Hogan Lovells

Overview of IVD Regulation by FDA

Association of Medical Diagnostics Manufacturers
2019 Annual Meeting
North Bethesda, Maryland

Jonathan Kahan
Hogan Lovells US, L.L.P
jonathan.kahan@hoganlovells.com
+1 (202) 637 5794

April 10, 2019

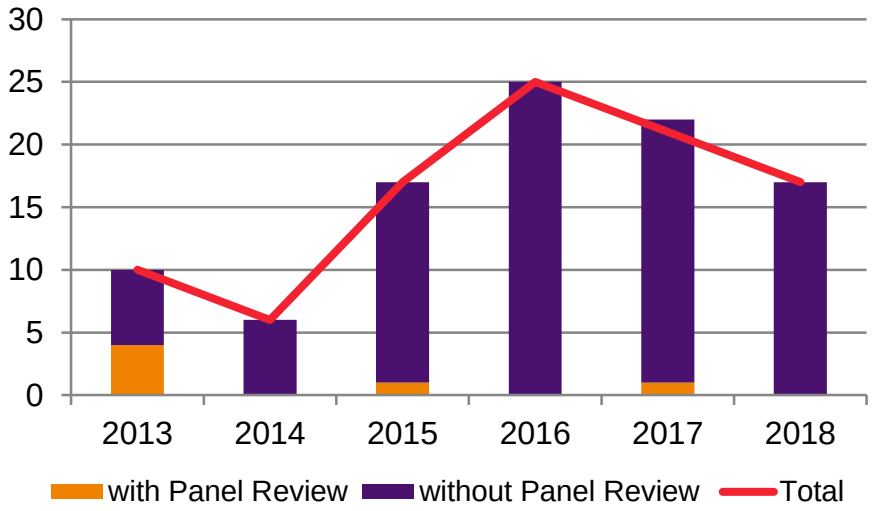
Discussion Topics

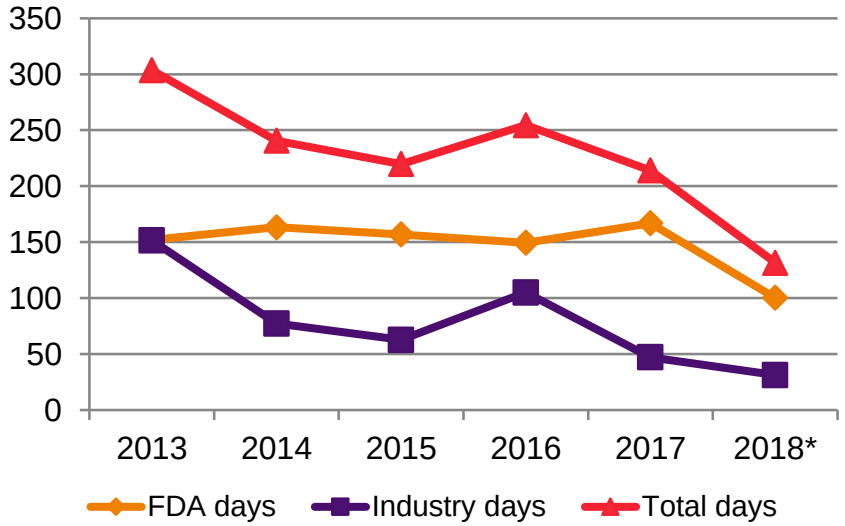
- Approval/Clearance Trends
- CDRH/OIR Updates
- Glucose Monitor and Delivery Devices
- Laboratory Developed Tests (LDT)
- Direct-to-Consumer (DTC) Tests
- Companion Diagnostic Tests (CDx)

Trends – PMA

- Number of PMAs and Panel-Track Supplements filed with OIR continued to decrease in FY 2018
- Already 8 PMA applications to OIR in Q1 FY 2019 (October–December, 2018)

- Time to MDUFA decision for PMAs filed with OIR without Panel Review
  - Decrease in total time and industry days in 2017 and again in 2018
    - Decrease in 2018 possibly because many are still pending
  - FDA days decreased in 2018





