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United States IVD Regulatory Updates

Association of Medical Diagnostics Manufacturers 2023 Annual Meeting – April 19, 2023

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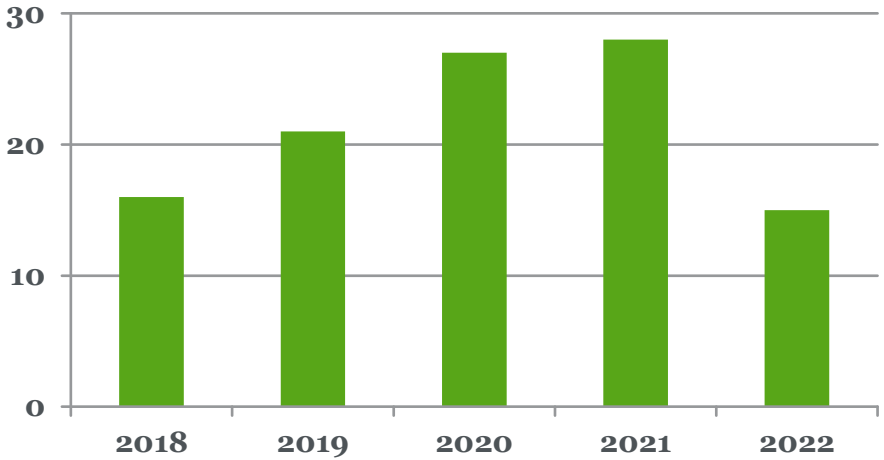
Discussion Topics

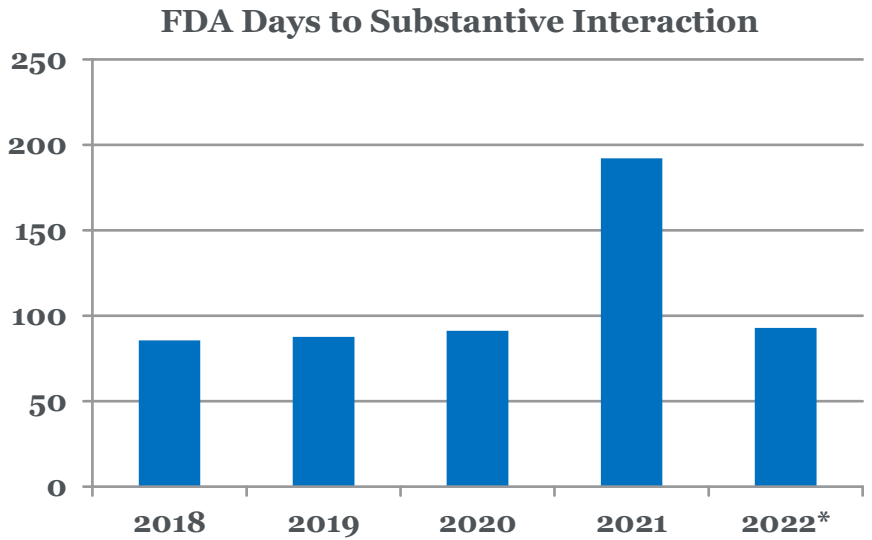
- Review Trends for FDA OHT7
- Post-EUA Transition
- LDT Enforcement - Update on VALID Act
- Companion Diagnostic Tests
- Emerging Issues
- Final Thoughts

Trends – PMA – OHT7

- Number of PMAs and Panel-Track Supplements filed with OHT7 were higher during the pandemic but went back to pre-pandemic level in FY2022



