience, the industry understands the FDA's desire to expand enforcement actions to regulate LDTs and the expectations to prove analytical and clinical validity if the tests are intended for medical applications. However, under the last administration, the HHS issued a finding prohibiting FDA from regulating LDTs.[3]

On August 19, 2020, the HHS announced that, effective immediately, it was rescinding all Guidance, compliance manuals, website statements, or other informal issuances concerning FDA premarket review of LDTs.[3] The announcement applies to all LDTs, including COVID-19 LDTs, and states that FDA may not require premarket review for these tests absent a notice-and-comment rulemaking process. Per the announcement, premarket review includes PMA, 510(k) notification, and EUA. HHS notes that laboratories may voluntarily submit an EUA request, PMA, or 510(k) for LDTs. FDA responded to this change in policy in early October, noting that it would "declin[e] to review EUA requests for LDTs at this time," including new EUA submissions and those already in the process of being reviewed.[8] In response, HHS directed the agency to review all voluntarily submitted EUA applications for COVID-19 LDTs, noting that submissions will be referred to the National Institute of Health's National Cancer Institute for review if the FDA's timeframe for review exceeds 14 days.[3] Therefore, clinical laboratories may voluntarily submit EUA applications for COVID-19 LDTs to FDA, and FDA must review them, but FDA may not require submission of such applications absent rulemaking.

Under the current administration, the status will likely be reviewed again. Thus, for the purpose of this essay, LDTs will not be considered. Instead, the focus will remain on FDA's potential use of the EUA process for future, non-emergency submissions.

[‡] 21 CFR 864.4020(a).

The FDA initiative to promulgate the de novo submission process was a significant step to modernize the 510(k) process. It eliminated the need for a predicate for new products whose perceived risks did not rise to the PMA level. For example, an early diagnostic de novo application was for the Triage B-type Natriuretic Peptide (BNP)[§] product, the first to diagnose congestive heart failure. Prior to that there were other diagnostics for acute heart failure and FDA reasoned the level of risk of these diagnostic products were about the same. Therefore, BNP qualified for the de novo rather than being placed into Class III requiring a PMA. It is this consideration of FDA, that is, allowing a new and enhanced form of submission process, that could lead to a new EUA-like process outside of national pandemic emergencies.

Proposed EUA-like Process

Several dominant players in the *in vitro* diagnostics industry proposed to the FDA a draft Guidance Document that would have created a new category of *in vitro* analytical tests. In 2003, FDA had considered a new abbreviated category of 510(k), called *In Vitro* Analytic Test (IVAT), that would rely on analytical sensitivity and specificity data instead of clinical sensitivity and specificity.[9] FDA lawyers had reviewed the draft guidance, which industry proposed. Under the IVAT proposal, companies could market diagnostic tests after establishing their analytical validity, but without establishing their clinical utility. One result of this proposal would be that IVAT manufacturers would not have to submit clinical data to the FDA and endure the lengthy premarket application process. They still would have to comply, however, with good manufacturing practices (GMPs) and demonstrate the specificity and sensitivity of their tests to, for example, the genetic mutations they are designed to detect. Through this proposed guidance, industries had already considered and supported an additional submission method that required less data for a subset of CDRH submissions. In addition, there could be a limitation to use the proposed EUA-like process, such as only for infectious agents being tested with antigen or molecular based methods.

This regulatory process would have sped the transfer of innovative tests from R&D labs to the marketplace, while protecting the public health by requiring FDA review of the tests' analytical performance. Under the proposed system, when an innovator developed a new test, the manufacturer could more quickly provide it to healthcare labs, bypassing the lengthy process of first establishing clinical validity. Furthermore, the FDA would have promulgated new regulations and updated submission guidance to state the timeframe that companies must

[§] De Novo Number DEN000010.

legally send a premarket submission. By providing industries with updated direction, FDA would have allowed testing exploration without compromising scientific innovation. In the end, while the IVD branch at CDRH supported further discussion of the approach, the leadership above did not. Instead, FDA initiated the de novo submission discussion in 2011.

Pros and Cons of an EUA-like Process For Routine Use

Though the current EUA proposal may be too sweeping for full implementation outside an emergency, it does represent much of the industry's perspective on regulatory reform. Changing the regulatory landscape could help reagent companies expand into the market for diagnostics and could help companies already active in the diagnostics business bring their products to market faster. It may even encourage laboratories engaged in LDT production to seek FDA clearances.

Potential concerns of the proposed new process include lack of a premarket requirement for establishing clinical validity to the same standard as a 510(k), which could diminish the incentive for sponsors to proceed with clinical trials, even though such research would be valuable. Other concerns also include the proposal approval process may not adequately assess the clinical risk of new products. However, in reviewing applications for *in vitro* tests that are considered low-risk and involve well-known established analytes, the agency has applied an IVAT-like model. Post-clearance commitments for clinical data and the same power to remove a product as under the EUA rules could help move this process ahead.

Using this proposed new strategy would replace many 510(k)s. To help encourage FDA, the fee for the new submission type should be at least as expensive as the current 510(k)s and to note that there would be more of them, allowing increased opportunities for competition from small companies. This would likely lower costs through increased competition. While the new strategy would potentially help accelerate products, the FDA's staffing would not be challenged for reduction due to faster review times. Consideration of an update to the EUA and naming this new pathway should also include a discussion to accelerate reimbursement. If FDA and Centers for Medicare & Medicaid Services (CMS) cannot address this, it may be necessary to involve Congress.