* Only 11 of 17 PMAs submitted in FY 2018 have already received MDUFA IV decisions.
Data source: December 14, 2018 MDUFA III Performance Report; February 22, 2019 MDUFA IV Performance Report

Trends – PMA

- Rate of Withdrawal increased in FY 2017 and FY 2018

OIR - CDRH – PMA Originals and Panel Track Supplements (without Panel Review)
Performance Metrics – Rate of Withdrawal and Not Approvable

Performance Metric	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
Number Filed	6	6	16	25	21	17
Number with MDUFA decision	6	6	16	25	18	11
Number of withdrawals	0	0	0	1	4	4
Number of Not Approvable	1	0	1	3	0	1
Rate of Withdrawals	0%	0%	0%	4.00%	22.22%	36.36%
Rate of Not Approvable	16.67%	0%	6.25%	12.00%	0%	9.09%

Data source: December 14, 2018 MDUFA III Performance Report; February 22, 2019 MDUFA IV Performance Report

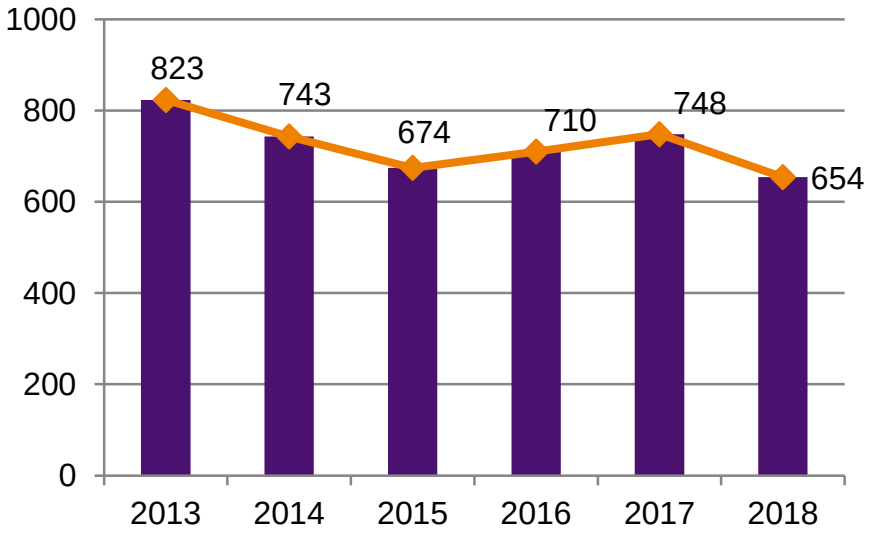
OIR PMA Approvals

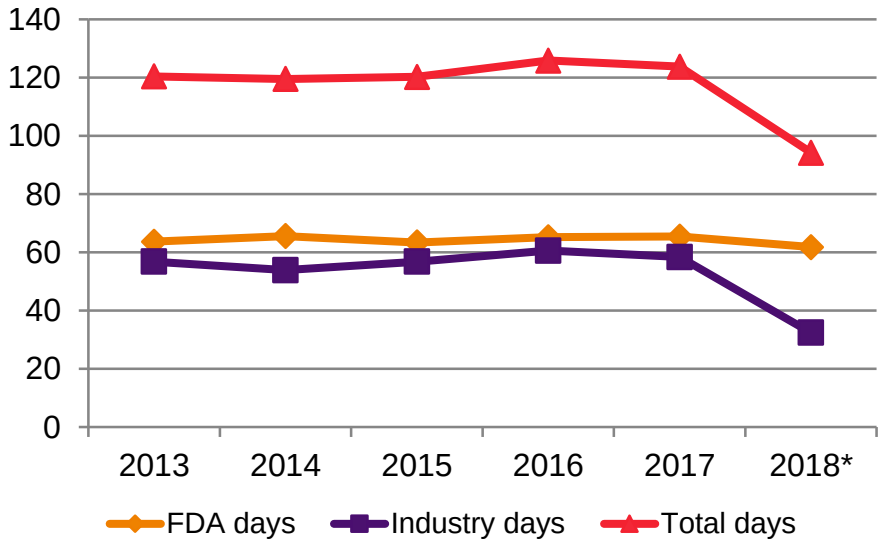
- Recent OIR approvals include glucose monitors, insulin pump, genetic tests, PSA test, test for risk of preterm birth
  - Sangia Total PSA Test (P170037) – Approved 1/31/2019
    - Point-of-care PSA test to quantitatively measure total PSA in whole blood as an aid in the detection of prostate cancer
  - Eversense Continuous Glucose Monitoring System (P160048) – Approved 6/21/2018
    - First FDA-approved continuous glucose monitoring (CGM) system with a fully implantable glucose sensor to detect glucose
  - T:slim X2 Insulin Pump With Basal-IQ Technology (P180008) – Approved 06/21/2018
    - First automated insulin delivery system approved for use by children as young as 6 years old, and first insulin pump designated as compatible with integrated continuous glucose monitoring (iCGM) devices
  - Abbott RealTime IDH1 (P170041) – Approved 7/26/2018
    - Companion diagnostic for AML drug TIBSOVO® (ivosidenib)
  - PartoSure Test (P160052) – Approved 04/27/2018
    - Qualitative test for markers in cervicovaginal secretions to assess the risk of spontaneous preterm delivery