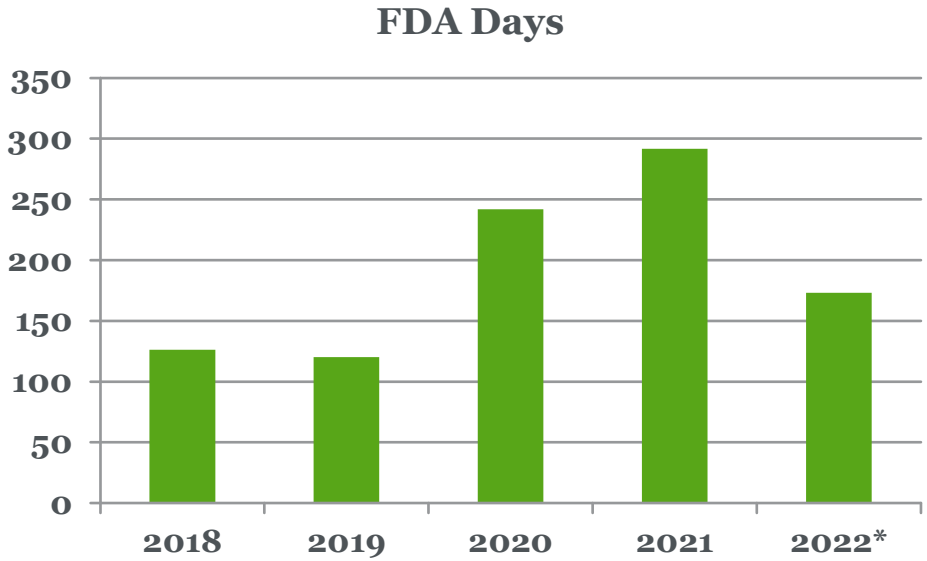
- PMA review time in OHT7 drops to normal after prolonged review during the pandemic



* 13 of 15 PMAs submitted in FY 2022 have already received substantive interaction.
Data source: March 1, 2023 MDUFA IV Performance Report

Trends – De Novo – OHT7

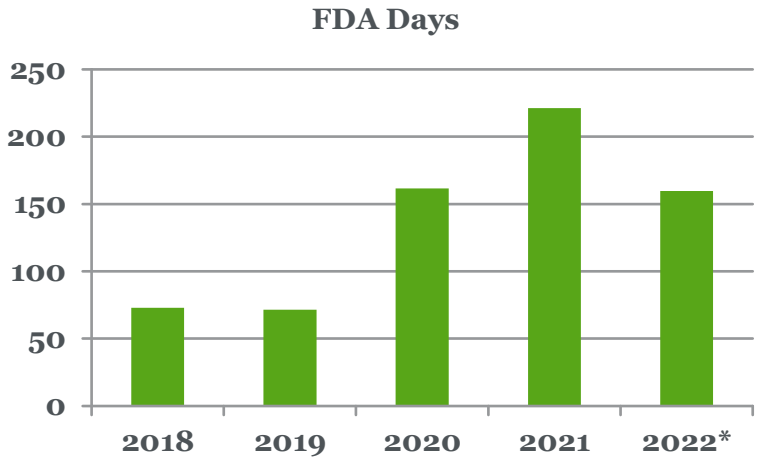
- De novo reclassification requests filed with OHT7 continue to be challenging, with approximately 50%-60% success rates
- Review time for de novo requests has been improved compared to the pandemic era



* Only 3 of 19 de novo requests accepted in FY 2022 have already received MDUFA IV decisions
Data source: March 1, 2023 MDUFA IV Performance Report

Trends – 510(k) – OHT7

- Review time for 510(k)s continued to be impacted by COVID-19, with more than 90% of submissions filed with OHT7 in FY 2022 did not meet the MDUFA performance goal
- 13% of the notifications filed in FY 2021 and 62% filed in FY 2022 are still pending MDUFA decisions as of the end of 2022



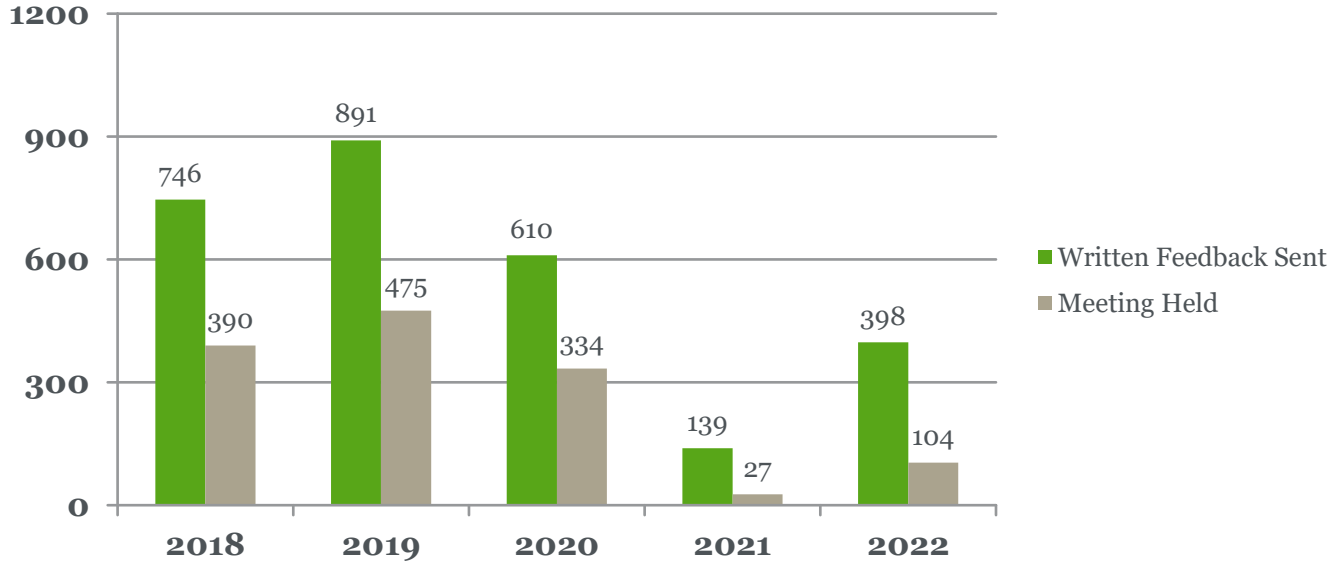
510(k) MDUFA IV Decision Performance Goal

