Molecular-Based Devices (HEA, HLA, HNA and HPA)

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Overview

- Molecular Erythrocyte Antigen Typing Devices
  - Previously Approved Devices
  - Format of Modular PMA submissions
  - Major PMA Content
  - Quality Control (QC) Material
  - Modifications to an Approved PMA
- HLA, HPA and HNA Typing Devices
  - 510(k) submission content

Molecular Erythrocyte Antigen Typing Devices

Previously Approved Devices

- Multiplex molecular assays
  - PreciseType™ HEA Molecular BeadChip Test: 36 blood group antigen phenotypes and a mutation in the beta-globin gene (hemoglobin S)
  - ID CORE XT™: 29 polymorphisms, 53 alleles and 37 antigens
- Submitted as modular PMAs

Format of Modular PMA submissions

- Suggested major content for each module
  - Module 1 – CMC
  - Module 2 – Non-clinical studies
  - Module 3 – Software (if applicable)
  - Module 4 (final Module) – Clinical studies, labeling

- Address the identified deficiencies before submitting the next module, or address them in the final module

Format of Modular PMA submissions (2)

- Include the following in the first module:
  - Intended Use
  - Instructions for Use
  - Device Description

- For the final module:
  - Notify FDA before submission
  - Include responses to all outstanding deficiencies
  - Provide any additional information required for a complete PMA submission

Traditional PMA

- Submit all PMA data at the same time, regardless of when testing is completed

- PMA review timeline:
  - 320 Days for submissions that require Advisory Committee input (PreciseType - Blood Products Advisory Committee meeting)
  - 180 Days for submissions that do not require Advisory Committee input (ID CORE XT)

CMC Information

- Include the following:
  - Detailed summary of device production
  - Device Master Record (DMR) of the subject device, such as
    - Production process specifications including the final manufacturing procedures (flow diagram)
    - Quality assurance procedures and specifications
    - Packaging and labeling specifications
    - Installation, maintenance, and servicing procedures and methods
  - Description of Facilities and Utilities

CMC Information (2)

- Validation lots
  - At least three distinct validation lots (produced using the final manufacturing procedures)
    - One lot manufactured using raw material near its expiration date

CMC Information (3)

- If the test kit component contains preservatives
  - Preservative effectiveness studies for applicable component
- If microbiologically controlled manufacturing
  - Provide bioburden limit, pre-filtration bioburden level (if applicable)
  - Microbial interference studies
  - In-process or release testing for bioburden
  - Level of microbial contamination in the facility during manufacturing

Non-clinical Studies

- Blood sample storage time before DNA extraction
- DNA sample preparation (DNA extraction methods)
- Purified DNA sample stability
- Assay Limit of Detection (LOD)
- Assay Guard Band
- Carryover/Cross Contamination

Non-clinical Studies (2)

- Interfering Substances
- Shipping
- Reagent stability including open-vial
- Cross Hybridization Studies
- Lot-to-lot Reproducibility Study
- Accuracy Study
- Submit any other non-clinical studies needed to demonstrate the device's performance

Multiplex Assay Considerations

- Submit information to support the prediction of each phenotype from polymorphism/genotype data
- Samples tested should cover as many primers/probes as possible and different genetic variants
- Determine number of invalid calls used to declare an entire test/sample invalid
- Determine negative control run validity criteria

Accuracy Study Considerations

- Use pre-selected samples to demonstrate that the test can accurately identify the phenotypes listed in the intended use statement
- Describe how the samples were well-characterized
  - Characterize antigen phenotypes using FDA-licensed reagents or approved molecular tests if available
  - Otherwise, you may predict phenotypes using bidirectional sequencing

Accuracy Study Considerations (2)

- Include comparison to bidirectional sequencing or an FDA-approved molecular test if reporting polymorphisms/genotypes as final results
- If DNA sequencing is used to characterize samples or to investigate discrepancies
  - Use independently designed and validated primers for sequencing
  - Independently convert the sequencing results to phenotypes

Accuracy Study Considerations (3)

- Internal accuracy study
  - Acceptance criteria:
    - The lower bound of the one-sided 95% confidence interval (CI) should be > 99%
    - For rare phenotypes with fewer than 299 samples – 100% agreement by point estimate
  - Analyze data and apply the criteria to each antigen phenotype (and genotype, if claimed), not to a blood group system

DNA Concentration and Quality

- Submit recommended nominal DNA concentration for assay based on LOD
  - May use the nominal DNA concentration rather than the entire range for performance studies
- DNA quality consideration
  - May accept commonly recommended OD A260/A280 ratios for well-established technologies
  - A much wider range should be supported by adequate data