Trends – 510(k)

- Number of 510(k)s accepted by OIR decreased in FY 2018
- 147 510(k)s accepted by OIR in Q1 FY 2019

- Time to MDUFA decision for 510(k)
  - Decrease in total time and industry days in 2017 possibly because many are still pending
  - FDA days relatively unchanged





* Only 536 of 654 510(k)s submitted in FY 2018 have already received MDUFA IV decisions
Data source: December 14, 2018 MDUFA III Performance Report; February 22, 2019 MDUFA IV Performance Report

Clearance Trends – De Novo

- De Novo Reclassification in OIR
  - FY 2013 – 8 reclassifications (4 direct; 4 post-NSE)
  - FY 2014 – 11 reclassifications (5 direct; 6 post-NSE)
  - FY 2015 – 3 reclassifications (3 direct; 0 post-NSE)
  - FY 2016 – 6 reclassifications (5 direct; 1 post-NSE)
  - FY 2017 – 13 reclassifications (12 direct; 1 post-NSE)
  - FY 2018 – 14 reclassifications (13 direct; 1 post-NSE)
- FDA started to report de novo review metrics in FY 2018 as the requirement of MDUFA IV
  - In FY 2018, OIR received 17 de novo applications – account for 30% of all de novo applications for CDRH
  - 10 OIR de novo applications have reached MDUFA IV decisions
    - Average FDA days: 117.6; average industry days: 83.2; average total days: 200.8
    - Industry days and total days will likely increase as the remaining applications reach decision
  - 5 de novo applications to OIR in Q1 FY 2019 (October – December 2019)

Recent OIR De Novo Reclassifications

- T:slim X2 Insulin Pump With Interoperable Technology (DEN180058) cleared 02/14/2019
  - First interoperable insulin pump intended to allow patients to customize treatment through their individual diabetes management devices
- 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports (DEN180028) cleared 10/31/2018
  - First direct-to-consumer test for detecting genetic variants that may be associated with medication metabolism
- Picoamh Elisa (DEN180004) cleared 10/24/2018
  - Diagnostic test to aid in the determination of menopausal status
- DreaMed Advisor Pro (DEN170043) cleared 6/12/2018
  - Software designed to provide continuous glucose monitoring
- Dexcom G6 Continuous Glucose Monitoring System (DEN170088) cleared 3/27/2018
  - First fully interoperable continuous glucose monitoring system

CDRH/OIR Updates

- New director of OIR: Tim Stenzel, MD, PhD
  - Duke's MD/PhD, pathology residency, and molecular genetics fellowship
  - 15 years in diagnostic industry
  - At this time, still unclear what direction OIR will move under his leadership
- CDRH reorganization does not affect OIR
- CDRH policy changes, however, will have impact on diagnostic products

