Clinical Studies Review for Donor Blood Screening Devices

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July 15, 2019

Outline

- Interactions with FDA for Clinical Study Design
- Clinical Sensitivity, Specificity and Reproducibility
- Assay Migration

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Numerous Opportunities are Available for Interactions with FDA on Study Design

- Meant to be dynamic process throughout the product life cycle – used during product development, licensure & modifications
- Beneficial both to FDA and sponsor
- Set expectations, ensure understanding

Interactions with FDA (1)

INTERACT meeting or Informational Qsub: early development stage

- Early informal consult at device development phase
- Beneficial both to FDA and sponsor
  - FDA: learn sponsor's plans, new assays or technology
  - Sponsor: learn FDA's current thinking, new guidances
- No written feedback but open discussion
- Feedback not binding

Interactions with FDA (2)

Pre-Sub for clinical studies (Pre-IND): device is ready for clinical trial or validation

- Discussion on clinical study protocol
- Discuss detection algorithm
- New analyte
  - The high risk population has been defined
  - Regions of endemicity stratified if disease is regional
  - Detection gold standard has been established if there are no licensed assays
- Well-designed clinical trial - streamlines licensure process

Interactions with FDA (3)

IND: allows initiation of clinical investigation

FDA's expectations

- Complete package as discussed in IND presentation
- Human subjects are not exposed to an unreasonable and significant risk of illness or injury
- Sufficient information to assess the risks to the subjects of the proposed study
- Subjects are adequately informed
- Clinical investigators are qualified
- Timely response to additional information

FDA's deliverables

- Decision in 30 days
- Recommendations regarding study design to help study achieve its goals
- Issues relevant for future submissions, if applicable (future marketing application)
- Provide you written response with hold issues (also non-hold issues, if any)

Interactions with FDA (4)

BLA: clinical data reviewed for safety and effectiveness

- *Clinical studies results*
  - Sensitivity, specificity, reproducibility
  - Clinical protocols agreed at IND – anticipate no major issues
  - Aim to resolve issues interactively – expectation of timely response

- *Complete Response (CR) Letter*
  - Submission issue meeting – Discuss issues raised by FDA

Interactions with FDA (5)

Licensure

- *BLA supplement*
  - Request approval for device change or upgrade
  - Pre-submission – to discuss the intended change
  - May require a new IND

- *Assay migration*
  - Assay transfer may be from one approved, licensed, or cleared old system to a new system
  - May require a new IND
  - Strongly suggest pre-submission – to discuss study design

Clinical Study Design (1)

Review focus: clinical protocol (IND) and clinical data (BLA) support the Intended Use

- Qualitative performance* – reactive or non-reactive
- All claimed specimen types – serum, plasma, whole blood
- Validation of all test formats – individual/pooled specimens
- Validation of clinical use – disease/condition
- Validation of clinical purpose – screening/diagnosis
- Testing in target population – Whole Blood donors/Source Plasma donors/ cadaveric samples
- Testing performed at the site of intended use

** Some licensed supplemental tests (e.g., western blots) – negative, indeterminate, positive results*

Clinical Study Design (2)

Design & review considerations:

- Disease prevalence and endemicity
  - Regional (e.g., *Babesia*): testing covers regions of different endemicity & how is it defined
  - National (e.g., HIV): testing planned in geographically distinct population
  - Include high and low risk population
- Seasonality
  - Timing of the trial
- Testing algorithm
  - Approved/licensed test used for confirmation of reactive result; or resolution of discrepant result
  - New analyte when no FDA approved/licensed test is available; how is the unapproved test validated

Clinical Study Design (3)

- Analyte detected
  - Antigen/antibody immunoassay or Nucleic Acid Test (NAT)
  - For NAT: individual testing (ID-NAT)/minipool NAT (MP-NAT)
  - MP-NAT: pool deconstruction algorithm

- Deconstruction (deconvolution):
  - Resolution of the reactivity of a minipool by testing subpools (original or freshly made) or samples from individual donors that formed the minipool

Clinical Study Design (4)

Tips & common issues:

Changes made during the study

- CMC change, software change, cut-off change
- Provide rationale and justification
- Risk and impact analysis that change does not affect previous data
- Provide clinical protocol along with redline version of changes

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Clinical Sensitivity Study (1)

Design & review focus: assay detects "**True Positive**"

- Definition of true positive
  - Based on clinical truth or best available gold standard
  - FDA licensed assay/ Laboratory Developed Test (LDT) for new analyte
- Sample size
  - Sensitivity requirements for blood screening assays guide sample size
  - Precedent from licensed assays
    - HIV, HCV – 1,000 samples; HBV – 500 samples
  - New analytes – discuss with FDA before IND is submitted
- Testing in high risk population (disease prevalence $\geq$ 1%)

Clinical Specificity Study (1)

Design & review focus: assay detects "**True Negative**"

