Genetic Testing in a Changing Regulatory Landscape

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Definition of a Diagnostic

- A product intended to be used to "diagnose a disease or other condition" is regulated as a device by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act.
- "Diagnose" also encompasses screening, monitoring, prognosis, etc.
- "Diagnose" has been given a broad interpretation by the courts.
- Testing for genetic traits would fall within the definition of a device.

Who Regulates?

- Office of In Vitro Diagnostic Safety and Effectiveness (OIVD), part of the Center for Devices and Radiological Health (CDRH), of the FDA regulates most in vitro diagnostics (IVDs).
- The Center for Biologic Evaluation and Research (CBER) regulates tests intended for use in blood banking and transfusion.
  - CBER also regulates HIV tests.
- Jurisdiction determined by intended use.

Intended Use: A Pivotal Concept

- "Intended Use" is governed by the objective intent of the company – 21 C.F.R. § 801.4.
- Intended use can determine whether premarket approval application (PMA), 510(k) premarket notification, or no FDA review.
  - PMAs are much more complex than 510(k)s.
- Intended use can determine how much data and what type, e.g., prospective large scale study for screening study vs. small retrospective study for monitoring.

Intended Use: A Pivotal Concept (cont'd.)

- Affects reimbursement.
- Needs to match clinical data and study population.
- Controls marketing claims for IVD once cleared/approved.

To sum up: Can determine whether PMA or 510(k), what data need to be collected (time and cost), reimbursement coverage, and what claim a company can make.

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In Vitro Diagnostics: Routes to the Market

- Thus far, only a handful of genetic tests have gone through the FDA process.
- Process is the same for genetic tests as any other test.
  - Premarket Approval Application (PMA)
  - 510(k) premarket notification
  - De Novo Reclassification
  - Investigational Use Only
  - Research Use Only
  - Laboratory Developed Tests

Getting FDA Feedback

- It is very important for companies to know what data to submit in an application.
- Some applications are routine, and no prior contact is necessary.
  - Well-defined, recent predicate device.
  - FDA has issued a guidance document.
- For novel products, FDA feedback can be very helpful to the company.
  - Obtained through a “pre-IDE” submission.
  - Do not have to actually submit an investigational device exemption (IDE) application to have a meeting.
- Data requirements have changed over time.

FDA Classification Scheme

- Level of regulation linked to product risk.
- Class I – low risk.
  - 510(k) generally not needed; may be exempt from Good Manufacturing Practice (GMP) regulation.
  - Example: Equine encephalomyelitis virus serological reagents.
- Class II – moderate risk.
  - Usually subject to 510(k) and Good Manufacturing Practice.
  - Example: Glucose.
  - May also need to meet special controls.
- Class III – highest risk.
  - PMA required.
  - Example: Human Papilloma Virus.

510(k) Premarket Notification

- Most common route to market with new assay.
- Need to show "substantial equivalence" to a "predicate device."
  - Predicate devices on the market before May 28, 1976 or cleared by FDA through a 510(k).
  - PMA approved device cannot be a predicate device for a 510(k), unless reclassified to Class II or I.

510(k) Premarket Notification (cont'd.)

- Substantial equivalence.
  - Same intended use, though FDA has some latitude in applying requirement.
- Same technology, or technological differences do not raise different issues of safety or effectiveness.
  - Typically, novel technology does not preclude 510(k) clearance. This has been helpful because of all the new technologies.
- Clinical data will be required for new types of assay.
- Laboratory test data, e.g., reproducibility of results using some samples in different laboratories, will be required.

510(k) Premarket Notification (cont'd.)

- FDA can find substantially equivalent, allowing IVD to be marketed.
- Can find 510(k) Not Substantially Equivalent, i.e., reject it.
- Ask for more information.
- 90 days per review cycle.
- Delays or data requests can become very costly.

De Novo Classification

- Some low or moderate risk devices lack predicate device.
- For these products, FDA can use de novo classification process.
  - Company submits 510(k)
  - Found Not Substantially Equivalent
  - Then submit petition for de novo classification
  - FDA can then approve the device
  - FDA will issue special controls guidance document
- FDA has used de novo process fairly frequently, e.g., circulating tumor cells for breast cancer and the newly cleared ovarian cancer test.
- Subsequent products can use 510(k) process.
- A good tool for some innovative products.

Premarket Approval Application

- Requires clinical data.
- Voluminous submission.
- 180 day review cycle.
- Advisory panel for at least the first submission for that type of assay.
- Pre-approval GMP inspection.
- FDA typically monitors study sites.
- More costly than 510(k)s and generally takes longer.
- Once obtain approval, harder to make changes to product or labeling.
- In general, 510(k) route is preferred.
- For some IVDs, and particularly for smaller markets, a PMA may not be economically viable.

Investigational Use Only (IUO)

- IUO products are intended for use in clinical investigations.
- Vehicle for generating clinical data to support marketing application.
- Manufacturer can charge for IUO products within limits.
- Product must be labeled as IUO.
- Manufacturer needs to receive some data back from investigators.

Investigational Use Only (IUO)
(cont'd.)

- Generally, FDA approval not needed to begin study for IVD.
  - Typically will need approval from an institutional review board for prospective studies, and possibly for retrospective.
  - May need to obtain patient informed consent, although "anonymized" banked specimens can often be used.

Research Use Only (RUO)

- RUO products are intended for use in basic research or to identify a potential clinical application.
- Cannot claim safe, effective, or has diagnostic utility.
- Manufacturer can charge for RUO products.
- No need for manufacturer to collect data.
- Exempt from GMPs.

Laboratory Developed Tests (LDTs)

- LDTs pre-date FDA regulation of devices.
- FDA first said it could regulate LDTs in 1992.
- According to FDA, all LDTs are medical devices and subject to full device regulation.
- FDA did not seek to exercise power until a few years ago.
- Exercising it more frequently, e.g., 2008 Warning Letter to LabCorp regarding OvaSure saying its test was not truly an LDT.
  - Letters to laboratories regarding direct access testing for patients.
  - Letters regarding H1N1 testing
  - Asserting jurisdiction more frequently over individual tests.
- Issue: How much work does a lab need to do for a test to qualify as LDT.

Laboratory Developed Tests (LDTs) (cont'd.)

- Historically, laboratories did not need to consider FDA regulation – those days are over.
  - Affects ability of IVD companies to use LDTs as initial avenue for entering market.
  - Has had an impact on access to funding.
- Vast majority of genetic tests are LDTs.
- Overwhelming majority of laboratory tests still not being regulated by FDA.
  - Could change with new legislation.
  - Genentech's December 5, 2008 citizen petition asked FDA to actively regulate LDTs "intended for use in drug or biologic therapeutic decision making."
- Area in a state of flux.

In Vitro Diagnostic Multivariate Index Assays (IVDMIAs)

- FDA draft guidance proposes regulating IVDMIAs as devices, which require clearance or approval.
- IVDMIAs take multiple measurements and provide a score.
- Considerable opposition to concept, e.g., based on technology, not risk; ambiguous terms.
- Current status?

Conclusion

- IVDs represent a large and growing industry.
- Complex, evolving regulatory environment.
- Regulatory uncertainty exists, and predictability is elusive.

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