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Guidance for Industry and FDA Staff

510(k) Submissions for Coagulation Instruments

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health**

**Division of Immunology and Hematology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety**

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852.

When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Guidance for Industry and FDA Staff

510(k) Submissions for Coagulation Analyzers

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

FDA has developed this draft guidance document to assist industry in preparing premarket notification submissions (510(k)s) for the instrument component of laboratory-based coagulation test system(s). FDA recognizes that multiple assays or reagents reasonably be evaluated in one submission (see also “**Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products; Guidance for Industry and FDA¹**”). Consistent with that policy, we recommend that you submit one application in the following situations:

- for a new instrument using a new assay or reagent system, **or**
- for a new instrument using previously cleared assay or reagent system(s), **or**
- for previously cleared instrument(s) using a new assay or reagent system.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the

¹ <http://www.fda.gov/cdrh/mdufma/guidance/1201.pdf>

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burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the “A Suggested Approach to Resolving Least Burdensome Issues” document. It is available on our Center web page at:

<http://www.fda.gov/cdrh/modact/leastburdensome.html>.

2. Background

A manufacturer who intends to market a device of this generic type should (1) conform to the general controls of the Federal Food, Drug & Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with coagulation analyzers identified in this guidance and, (3) obtain a substantial equivalence determination from FDA prior to marketing the device, unless exempt from the premarket notification requirements of the Act (refer to 21 CFR 807.85).

This guidance document identifies the classification regulations and product codes for the coagulation analyzers (Refer to Section 4 – **Scope**). In addition, other sections of this guidance document list the risks to health identified by FDA and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these coagulation analyzers and lead to a timely premarket notification [510(k)] review and clearance. This document supplements other FDA documents regarding the specific content requirements of a premarket notification submission. You should also refer to 21 CFR 807.87 and other FDA documents on this topic, such as the **510(k) Manual - Premarket Notification: 510(k) - Regulatory Requirements for Medical Devices**, <http://www.fda.gov/cdrh/manual/510kprt1.html>.

Under “**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**²,” a manufacturer may submit a Traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once FDA has issued a guidance document. Manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

3. The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21

² <http://www.fda.gov/cdrh/ode/parad510.html>

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CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this guidance document was used during the device development and testing and should briefly describe the methods or tests used and a summary of the test data or description of the acceptance criteria applied to address the risks identified in this document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of 807.87 as well as some other items that we recommend you include in an Abbreviated 510(k).

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this guidance document.

Proposed labeling

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Refer to Section 7 for specific information that should be included in the labeling for devices of the types covered by this guidance document.)

Summary report

We recommend that the summary report contain:

- Description of the device and its intended use. We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device. You should also submit an "indications for use" enclosure.³
- Description of device design requirements.
- Identification of the Risk Analysis method(s) used to assess the risk profile in general as well as the specific device's design and the results of this analysis. (Refer to Section 5 for the risks to health generally associated with the use of this device that FDA has identified.)
- Discussion of the device characteristics that address the risks identified in this guidance document, as well as any additional risks identified in your risk analysis.
- A brief description of the test method(s) you have used or intend to use to address each performance aspect identified in Sections 6 and 7 of this guidance document. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the

³ Refer to <http://www.fda.gov/cdrh/ode/indicate.html> for the recommended format.

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acceptance criteria that you will apply to your test results.⁴ (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

- If any part of the device design or testing relies on a recognized standard, (1) a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed, or (2) a declaration of conformity to the standard.⁵ Please note that testing must be completed before submitting a declaration of conformity to a recognized standard. (21 USC 514(c)(2)(B)). For more information, refer to the FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA**, <http://www.fda.gov/cdrh/ode/guidance/1131.html>.

If it is not clear how you have addressed the risks identified by FDA or additional risks identified through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess the adequacy of your acceptance criteria. (Under 21 CFR 807.87(l), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you can submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A Traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering modifications to their own cleared devices should consider submitting Special 510(k)s.

4. Scope

The device technology may include, but is not limited to, the following automated methodologies: optical, fluorescence, mechanical, and impedance. This generic type of device includes:

21 CFR 864.5400. Coagulation instrument. A coagulation instrument is an automated or semi-automated device used to determine the onset of clot formation for in vitro coagulation studies.

⁴ If FDA makes a substantial equivalence determination based on acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria and, thus, differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

⁵ See Required Elements for a Declaration of Conformity to a Recognized Standard (Screening Checklist for All Premarket Notification [510(K)] Submissions), <http://www.fda.gov/cdrh/ode/reqrecstand.html>.