The need for robust post-marketing surveillance and post-market review tools to proactively establish extensive adverse event reporting systems, to help reduce concerns regarding safety and effectiveness, is a given and a reasonable trade-off for accelerated marketing opportunities. FDA has developed a reporting system, MedWatch (http://www.fda.gov/medwatch/) to make reporting of medical product problems to the FDA more

user friendly. For IVDs, monitoring of MedWatch reports is performed by technical analysts who also participate in premarket review and compliance actions. Most recently, OIVD has launched a pilot based on the active surveillance program, the MedSun program, developed by the Office of Surveillance and Biometrics.[10] The goal is better post-market regulatory oversight, and sophisticated outreach and educational initiatives for more informed premarket decision making. These programs help justify quicker and less clinical data intense submission and clearance processes.

Additional Safety Considerations

During the pandemic, an increase of fraudulent products has been observed by the FDA with claims to prevent, treat, mitigate, diagnose or cure the COVID-19 disease, offered for sale and distributed in the U.S. directly to consumers for at-home use. Many of these companies advertise their products on Facebook[**] and/or Instagram[††] without prior FDA approval, clearance, or authorization.[11] Verification of registration did not occur for the COVID-19 new manufacturer registrations and there is no compliance option other than recall orders when enforcement action is required. A way to prevent occurrences like these is to have a registration verification system to ensure that the manufacturing entity and facility is registered and legitimate.[12] In addition, importers should have an Authorized Representative in the U.S. for liability purposes. This process may help to ensure control and liability for poor players, potential fraud and timely actions when recalls or other Federal activities are needed.

Conclusion

The FDA regulatory program for IVDs is a complex system that considers IVD performance in its Classification system and for all phases of the devices life cycle. FDA has done an exceptional job expediting the COVID-19 EUA process safely while continuing to monitor it. In fact, the EUA clearance for marketing has been a critical tool for the medical and public health communities and is likely applicable for authorizing products outside of emergencies. It fills the need for timely and practical medical assessment and treatment

[**] EnMed MicroAnalytics, Inc.'s Blood Spot Collection Packet listed on https://enmedmicroanalytics.com and https://facebook.com/EnMedMicroAnalytics/ indicate that the "COVID-19 Blood Spot Collection Packet" is intended to be used for at-home blood sample collection for COVID-19 serology testing. FDA has observed this as adulterated and misbranded products related to Coronavirus Disease 2019.

[††] Avazo-Healthcare, LLC's COVID-19 antigen test kit products listed on https://www.instagram.com/cbdmarketweb/ indicate that the product is "intended to mitigate, prevent, treat, diagnose, or cure COVID-19 in people." FDA has observed this as adulterated and misbranded products related to Coronavirus Disease 2019.

whether or not the relevant product has already been cleared or approved by the FDA. An understanding of this new product clearance category, which has proved its effectiveness, should be considered for selective implementation as routine going forward. FDA should use the historical de novo guidance and promulgation process to add another more streamlined process to the IVD submission system.

Appendix 1 – Figure 1: Emergency Use Authorization – FDA Archived Information[2]

Medical Product	Date of EUA Issuance
Anthrax: National Postal Model Anthrax EUA Information	
Oral formulations of doxycycline products for the post-exposure prophylaxis (PEP) of inhalational anthrax	October 14, 2011 (originally issued on October 6, 2008, with subsequent amendments)
Oral formulations of doxycycline products for the post-exposure prophylaxis (PEP) of inhalational anthrax ("Doxycycline mass dispensing EUA")	July 21, 2011
Anthrax Vaccine Adsorbed (AVA)	January 14, 2005
H1N1 EUAs	
Antiviral Disposition: Oseltamivir (Tamiflu), Zanamivir (Relenza), and Peramivir	June 22, 2010
Antivirals	Peramivir • November 2, 2009 • April 19, 2010 Tamiflu • August 4, 2009 • April 19, 2010 Relenza • August 4, 2009 • April 19, 2010
In vitro diagnostics	2009
Personal Protective Equipment (PPE)	May 1, 2009
Middle East Respiratory Syndrome Coronavirus (MERS-CoV) EUA	
CDC Novel Coronavirus 2012 Real-time RT-PCR Assay	June 5, 2013
RealStar MERS-CoV RT-PCR Kit U.S.	July 17, 2015
Ebola Virus EUA	
In vitro diagnostics	Various
ReEBOV Antigen Rapid Test (Zalgen Labs, LLC)	February 24, 2015 (initial issuance) March 16, 2015 (reissuance) November 3, 2016 (reissuance) May 18, 2019 (revoked)
OraQuick Ebola Rapid Antigen Test - for use with whole blood (OraSure Technologies, Inc.) and OraQuick Ebola Rapid Antigen Test - for use with cadaveric oral fluid (OraSure Technologies, Inc.)	Whole blood July 31, 2015 (initial issuance) January 30, 2019 (amended) October 10, 2019 (revoked) Cadaveric oral fluid March 4, 2016 (initial issuance) September 26, 2016 (reissuance) February 1, 2019 (amended)

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