CDRH/OIR Updates

- Modernizing the 510(k) pathway
  - FDA issued a statement on November 26, 2018 to lay out its intent for modernizing the 510(k) pathway
  - In January 2019, FDA issued a final guidance on what the Agency calls "Safety and Performance Pathway"
    - Instead of testing a new device in comparison to predicate devices, new device seeking clearance can be measured against a set of "objective, transparent and well validated safety and performance metrics"
  - Along with the new 510(k) pathway, FDA is looking ways to promote the use of more recent predicates based on the belief that "newer devices should be compared to the benefits and risks of more modern technology"
    - FDA seeks comment to its proposal to publicize 510(k)-cleared devices with predicate devices more than 10 years old
  - This may have unintended impact on diagnostic products that use old technologies
    - Old technology does not necessarily mean it is less reliable

Blood Glucose Monitor

- In the past two years, OIR has made a significant change in the monitoring of blood glucose level and the management of insulin for patients with diabetes, through the approval and authorization of multiple devices that automate the glucose monitoring and insulin delivery. Specifically
  - Dexcom G6 Continuous Glucose Monitoring System, which is a fully interoperable continuous glucose monitoring system, was downclassified (DEN170088) on 3/27/2018
  - DreaMed Advisor Pro CGM software was downclassified cleared 6/12/2018
  - Software FDA approved the Eversense Continuous Glucose Monitoring System (P160048) as a fully implantable glucose sensor
  - FDA also approved T:slim X2 Insulin Pump With Basal-IQ Technology (P180008), which was the first insulin pump designated as compatible with integrated iCGM devices
- These pumps, CGM, and software, when used together, can be used to allow automated insulin dosing (AID)

Update on LDT

- Diagnostic Accuracy and Innovation Act (DAIA)
  - Proposed by Representatives Larry Bucshon (R-IN) and Diana DeGette (D-CO)
  - Published as a working draft in 2017
  - Under the proposed legislation, the LDTs would be regulated not as medical devices, but as a new category, in vitro clinical tests (IVCTs)
  - On August 3, 2018, FDA provided the legislators more detailed recommendations for the DAIA. The so-called "*Technical Assistance*" (TA) document included specific proposed languages, some of which departed significantly from the draft bill

Update on LDT

- FDA's recommendations for DAIA
  - The definition for IVCTs was more expansive
    - In FDA's version, the definition would also include test platforms, collection kits, and software
  - Only included high- and low-risk test categories
  - Catch-all provision to require premarket review for tests that would otherwise be exempted but have a reasonable risk of causing death or serious adverse health consequences, or are lack of validation, or are offered with materially deceptive or fraudulent claims
  - Propose to adopt the precertification mechanism that was developed in the medical software space
    - A test developer could submit premarket review for one test that is representative of a group of tests using the same technology, reagents, or method. In two years following the precertification, the test developer will be able to launch new tests in that group without premarket review.
  - Allow more use of third-party reviewers
  - No new center inside the Agency for IVCTs

RUO products

- In the "*Technical Assistance*" document for DAIA, FDA did not include the same exemption for RUO products as it did for other non-clinical products.
  - RUO products may only be exempted from the labeling requirements and performance standards
  - The document also states that FDA should modify the applicable regulations as needed.
  - As such, it is unclear whether FDA will change its current position regarding RUOs

DTC Testing

- Despite FDA's heightened scrutiny over Direct-to-Consumer testing in the past years, recently FDA has not issued new warning letters with regard to DTC promotion
  - No warning letter of such type was issued during the past two years
- In addition, FDA has authorized more DTC tests to come to market, including 23andme's pharmacogenetic test (DEN180028, approved 10/31/2018)
- On the next day, FDA issued a safety communication to warn against the use of many genetic tests with unapproved claims to predict patient response to specific medications

Next Generation Sequencing

- Allows rapid sequencing of large segments of individual's DNA, potentially even the entire genome
- A single NGS test can identify thousands or millions of genetic variances, in contrast to traditional laboratory tests that identify a single or a limited number of variances
- FDA believes that NGS technology can accelerate personalized medicine