- Definition of true negative
  - Resolution algorithm for false positive
  - Protocol for donor follow up and recipient tracing

- Study usually conducted in a setting resembling that intended for use post-licensure
  - Samples from U.S. donor populations in geographically separate donor collection sites must be collected (if disease is regional – regions of high, medium & low endemicity)

Clinical Specificity Study (2)

- **Sample size**
- Disease prevalence and specificity requirements for blood screening assays guide sample size
- Precedent from licensed assays
  - Whole Blood donations: At least 10,000 individual specimens and/or 10,000 pools of the maximum pool size
  - Source Plasma donations: At least 1,000 pools at its claimed pool size
  - Considerations for other sample sizes should be discussed with FDA
- New analytes – discuss with FDA before IND is submitted

Reproducibility Study

Determination of how well the assay yields the same result

- Reproducibility vs precision
- Reproducibility panels - formulated with positive specimens below, near and above LODs
- Panels used to assess variations among the testing sites, instruments, days, operators and runs, and reagent lots

Clinical Studies

Tips & common issues:

- Multiple reagent lots not used in clinical studies

- Invalid run rate & data exclusion – Incomplete information
  - Document for each study report
  - Criteria and justification for excluding any data
  - Reasons if invalid rate is high
  - Intent to lower the invalid run rate

- Instrument errors
  - Document for each study, with details on type of errors
  - Depending on rate, discuss impact on instrument reliability
  - How is the issue addressed

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Assay Migration (1)

Least burdensome scientific and regulatory pathway for manufacturers to transfer a previously approved or licensed assay with full clinical data from an old system to a new system

May be used to validate the transfer of:

- Assay from manual system to an instrument platform
- Assay from semi-automated to a fully automated instrument system
- Assay from one instrument platform to another (new, improved, or different automation)

Assay Migration (2)

May apply if the following are unchanged:

- Intended Use
- Reagent and assay parameters (e.g., cut-off) except for minor differences (as incubation times) to optimize the assay on the new system
- Assay and system technologies: biochemical (as Ag-Ab interactions or DNA probe construct) and physical detection (as colorimetric or chemiluminescence) technologies should be unchanged from the old system

Note: Some assay technologies may not be good candidates - assays with relatively high imprecision near the cut-off

Assay Migration (3)

Regulatory outcome:

- Dependent if the acceptance criteria is met or not
- Significantly higher false positive or false negative rate – migration study failure

Study design - Assay Migration Studies for In Vitro Diagnostic Devices Guidance for Industry and FDA Staff April 2013

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assay-migration-studies-vitro-diagnostic-devices

Appendix I - Migration studies for blood donor screening assays

Assay Migration (4)

Serial migrations

System A (full clinical study) → System B (migration study)

Yes

System B (migration study) → System C (migration study)

No

System A (full clinical study) → System C (migration study)

Yes

Strong recommendation – discussion with FDA on proposed migration studies early in the product design phase

Recap

- Clinical study should demonstrate safety and effectiveness of device
- Clinical data should substantiate claims in intended use and package insert
- Each study report should discuss implications of data exclusions, deviations, instrument errors and provide impact analysis
- Justification and impact analysis for any changes to clinical protocol while clinical study in progress
- Use FDA's Q-Submission program – course correction is least burdensome when addressed early

Thanks!

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Urgent Use Blood Donor Screening Claim for an HIV Diagnostic test

When a traditional donor screening test is not available or its use is impractical

- Test should meet the following criteria:
  - Can detect both HIV-1 p24 antigen and antibody
  - Capable of providing a result within a relatively short time (approx. 1 hour)
  - Assay sensitivity is comparable to that of a licensed donor screening assay (>99.9%)
  - Specificity of the HIV Ag/Ab test should be at least 99%
- Not applicable to rapid and point of care HIV tests

Limited Supplemental Claim for a Donor Screening NAT (1)

History: When a donor screening serology tests (HIV antibody, HCV antibody and HBsAg) have repeatedly reactive (RR) result, this result must be confirmed using a more specific supplemental test

- Supplemental tests usually labor intensive and interpretation is subjective, requires skilled technicians
- Blood establishments approached FDA for an alternative. PHS blood working group recommended that NAT can be considered as a supplemental test
  - If RR on a serology assay, but non-reactive on NAT - further tested using a licensed supplemental test (e.g., WB, IFA)

Limited Supplemental Claim for a Donor Screening NAT (2)

- **Requirements for claim:**
  - Demonstrate that combination of a RR serology test and a reactive NAT is predictive of infection in the donor
  - Test RR samples with NAT and demonstrate that all individuals whose samples are reactive on the NAT are actually infected
  - A positive infection status for the donor may be proven by additional testing on the same sample (e.g., by a positive western blot for HIV) or by follow-up testing of the donor during the investigational studies

- **Regulatory outcome**:
  - Occurrence of false positives - claim not granted