In Vitro Diagnostic Testing for Direct Oral Anticoagulants- Premarket Review

Cardiac Safety Research Consortium

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Objectives

- Overview of the regulatory requirements for clearance of IVDs intended for coagulation testing in patients treated with DOACs
- Identify clinical circumstances/conditions where testing of DOACs anticoagulant activity or concentration would be relevant
- Understand limitations of assays used to monitor novel anticoagulants

FDA Regulated Uses of IVDs

- **Diagnosis** – Diagnose disease, identify, confirm or rule out a condition in symptomatic patients
- **Screening** – Intended use population includes individuals **without** signs or symptoms of disease
- **Monitoring, prognosis, prediction**

What kind of submission should be prepared?

Classification of IVD Devices

- Regulatory path determined using a risk-based approach
  - Class I: low likelihood of harm, most are 510(k) exempt
  - Class II: Premarket notification, 510(k)
  - Class III: High or unknown likelihood of harm or how to prevent harm is unknown – Premarket Approval (PMA)
- Classification (I, II, or III) depends on risk

Risk Depends on Intended Use

- Risk (and subsequently device classification and submission type) is inherently tied to the claimed Intended Use of a device
- Level of FDA review and type of studies requested generally depend on the IU claims

Terminology

Class	Premarket Submission	Success Metric	Action/Decision
III	PMA	Safety and Effectiveness	Approval
II	510(k)	Substantial Equivalence	Clearance
I	None (if exempt)		
II (De novo)	510(k)	Safety and Effectiveness	Clearance

FDA Regulatory Considerations

- Intended Use/Indications for Use - who should be tested?
- What clinical evidence is needed to support claims?
- Can effectiveness of test system be reliably determined from data/information provided?
- What are the analytical performance requirements?
- Is it necessary to restrict use of test system – settings/conditions?
- How is the device output to be clinically interpreted?

Review Elements of IVD Submissions

- **Intended Use: how and by whom the device is to be used**
  - Measurand (analyte, biological activity)
  - Testing population
  - Quantitative, Semi-quantitative or Qualitative
  - Specimen type(s)
  - Conditions for use/clinical setting/intended user
- **Indications for Use: for what and for whom the device is to be used**
  - Conditions or disease
  - Target population (e.g. age)
  - Time and frequency of use

Performance Characteristics

- **Analytical performance** – does the test device measure the analyte correctly? How reliably?
- **Clinical performance** – does the test result correlate with the expected clinical presentation? How reliably?
  - Appropriate study design, description?
  - Samples tested near cut-off or relevant medical decision points?
  - Informative in the context of intended use?
  - All sample matrices evaluated?
  - Pre-analytical steps included in evaluation?

Review Elements of IVD Submissions

- Performance characteristics: **Analytical**
  - Establish basic performance parameters
  - Precision/reproducibility, reference range/cut-off, analytical sensitivity & specificity
  - Acceptance criteria (established *a priori*)
    - Are the established limits reasonable to support validation of the proposed intended use?
  - What are the appropriate studies to evaluate performance as defined in the intended use?
  - Use of traceable reference materials and methods, if available; calibrators and controls

Review Elements of IVD Submissions

- Performance characteristics: **Clinical**
  - Study design should include the target population
  - Prospective vs. Retrospective samples
  - Matrix considerations, claimed sample type(s)
  - Number of sites
- Comparator
  - Predicate or Reference method
  - Clinical performance

Key Issues

- Manufacturers are developing devices to assess effect or concentration of Direct Oral Anticoagulants (DOACs)
- Acceptable result – numerical value/qualitative detection
- Monitoring is not routinely required
- Currently no cleared or approved devices

FDA's Goal: To ensure that we enable timely access to safe, effective, and high-quality medical devices

Regulatory Challenges

- Lack of good correlation with drug concentration; relation to clinical outcomes
- Adequacy of expected values, reference ranges to support regulatory assessment for clinical use
- Appropriate time interval required to access drug effect in coagulation assays post dosing
- Availability of published data on therapeutic levels

Clinical Laboratory Testing

- Potential situations where laboratory measurement of DOAC drug effect may be useful:
  - Assess compliance
  - Hemorrhagic or thrombotic complications
  - Determination of overdose
  - Pre-operative, urgent surgery

Early Interactions with CDRH

- Utilize the Pre-submission process
  - Highly recommended, offers free FDA consultation
- Provide a clear, carefully crafted intended use
- Provide protocols with as much detail as possible, include specific questions
- Make sure proposed studies support IU claims
- Open communication with the Agency to discuss regulatory strategy and study design

Questions?

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