NGS Guidance

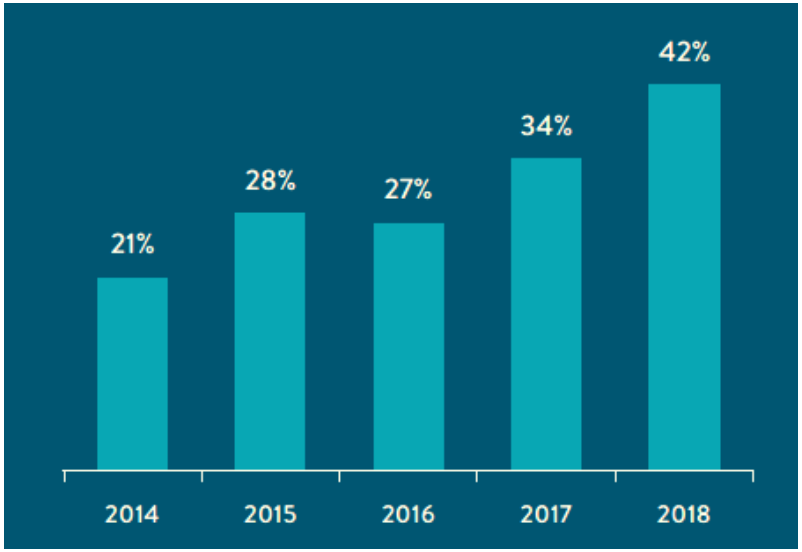
- In 2016, FDA issued two draft guidance documents on the oversight of NGS-based IVD tests
  - First guidance: Use of Standards in FDA's Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases
  - Second guidance: Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics
- The two guidance documents were finalized on April 13, 2018

Personalized Medicine

- Expanding knowledge in the areas of genomics and proteomics provides opportunities for:
  - Development of novel therapies
  - Designing and managing more effectively the clinical evaluation of therapeutic products (drugs and biologics)
  - Improving the use of existing therapeutics
  - Targeting treatment, taking into consideration a patient's genomic profile or their specific molecular characteristics related to a disease

Personalized Medicine

- IVDs will play a key role in assessing a patient's specific state or disease condition, and in developing essential information in drug/biologic use
- In 2018, for the second year in a row, personalized medicines accounted for more than 30 percent of all new molecular entities (NMEs) approved by FDA