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The product codes are:

GIE Fibrometer

KQG Instrument, Coagulation

GKP Instrument, Coagulation

21 CFR 864.5425 Multipurpose system for in vitro coagulation studies. A multipurpose system for in vitro coagulation studies is a device consisting of one automated or semi-automated instrument and its associated reagents and controls. The system is used to perform a series of coagulation studies and coagulation factor assays.

The product codes are:

GKN Timer, Clot, Automated

JBT Timer, Coagulation

JPA System, Multipurpose In Vitro Coagulation

These generic coagulation instruments are Class II, Hematology and Pathology Devices Panel.

5. Risks to Health

There are no known *direct* risks to patient health. However, failure of the test system to perform as indicated or an error in interpretation of results may lead to improper patient management.

In the table below, FDA has identified the risks to health generally associated with the use of the coagulation analyzers addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. We recommend that you conduct a risk analysis, prior to submitting your premarket notification, to identify any other risks specific to your device. The premarket notification should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this document, or have identified risks additional to those in this document, you should provide sufficient detail to support the approach you have used to address that risk.

Identified risk	Recommended mitigation measures
Improper patient management	Section 6, 7, and 8

6. Performance Characteristics

General Study Recommendations

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Whenever possible, we recommend that you include patient samples or sample pools, derived from the intended use population (e.g., patients under evaluation for coagulation abnormalities) for the analytical protocols described below. We recommend that you conduct your studies using a final production model device, and not a prototype.

FDA recommends that you evaluate the analyzer in at least two external sites in addition to that of the manufacturer. Generally, we recommend that performance be assessed in the testing environment where the device will ultimately be used (i.e., central laboratory) by individuals who will use the test in clinical practice (e.g., trained technologists). We recommend that you initially analyze data separately to evaluate any inter-site variation and include results of the analysis in the 510(k) summary report. You can pool method comparison results from the individual sites in the package insert if you demonstrate that there are no significant differences in the results among sites. Before initiating any clinical study, you may contact the Division of Immunology and Hematology Devices.

Although spiked samples can be used to supplement the studies, FDA cautions against using spiked samples as the only matrix in the evaluations, because spiked samples may not provide an accurate assessment of the performance characteristics. FDA recommends that you do not use hemolysates (often found in control or calibrator material) in the analytical studies because these specimens may not test the effects of all preparatory steps on test performance.

So that acceptance criteria or data summaries can be best interpreted during the review, we recommend that you provide appropriate specifics concerning protocols. These specifics are also necessary to aid users in interpreting information in your labeling. For example, when referring to NCCLS protocols or guidelines, we recommend that you indicate which specific aspects of the protocols or guidelines you followed.

Specific Performance Characteristics

Precision

We recommend that you characterize within-run, and total precision according to guidelines provided in “Evaluation of Precision Performance of Clinical Chemistry Devices;” Approved Guideline (1999) National Committee for Clinical Laboratory Standards (NCCLS), Document EP5-A. That document includes guidelines for experimental design, computations, and a format for stating performance claims. We recommend that you evaluate precision at relevant concentrations near medical decision points and concentrations near the limits of reportable range.

We recommend that you include the items listed below:

- a description of sample types
- point estimates of the concentration

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- standard deviations of within-run and total precision
- sites at which precision protocol was run
- number of days, runs and observations
- number of lots used

We recommend that you identify which factors (e.g., instrument calibration, reagent lots, operators) were held constant, which were varied during the evaluation, and describe the computational methods, if they are different from that described in NCCLS EP5-A.

Interference

We recommend that you characterize the effects of potential interferents on each test parameter for which you are seeking clearance on the analyzer. Examples of experimental designs, including guidelines for selecting interferents for testing, are described in detail in “Interference Testing in Clinical Chemistry; Proposed Guideline” (1986) National Committee for Clinical Laboratory Standards, Document EP7-P. Typically, interference studies involve adding the potential interferent to the sample and determining any bias in the recovery of the test parameter relative to a control sample (to which no interferent has been added).

We recommend that you include the following items:

- types and levels of interferents tested
- sample type
- concentrations of the test parameter in the sample
- number of replicates tested
- definition or method of computing interference.

You may not need to perform additional interference testing with potential interferents identified in literature or by other sources. However, we recommend that you include them in the labeling.

Linearity (if quantitative or semi-quantitative assay)

We recommend that you characterize the linear range of the assay by evaluating samples whose concentration levels are known relative to each other. “Evaluation of the Linearity of Quantitative Analytical Methods, Proposed Guideline” NCCLS Document EP6-P describes a protocol for sample preparation and value assignment as well as a format for stating performance characteristics.

