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United States Regulatory Updates

Association of Medical Diagnostics Manufacturers 2022 Annual Meeting – April 27, 2022

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Discussion Topics

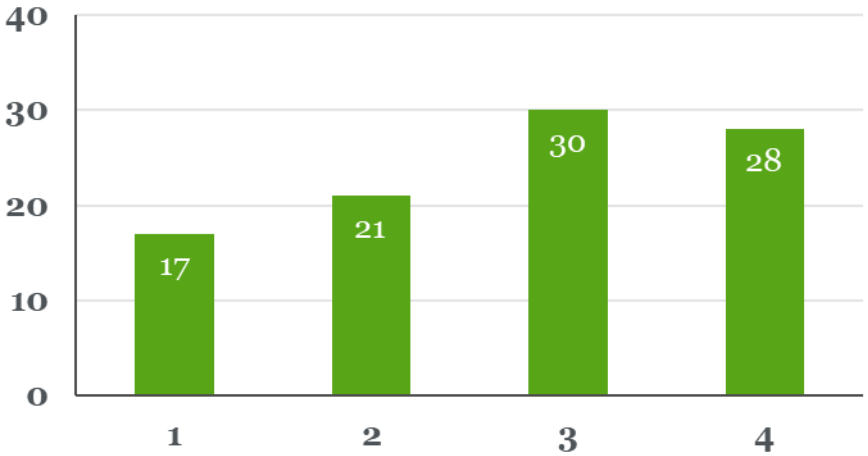
- Impact of COVID-19 Pandemic
- Laboratory Developed Tests (LDT)
- Companion Diagnostic Tests (CDx)
- Multi-Cancer Early Detection (MCED) Tests
- Tests powered by Artificial Intelligence / Machine Learning

COVID-19 EUAs

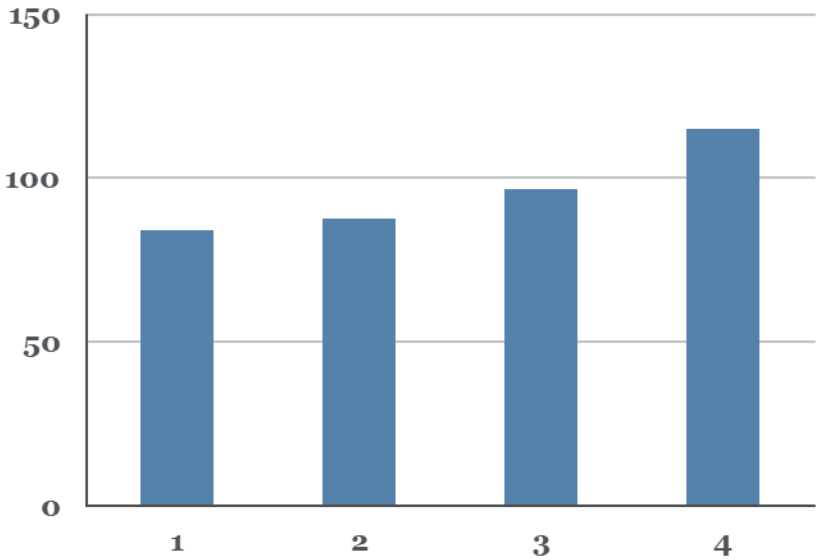
- Since the declaration of Public Health Emergency by HHS, FDA has received and reviewed thousands of EUA applications, with a significant portion of them being diagnostic or serology tests for SARS-CoV-2 reviewed by OHT7/OIR
- EUA applications are reviewed based on prioritizing significant public health benefits (such as test volume), as determined by FDA
- At the current stage in the pandemic, FDA stated that the agency will prioritize diagnostic tests that will "significantly increase testing capacity and accessibility", and serology assessments with "quantitative and neutralizing antibody tests that promote an increased understanding of immune responses to SARS-CoV-2"
  - To be prioritized, the EUA requestor should indicate the ability to scale up manufacturing capacity shortly after authorization (e.g., a manufacturing capacity of ≥500,000 tests per week within 3 months of authorization),

Trends – PMA – OHT7

- Number of PMAs and Panel-Track Supplements filed with OHT7 were higher during the pandemic