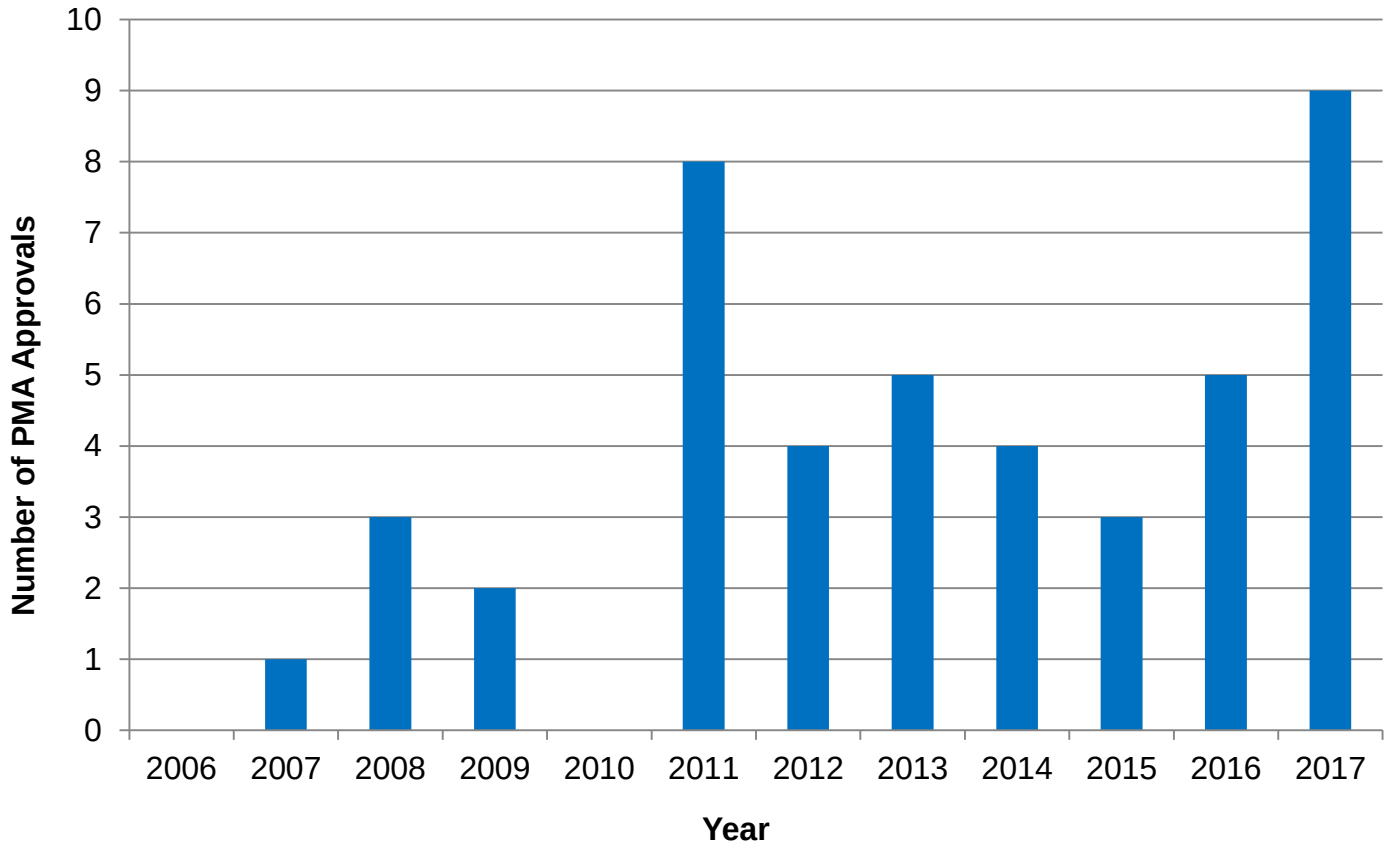
Source: Personalized Medicine Coalition

Companion Diagnostics

- 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”
- These tests can be cleared in some cases via pathways other than a PMA

Approval Trend for Companion Diagnostics

- There were 40 PMA companion diagnostic approvals, one clearance via the de novo process, one 510(k) clearance, and 2 HDE approvals between 2007 and 2017



Companion Diagnostics

- In December 2018, FDA issued the guidance "*Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group or Class 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 class of oncology therapeutic products
  - Under the draft 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 class
  - Some developers are concerned that the proposal would disincentivize the development of new test if an existing test applies to the entire class
  - Further clarification and examples would be needed

Issues Facing the IVD Industry

- LDT and DTC
  - Legislation activity around DAIA
  - Instead of enforcement actions, FDA appears to encourage DTC test developers to seek FDA review
- RUO product
  - Uncertainty on which direction FDA will head to with regard to RUO products
- NGS guidance
  - The guidance documents laid out the new approaches FDA will take for the premarket regulation of NGS-based tests
  - How FDA would implement those approaches is yet to be seen
- Emerging technologies
  - Novel sample types (e.g., liquid biopsy), SaMD, etc.

Final Thoughts

- FDA regulatory initiatives relating to IVDs continue to be frequent, increasing in number, and may involve legislative and refocused regulatory initiatives
- Manufacturers, laboratories, and physicians should try to keep abreast of new developments
- 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
- Agency feedback and open communication a must

www.hoganlovells.com

Hogan Lovells has offices in:

Abu Dhabi	Caracas	Ho Chi Minh City	Moscow	San Francisco
Alicante	Chicago	Hong Kong	Munich	Shanghai
Amsterdam	Colorado Springs	Houston	New York	Silicon Valley
Baltimore	Denver	Jeddah*	Northern Virginia	Singapore
Beijing	Dubai	London	Paris	Tokyo
Berlin	Dusseldorf	Los Angeles	Philadelphia	Warsaw
Boulder	Frankfurt	Madrid	Prague	Washington DC
Brussels	Hamburg	Miami	Riyadh*	Zagreb*
Budapest*	Hanoi	Milan	Rome	

* Associated offices