Office of In Vitro Diagnostic Device Evaluation and Safety

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Premarket and Postmarket Findings for Home-use Prothrombin Time & International Normalized Ratio (PT/INR) Devices:

Patient self-testing of oral anticoagulation therapy

Outline

- Oral anticoagulation
- Point-of-care & Patient self-testing
- Performance Information
- Medical device reporting/adverse events
- Summary

Objectives

- Understanding the value and limitations of home-use patient self-testing
- Performance Characteristics: analytical and clinical validity of home-use (PST) devices
- Device reliability of home-use measurement
- Summary findings of medical device reporting associated with home-use PT/INR devices

Warfarin

- Most commonly used anticoagulant
- Vitamin K antagonist; inactivates generation of vitamin K dependent factors used in clot formation
- Clinical indications: deep venous thrombosis, pulmonary embolism, atrial fibrillation, myocardial infarction, stroke, artificial (prosthetic) heart valves
- Narrow therapeutic window

Warfarin

- Annually 2-3 million Americans prescribed oral anticoagulant therapy (OAT)
- Response dependent on age, sex, body size, concomitant drugs and diseases, patient diet and genetics
- Second most common cause of drug-related adverse events (AE) in outpatients
- Nearly 43,000 bleeding complications requiring ER treatment

Warfarin Monitoring

Prothrombin Time and International Normalized Ratio (PT/INR)

$$INR = \left[\frac{PT\ patient}{PT\ normal\ population\ geometric\ mean}\right]^{ISI}$$

INR: offsets variation in thromboplastin reagent responsiveness

ISI: International Sensitivity Index - calibration parameter that defines responsiveness of reagent relative to a WHO International Reference Preparation (IRP)

Point-of-Care Testing (POC)

- Also known as bedside testing or near patient testing capable of producing results within seconds or minutes
- Portable analyzers intended to provide results more rapidly than hospital or reference laboratories
- Settings include ICUs, ERs, physician offices, outpatient and anticoagulation clinics, and home environment (patient self-testing)

POC Coagulation Testing: Self-testing at Home

- Provides increased access and convenience for the patient and/or caregiver to improve quality of care
- POC testing must provide equal clinical information, but not identical results to that of a hospital or reference laboratory
- Only some patients requiring oral anticoagulant therapy are candidates for self-testing at home

Prescription Home-Use Patient Self-Testing (PST)

- Patient eligibility:
  - Demonstrate the knowledge, technical skill and willingness to use the monitor
  - Anticoagulated at least 3 months prior to home use
  - Ability to comprehend basic aspects of OAT monitoring including risks
  - Poor venous access, life-long OAT, fluctuating response to OAT, unable to visit testing facilities, increased risk for thomboembolic and hemorrhagic complications

Prescription Home-Use Patient Self-Testing

- Training and Education Programs:
- Manufacturer requirement unique to self-testing
- Manufacturer establishes a training program for healthcare providers and an education program for patients and other device users

Prescription Home-Use Patient Self-Testing

- Home-users must complete educational program on anticoagulation management and demonstrate proficient use of device to obtain accurate results
- Verification and assessment of self-testing performance is recommended at specified intervals

Submitting Home-use PT/INR Meters

510(k) premarket notification should include:

- Intended Use/indications for use
- Device description
- Performance Characteristics – analytical and clinical (method comparison) in the hands of professional and lay users
- Applicable software information
- Proposed labeling & training materials

Analytical Performance

- Precision / Reproducibility
- Accuracy
- Interference
- Reagent stability
- Calibration traceability to international reference material and method

Analytical Performance

Precision / Reproducibility:

- Demonstrate device will generate accurate and reliable results with intended users

Accuracy:

- Per ISO 17593 – measured by the extent to which measurements of blood samples from different patients agree with INR values traceable to a thromboplastin International Reference Preparation

Analytical Performance

- Interference – physiological conditions known to affect accuracy of results hemolysis, bilirubin, lipemia, antiphospholipid syndrome, lupus anticoagulant, concomitant drugs
- Stability:

  Reagent – real-time

  Sample – fingerstick specimens inherently unstable
- Traceability – measurement procedure traceable to WHO (manual tilt tube + IRP)

Clinical Performance

- Clinical study designed to demonstrate system accuracy verification to include systematic bias and imprecision that would be experience by intended users in anticipated conditions of use
- Recommend use of oral-anticoagulated subjects enrolled at a minimum of three sites (include patient demographics)
- INR values of study subjects should cover the measurement interval of the device

Reference: ISO 17593

Other Performance Requirements

- Quality Control:
  - Verifies device performance (internal & external)
  - Provide procedure and control materials
- Risk Analysis:
  - Manufacturers will anticipate and mitigate the effect of reasonably foreseeable misuse, including potential deviations from recommended maintenance, operating and control procedures by intended users

Reference: ISO 17593

POC/Home-Use PST: Advantages

- Transportable, rapid & accurate
- Increased convenience for patient/HCP
- Decrease need for venous access
- Increased testing frequency
- Increased time in therapeutic range
- Less expensive, reimbursable

POC/Home-Use PST: Disadvantages

- Pre-analytical variables: patient specimen collection, eyesight, memory, ability to follow instructions
- Manual dexterity in a primarily elderly population, mental cognition
- Lack of control of patient adherence, co-morbid conditions, dietary changes

Issues Affecting Success of Home-Use PT/INR testing

- Causes of erroneous results and adverse events for home-use devices:
  - Suitability of operator for PST
  - Operator error (especially not following prescription and device directions)
  - Improper or lack of training/periodic competency assessment
  - Device failure/instrument malfunction
- Consequences:
  - Patient injury and/or Death

Medical Device Reporting

- MDR reporting enacted by Congress in 1984
- 21 CFR 803: Establishes requirements for medical device reporting for device user facilities, manufacturers, importers and distributors
  - Manufacturers must report within 30 days of becoming aware of an event that reasonably suggests their marketed device may have contributed to a death or serious injury
  - 21 CFR 803.53 - report filed within 5 days for event which necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health

Medical Device Reporting

- Government Accounting Office study (1986 & 1989) showed <1% of device problems occurring in hospitals were reported to FDA and the more serious the device problem, the less likely to be reported
- Manufacturer and User Facility Device Experience (MAUDE) database for adverse events involving medical devices

Medical Device Adverse Events are UNDERREPORTED!

Adverse Events Database Results (MAUDE)

- FDA encourages health-care providers to voluntarily report product problems or concerns related to medical devices to MedWatch
- Adverse event categories examined from the Manufacturers and User Facility Device Experience (MAUDE) database:
  - Instrument malfunction
  - Patient injury
  - Device associated with death

Medical Device Reporting

Year	Malfunction	Injury	Death
2005	154	26	2
2006	566	37	2
2007	783	51	1
2008	911	77	1
2009	774	105	4
Total	3,188	296	10

Summary

- Establishing requirements for oral anticoagulant monitoring systems enables lay users to achieve acceptable performance and to specify procedures for manufacturers to demonstrate conformance to this standard (IS0 17593)
- A need remains for continued strictly enforced safety surveillance of POC and home-use devices encouraging enhanced AE reporting by industry, healthcare providers, and consumers

Resources for PT/INR Self-Testing

- Guidance for Industry and FDA Staff. Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests, March 13, 2007
- ISO 17593 Clinical laboratory testing and in vitro medical devices – Requirements for in vitro monitoring systems for self-testing of oral anticoagulant therapy, 2007
- CLSI H54 Procedures for Validation of INR and Local Calibration of PT/INR Systems

Thank you.

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