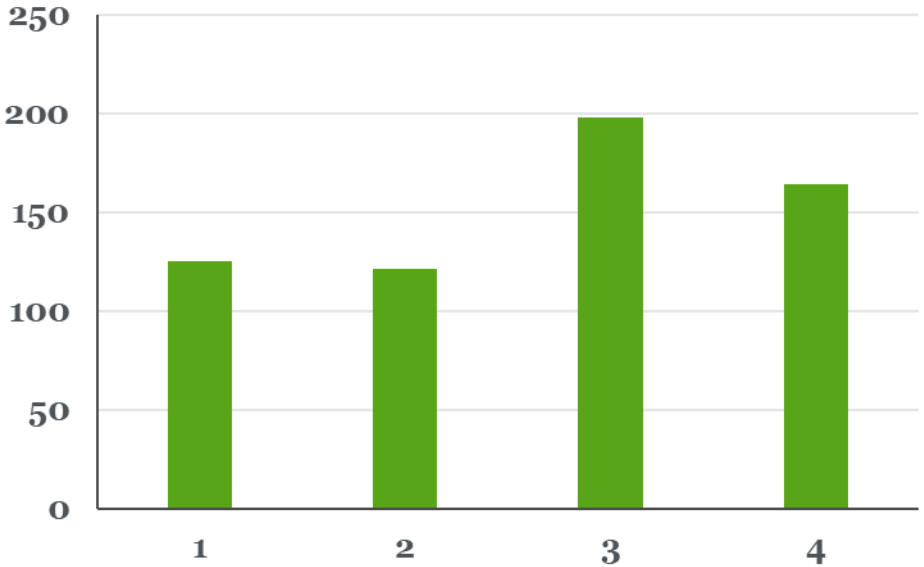
- OHT7 continued to review PMAs, with prolonged review time



* Only 17 of 28 PMAs submitted in FY 2021 have already received substantive interaction.
Data source: February 25, 2022 MDUFA IV Performance Report

Trends – De Novo – OHT7

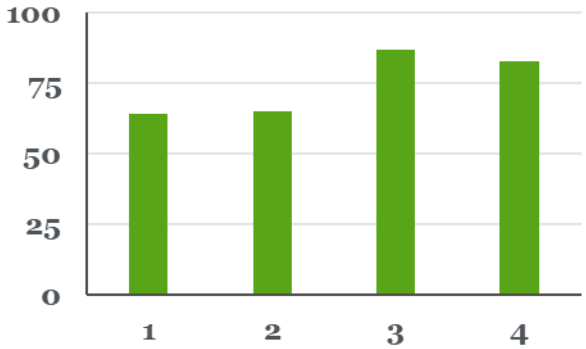
- De novo reclassification requests filed with OHT7 continue to be challenging, with approximately 50% success rates
- Review time for de novo requests has been longer due to COVID-19



* Only 3 of 15 de novo requests accepted in FY 2021 have already received MDUFA IV decisions
Data source: February 25, 2022 MDUFA IV Performance Report

Trends – 510(k) – OHT7

- Review time for 510(k) has also been significantly impacted by COVID-19, with more than 30% of submissions filed in FY 2021 did not meet the MDUFA performance goal
- 42 notifications filed in FY 2020 and 203 filed in FY 2021 are still pending MDUFA decisions



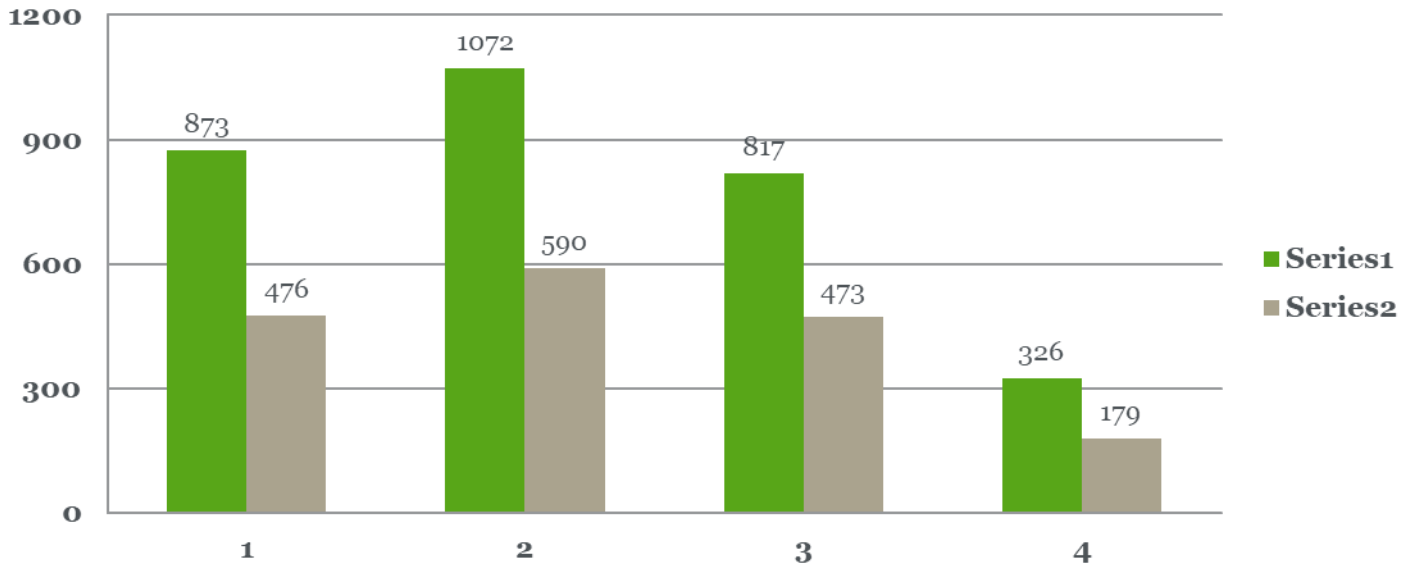
510(k) Performance Metric - Submissions Missing Performance Goal