Assay Guard Band Studies

- Comprehensively validate assay parameters outlined in the Instructions for Use
  - May test together with the assay QC material to demonstrate the QC material is sensitive to anticipated analytical variables

Shipping, Drop Test and Stability Studies

- Use actual packaging configurations
- Challenge the worst case shipping conditions
- Show functionality of the kits, not just visual inspection of the kits

Software

- Complete all development and software testing before submitting the PMA software module
- Delineate limitations of the software in the User Manual
- Recommend that no results are provided for invalid runs or invalid test samples

Software (2)

- *Guidance for Industry and FDA Staff, Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* issued May 11, 2005
- *General Principles of Software Validation* issued January 11, 2002
- *Guidance for Industry and Food and Drug Administration Staff Design Considerations and Premarket Submission Recommendations for Interoperable Medical Devices* issued September 6, 2017
- *Guidance for Industry and FDA Staff, Guidance for the Content of Premarket Submissions for Management of Cybersecurity in Medical Devices* issued October 2, 2014

Clinical Comparison Studies

- At least three sites representing US population
- Test random samples
  - Could be leftover de-identified samples
  - Collected from donors and patients
- Use at least two reagent lots
- Compare to phenotype results for antigens if FDA-licensed regents or approved molecular tests are available; otherwise, compare to phenotype results predicted from bidirectional sequencing
- For genotype results, compare to results from FDA approved test or bidirectional sequencing

Clinical Comparison Studies (2)

- Use a pre-defined algorithm to resolve discrepancies
- Investigate and report any discrepancies
- Conduct the study in accordance with the study protocol; report any study protocol deviations
- Calculate all agreement using initial test results prior to discrepancy resolution
- Apply acceptance criteria to each antigen phenotype (and genotype, if applicable)

Precision Study (Reproducibility and Repeatability)

- Test panel of well-characterized DNA samples
  - The samples should cover different types of genetic variants targeted by the assay, and most, if not all, phenotypes
- Use at least three sites
- Capture possible sources of variation including within run, run-to-run, lot-to-lot, day-to-day, operator-to-operator, instrument-to-instrument and site-to-site variation
- Lot-to-lot study can be performed at an internal site
- Investigate and report any disagreement

Labeling

- 21 CFR 809.10 for labeling requirements
  - Intended Use – include the polymorphisms, alleles and antigens that the device interrogates and reports as final results
  - Limitations of the procedure – discuss the genetic variants that are not targeted by the test but known to affect phenotype prediction
- Include labeling of other components such as user manuals
- Subject to the requirements of the Unique Device Identification (UDI) Rule (21 CFR 801.20)

Quality Control Material

- If not human gDNA (e.g., plasmid DNA)
  - Demonstrate the QC material is as sensitive as actual human gDNA to anticipated analytical variables
- Limitation: Not intended to monitor the DNA extraction
- FDA guidance: *Assayed and Unassayed Quality Control Material*

  https://www.fda.gov/media/71538/download

Device Modifications After Initial PMA Approval

- FDA guidance: *Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process*

  https://www.fda.gov/media/81431/download

  - Traditional PMA
  - 180 Day supplement
  - 30-Day Notice
  - Panel-Track supplement
  - Real-Time supplement
  - Special supplement/CBE
- See 21 CFR 814.39
- Annual Report: changes that do not affect device's safety or effectiveness

Device Modifications: New Molecular Variants

- Manufacturers may become aware of new molecular variants after approval for example, through feedback from customers or review of literature
- Applicable package insert changes should be incorporated
- New molecular variants or markers should be evaluated through the design and development process, and potentially incorporated into the device following FDA review and approval

HLA, HPA and HNA Typing Devices

HLA, HPA and HNA Typing Devices

- Require 510(k) submission
- General recommendations for HLA 510(k) submission are in FDA guidance
  - *Recommendations for Premarket Notification (510(k)) Submissions for Nucleic Acid-Based Human Leukocyte Antigen (HLA) Test Kits Used for Matching of Donors and Recipients in Transfusion and Transplantation*

    https://www.fda.gov/media/87197/download
- Some recommendations in the HLA device guidance may apply to HPA and HNA assays

HLA Genotyping Tests

- Submit an internal accuracy study tested with nationally or internationally recognized well-characterized samples
  - For ambiguous typing results, concordance is determined if one pair alleles is the same as the known result
- For precision study, the list of ambiguities (if any) should be compared
- Submit a traditional 510(k) for a new test kit locus

Summary

- Molecular erythrocyte antigen typing test: modular PMA or traditional PMA
- Major content of PMA: CMC, non-clinical studies, software, clinical studies and labeling
- QC material: sensitive to anticipated analytical variables
- Monitor new variants and make changes to an approved test as needed
- HLA, HNA and HPA typing devices: 510(k)

Thanks!

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