NGS related HIV Efforts in CBER

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FDA Disclaimer
My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.”
Responsibility of HIV Test Regulation

• The Center for Biologics Evaluation and Research (CBER) within the FDA is responsible for regulating all human retroviral tests, including those for HIV according to FDA Inter-center agreement of 1991.
• In CBER, the Division of Emerging and Transfusion Transmitted Diseases (DETTD) in the Office of Blood Research and Review (OBRR) is responsible for review and approval of all in vitro tests for HIV:
  • blood donor screening tests and diagnostic assays including OTC
  • viral load, drug resistance, tropism.
• Our laboratory, LMV in DETTD
  • participates in the review and approval of these HIV tests
  • performs research on HIV diagnostics including emerging technologies for HIV characterization, e.g. Next Generation Sequencing (NGS)
  • develops reference panels for evaluation of tests and criteria for approval of assays.
NGS for HIV characterization

- Test manufacturers are now using NGS for HIV genotyping and other applications.
- NGS based multi-pathogen detection assays are being developed for potential use in donor testing and diagnostics.
- There is a need to understand scientific and regulatory issues involved with NGS as well as the complex bioinformatics used for interpretation of results.
- LMV in DETTD is performing research on NGS for full length HIV characterization to study HIV genetic diversity, drug resistance and tropism.
- Knowledge gained through this research will help CBER with review of future submissions for HIV/NGS diagnostics and NGS based donor screening tests.
• All HIV diagnostics and viral load assays are currently approved as Class III devices requiring pre-market approval.

• Sanger sequencing based HIV drug resistance assays were reviewed and cleared by CBER as Class II 510(k)s: an Example of Down-Regulation.

• The assays were intended for use in detecting HIV genomic mutations that confer resistance to specific antiretroviral drugs, as an aid in monitoring and treating HIV infection.

• The 510(k) for the first HIV drug resistance genotyping assay was cleared in 2002.
Device Classification (860)

- **Class I**
  - General controls are sufficient to provide reasonable assurance of the safety and effectiveness of the device

- **Class II**
  - General controls alone are insufficient to provide reasonable assurance of safety and effectiveness and there is sufficient information to establish special controls (510K)

- **Class III**
  - Insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness
  - Premarket approval is required
Class II Special Controls Guidance

Studies to be Performed

- Performance of the interpretive algorithm
  - Validation of phenotypes predicted by genotyping: in vitro studies
  - Verification of phenotypes predicted by genotyping: in vivo studies
Studies to be Performed (1)

- Performance of the assay in determining genotype
  - Analytical sensitivity, range of detectability, precision, reproducibility, lot acceptance testing, specificity, assay interference, reagent characterization, specimen collection and handling conditions

- Stability

- Assay performance on clinical specimens
  - Sensitivity, specificity, reproducibility

- Clinical trial data showing performance as an aid in treatment of subjects with HIV
  - Not necessary if complete analytical studies performed
Additional Considerations

- Design controls
- Statistical methods
- Devices used to generate data for submission
- Instruments and software
- Product modification
- Labeling
- Special 510(k) to update interpretation algorithms
  - New information on resistance mutations
Additional Information

  

- Class II Special Controls Guidance Document: In Vitro HIV Drug Resistance Genotype Assay
  
Path forward

• Test developers should consider using the Pre-submission program at CBER to get feedback from Agency regarding development of NGS based HIV diagnostics.

• Please contact the Regulatory Project Staff in OBRR regarding questions as to the regulatory requirements for FDA approval of tests using NGS for HIV genotyping and diagnostics.
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