Performance Metric	FY 2018	FY 2019	FY 2020	FY 2021
Number of Submissions that Missed the Goal	1	4	60	51
Mean FDA Days for Submissions that Missed the Goal	93.00	370.00	288.33	207.98

* Only 405 of 622 notifications accepted in FY 2021 have already received MDUFA IV decisions
Data source: February 25, 2022 MDUFA IV Performance Report

Trends – Pre-submissions – OHT7

- OHT7 has limited the number of pre-sub due to reallocation of resources to COVID-19 activities
- For most of FY 2021, OHT7 has declined to review pre-subs unless they are COVID-19 related or within certain prioritized categories (breakthrough designation, cancer diagnostic, etc.)



Data source: February 25, 2022 MDUFA IV Performance Report

Post-EUA Era

- The process of preparing for and winding down the Public Health Emergency appears to be underway
- FDA is clearing its dockets for EUAs, and is unwilling to accept new EUA applications if the product does not meet the prioritization criteria
- FDA is also moving toward regular marketing submissions (de novo and 510(k)) for COVID-19 tests
  - So far FDA has only de novo reclassified one COVID-19 test (BioFire Respiratory Panel 2.1), although other test developers have submitted marketing submissions
  - There will likely be an influx of regular marketing applications for the authorized EUAs
- Review timelines for non-COVID related submissions are still delayed, but are slowly getting back to normal

Opportunities from COVID-19 Tests

- New opportunities have emerged to leverage FDA's review of COVID-19 tests
- FDA gained significant experience with home tests, point-of-care tests, and tests involving telehealth
- FDA's technological questions and submission requirements under the EUA process may be indicative of likely regulatory standards for future marketing submissions of these types of tests for other analytes
- Novel technologies to detect SARS-CoV-2 pave the way for broader use of the technology
  - For example, FDA recently authorized the EUA for InspectIR COVID-19 Breathalyzer test
  - The review would shed light on future applications of breath tests for broader uses in detecting infectious microorganisms, clinical chemistry and immunological assessments, and monitoring metabolism where analytes can be shown to exist in respired breath

Update on LDTs

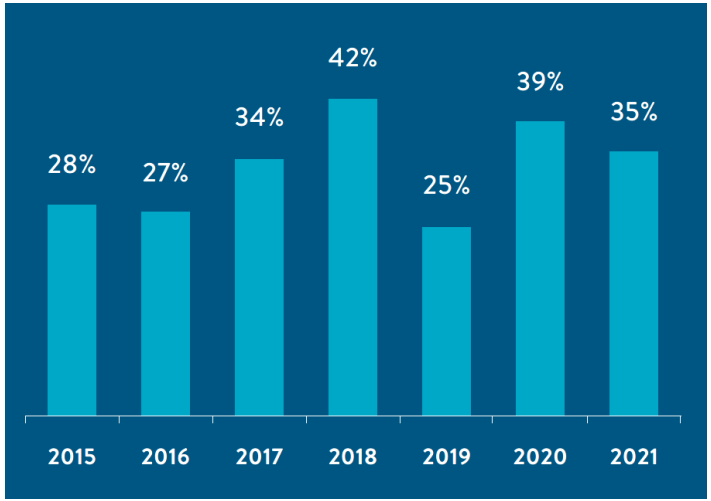
- On August 19, 2020, HHS announced the rescission of guidances and other FDA issuances concerning LDTs, preventing FDA from requiring premarket review of LDTs without notice and comment rule making
  - This included LDT COVID-19 tests
- HHS withdrew the policy on November 15, 2021, effectively restoring the LDT status quo prior to the 2020 policy
- Under FDA's revised EUA guidance that remains effective, FDA generally expects labs performing a COVID-19 LDT to obtain an EUA
  - For existing COVID-19 LDT tests, the Guidance states that the laboratory should either submit an EUA by January 14, 2022, or cease marketing by that date
  - For tests with a pending EUA submitted, if FDA declines to issue an EUA, the lab should cease offering the test within 15 calendar days after being notified by FDA
- FDA's guidance does not speak to non-COVID LDTs
  - It appears that FDA is still applying past enforcement discretion policies for existing LDTs