Performance Metric	FY 2018	FY 2019	FY 2020	FY 2021	FY 2022
	95% Within 90 FDA Days	95% Within 90 FDA Days	95% Within 90 FDA Days	95% Within 90 FDA Days	95% Within 90 FDA Days
Current Performance Percent Within 90 FDA Days	99.57%	98.35%	59.90%	8.23%	6.60%

* Only 73 of 222 notifications accepted in FY 2022 have already received MDUFA IV decisions
Data source: March 1, 2023 MDUFA IV Performance Report

Trends – Pre-submissions – OHT7

- OHT7 has resumed the review of pre-submissions
- FDA continued to offer written feedback instead of meeting for some submissions due to limitation of resources



Data source: March 1, 2023 MDUFA IV Performance Report

Post-EUA Transition

- On March 27, 2023, FDA finalized two final guidance documents on the transitioning plan for devices authorized under EUA and devices subject to enforcement policies during the COVID-19 Public Health Emergency (PHE)
  - For EUA authorized devices, FDA confirms that EUAs will not be automatically terminated
    - Instead, authorized EUAs will remain in effect until FDA terminates the EUA declaration or otherwise revokes a specific EUA, even if the PHE declaration related to COVID-19 expires before then
  - FDA will not object to the continued distribution of devices after the EUA termination date if (1) the manufacturer has submitted a marketing submission that is accepted by FDA, and (2) FDA has not taken final action on the marketing submission

Post-EUA Transition

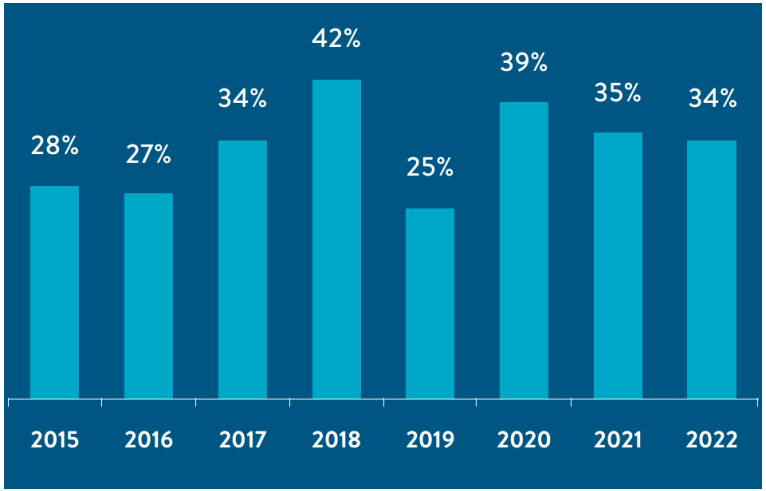
- For devices subject to enforcement policies, FDA confirms that the policies will remain in effect until 180 days after the end of the PHE
- Phased Transition Plan
  - Phase 1 (May 11, 2023): Adverse event reporting requirements
  - Phase 2 (August 9, 2023): Registration and listing requirements and requirements associated with reports of corrections and removals (21 C.F.R § 806)
  - Phase 3 (November 7, 2023): The enforcement discretion will no longer be in effect; however, FDA does not intend to object to continued distribution of devices if (1) the manufacturer has submitted a marketing submission that is accepted by FDA, and (2) FDA has not taken final action on the marketing submission
- FDA recommends manufacturers submit a "Transition Implementation Plan" with their marketing submissions
- Manufacturers should plan to submit the marketing application well in advance of the start of Phase 3 to avoid potential delays due to expected large influx of submissions