Update on LDT – Update on Legislation

- Verifying Accurate, Leading-edge IVCT Development (VALID) Act
  - Introduced by Senators Richard Burr (R-NC) and Michael Bennet (D-CO) on March 5, 2020, reintroduced on June 24, 2021
  - Would give FDA authority over LDTs by creating a risk-based regulatory framework for LDT tests
  - House Energy & Commerce oversight subcommittee Chair Diana DeGette (D-CO) and member Larry Bucshon (R-IN) co-sponsor the House version of the bill
- Verified Innovative Testing in American Laboratories (VITAL) Act
  - Introduced by Senator Rand Paul (R-KY) on March 5, 2020, reintroduced on May 18, 2021
  - Would take regulation of LDTs away from FDA and assign it exclusively to CMS
- On March 15, 2022, Senate health committee tabled discussion on Paul's bill
  - Health committee Chair Patty Murray (D-WA) indicated that she hopes to include the VALID Act discussion as part of the FDA user fee legislation

Companion Diagnostics

- IVDs play a key role in assessing a patient's specific state or disease condition, and in developing essential information in drug/biologic use
- Personalized medicines accounted for more than 25% of FDA approvals of new molecular entities (NMEs) for each of the last seven years



Source: Personalized Medicine Coalition

Companion Diagnostics

- Most companion diagnostic tests have been approved under the PMA pathway
  - Although CDx can be cleared in some cases via pathways other than a PMA, such as HDE, de novo, or 510(k)
- Some drugs involve a diagnostic test, but the test is not considered a true "companion"
- Genetic tests that are part of the standard of care for evaluation of a disorder or condition are not regarded as "companions"
- CDx tests have been accelerated by the Next Generation Sequencing technology
  - NGS allows rapid sequencing of large segments of individual's DNA, potentially even the entire genome
  - CDx based NGS technology can identify multiple variances and often can be used for multiple drugs, and even multiple diseases
    - E.g., FoundationOne CDx (P170019), Oncomine™ Dx (P160045)
  - Liquid biopsy has emerged as a prominent tool for CDx
    - E.g., FoundationOne Liquid CDx (P190032), Guardant360 CDx (P200010)

Companion Diagnostics

- In April 2020, FDA issued the guidance "*Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products*"
  - Certain CDx were cleared/approved based on clinical studies to evaluate the test in relation to a single oncology therapeutic product within a group of oncology therapeutic products
  - Under the guidance, the study data can be used to support the use of that same approved or cleared diagnostic test to the associated oncology therapeutic product group
- The specific group refers to the indication that the therapeutic products have in common which is captured in the therapeutic products' labeling (including sections other than the indications and usage section)
  - FDA noted that while the draft of the guidance and other CDx guidances uses the term "therapeutic class," the current draft uses "specific group of oncology therapeutic products" because depending on the indication, a specific group could be a therapeutic class, a subset of a class, or broader than a class
  - FDA provides in the guidance specific examples of how a group can be defined

Multi-Cancer Early Detection (MCED) Tests

- Multiple companies are developing cancer screening tests that can simultaneously detect different cancer types
  - E.g., Grail, Exact Sciences, Guardant Health, among others
- These tests typically use blood drawn from individuals (i.e., liquid biopsy)
- Given the enormous potential benefits and counter-balancing diagnostic risks of such tests, FDA will likely be cautious with reviewing and approving such tests
- There are several regulatory challenges for these MCED tests
  - Whether cancers with and without known screening tools should be treated differently
  - What performance goals (sensitivity and specificity) will FDA expect for each cancer type to support a favorable benefit-risk profile
  - What would be the performance requirements for tumor/tissue origin predication
  - What would be the standard of care diagnostic follow-up for currently unscreened cancers

Artificial Intelligence and Machine Learning

- AI/ML has been used in the development of many diagnostic devices
- A number of AI/ML based software products have been approved/cleared for reading radiological and ophthalmic images
- AI/ML is also utilized for in vitro diagnostic tools, in particular genetic testing
  - E.g., ArcherDx/Invitae, SOPHiA Genetics
  - Patients' genetic data, often from NGS, can be analyzed for variant detection, analysis, and interpretation
  - Other data, such as patients' EHR, can also feed into the algorithm
- It is unclear how such software/tests will be regulated by FDA

Final Thoughts

- COVID-19 may have long-lasting impact on FDA regulation of diagnostic products
- FDA regulatory initiatives relating to IVDs continue to be frequent, and may involve legislative and refocused regulatory initiatives
- New technologies continue to bring opportunities for developments as well as regulatory challenges
- Where possible, trade associations, professional associations, and interested parties should make their views known about the need to continue streamlining the IVD clearance/approval process

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