FDA and LDT Enforcement - Update on VALID Act

- After failures to secure legislative passage last year through FDASLA and the omnibus bill, the VALID Act has been revived
  - The March 30, 2023 bill has been reintroduced by U.S. Reps. Diana DeGette (D-CO) and Larry Bucshon (R-IN)
  - Notably, the proposed version of the new bill excludes some carveouts for academic medical centers that were included in a previous discussion draft of the bill
- FDA has indicated continued interest
  - Andi Fristedt, FDA deputy commissioner, noted earlier this year that the Pandemic and All-Hazards Preparedness Act (PAHPA) could be a pathway to get VALID passed this year
  - In March, Elizabeth Hillebrenner, associate director of CDRH, said that the agency is willing to regulate LDTs through administrative action, including the rulemaking process

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 eight years



Source: Personalized Medicine Coalition

Companion Diagnostics (cont'd)

- Most companion diagnostic tests have been approved under the PMA pathway

  Note: CDx can be cleared in some cases via pathways other than a PMA, such as HDE, de novo, or 510(k)

- Tests that identify a biomarker-defined subset of patients responding particularly well to a drug but are not pre-selecting patients receiving the drug are not companion diagnostics
  - "Complementary Diagnostics" – no formal definition or guidance yet
- Rapidly evolving biomarker landscape and novel technologies bring new regulatory challenges
  - 1 analyte, 1 drug, 1 indication: e.g., Her2/HercepTest
  - 1 analyte, many tests, many drugs, 1 indication: e.g., EGFR for NSCLC
  - 1 analyte, multiple tests, multiple drugs, multiple indications: e.g., various PD-L1 IHC tests
  - Multiple analyte, multiple tests, 1 drug, multiple indications: e.g., KIT, PDGFRB Tests for Gleevec
  - Single test, multiple analyte, multiple drugs, multiple indications: e.g., NGS Onco panels

Emerging Issues

- IVDs for home and OTC use
  - Over the past several years, there has been a rapid increase in point-of-care (POC), at-home, and over-the-counter (OTC) tests, and it is expected that these non-laboratory-based tests will continue to increase in the coming years
  - During the review of COVID-19 tests, FDA gained significant experience with home tests, point-of-care tests, and tests for over-the-counter use
    - 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
    - For example, FDA authorized the first OTC at-home diagnostic test that can differentiate and detect influenza A and B, and SARS-CoV-2
      - In the press release, FDA indicated that the Agency "strongly supports innovation in test development, and we are eager to continue advancing greater access to at-home infectious disease testing to best support public health needs"
    - Concerns about the safety and validity of home or lay user collection of certain sample types (e.g., oral fluids, throat swabs) may, however, present technological hurdles for specific kinds of IVDs

Emerging Issues (cont'd)

- Multi-Cancer Early Detection (MCED) Tests
  - Multiple companies have reported interest in developing cancer screening tests that can simultaneously detect different cancer types, even in asymptomatic, low risk patients
    - 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
  - 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

Emerging Issues (cont'd)

- Test based on microfluidic technology
  - Microfluidic medical devices require only small fluid volumes and offer the potential of shorter analysis times with better sensitivity
  - To prepare for evaluating these novel technologies, CDRH has created a Microfluidics Program
    - FDA is particularly interested in potential flow-related issues such as leakage, the presence of bubbles, clogging, and cross-contamination
    - There are no FDA-recognized standards or regulatory tools specific to microfluidics

Emerging Issues (cont'd)

- Artificial intelligence/machine learning and software-based diagnostics
  - 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
  - FDA issued a guidance document on Clinical Decision Support Software to clarify the types of CDS software functions that are excluded from the definition of device software functions that meet the definition of a device
    - The guidance also provides many examples of how FDA intends to consider different kinds of software functions

Final Thoughts

- Despite the end of PHE declaration, 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
- FDA's regulation of LDTs is likely to remain as an active issue
- 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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