We recommend that you describe the sample types and preparation, concentrations and number of replicates. When describing your acceptance criteria or summary data, we recommend that you include the slope, intercept, confidence intervals of the

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estimated line, the range of linearity and the degree of deviations (biases) from the estimated line that were observed or that are considered acceptable for the various concentration levels. Often these deviations can be best described by listing observed or acceptable values relative to the expected values for each level evaluated.

Calibration

We recommend that you provide the following information about the calibrators in the assay kit:

- Protocol and acceptance criteria for real-time or accelerated stability studies for opened and unopened calibrators.
- Protocol and acceptance criteria for value assignment and validation, including any specific instrument applications or statistical analyses used.
- Identification of traceability to a domestic or international standard reference material.
- Protocol and acceptance criteria for the transfer of performance of a primary calibrator to a secondary calibrator.

For information about calibrators marketed separately as class II devices under 862.1150, see the guidance “Abbreviated 510(k) Submissions for *In Vitro* Diagnostic Calibrators,” <http://www.fda.gov/cdrh/ode/calibrator.html>.

Reference Values

We recommend that you establish expected values following the NCCLS document:

How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline—Second Edition, NCCLS document C28-A2, (ISBN P56238-269-I), NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898, 2000.

Software

For software controlled devices, we recommend that you provide validation and verification data, as well as a hazard analysis as described in FDA’s “*Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* (<http://www.fda.gov/cdrh/ode/57.html>). You may also refer to: *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management* (<http://www.fda.gov/cdrh/humfac/1497.html>), or *General Principles of Software Validation* <http://www.fda.gov/cdrh/comp/guidance/938.html>

7. Method Comparison

We recommend for coagulation analyzers that you compare your device to a legally marketed predicate device or appropriate reference method with the same intended use as the analyzer you intend to market. As with studies to evaluate performance characteristics, you may contact the Division of Immunology and Hematology Devices for FDA input on your study plan prior to initiating comparison studies.

FDA recommends that you follow guidelines provided in the document, “Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline” (1995) NCCLS, Document EP9A concerning experimental guidelines and statement of performance characteristics.

Banked (retrospective) samples may be appropriate for some studies as long as information below concerning sample characterization is available.

Specimen collection and handling conditions

We recommend that you substantiate statements in your labeling about specimen storage and transport by assessing whether the device can maintain acceptable performance (e.g., precision) over the storage times and temperatures recommended to users. For example, an appropriate study may include an analysis of aliquots stored under the conditions of time, temperature, or allowed number of freeze/thaw cycles. We recommend that you state the criteria for acceptable range of recoveries under the recommended storage and handling conditions.

Sample selection, inclusion and exclusion criteria

We recommend that you evaluate patient samples from the target population specified in your intended use, (i.e., with and without the test parameter of interest) with parameter values distributed across the reportable range of the assay, including specimens that are close to the clinically relevant decision point(s). Regardless of whether prospective or retrospectively collected samples are used, FDA suggests that you provide a clear description of how the samples were selected, including reasons that samples are excluded. We recommend that you indicate whether samples are chosen from patients with specific clinical outcome or other characteristic.

Appropriate sample size depends on factors such as precision, interference, range, and other performance characteristics of the test. We recommend that you provide a statistical justification to support the study sample size. The number of patients should be large enough so that inter-individual variation would be observed.

Presentation of results

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We recommend that you conduct separate analyses of data for each group that you study. When providing the results of the method comparison study, we recommend that you include the following information:

- If the assay is quantitative or semi-quantitative: plots of results from the new assay (y-axis) versus the reference method (x-axis), including all of the data points, the estimated regression line and the line of identity. Data points should represent individual measurements.
- A description of the analytical method used to fit the regression line and results of regression analysis including the slope and intercept with their 95% confidence limits, the standard error of the estimate (calculated in the y direction), and a correlation coefficient, **or** derive the percent positive, percent negative and overall agreement between the methods, including the 95% confidence intervals or other measure of robustness where appropriate.
- If qualitative: a 2 X 2 table showing agreement between the new assay (rows) versus the predicate test or reference method (columns).

8. Labeling

The premarket notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR 807.87(e).⁶

Directions for use

As a prescription device, under 21 CFR 801.109, the device is exempt from having adequate directions for lay use. Nevertheless, under 21 CFR 807.87(e), we expect to see clear and concise instructions that delineate the technological features of the specific device and how the device is to be used on patients. Instructions should encourage local/institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

Warning

We recommend that devices that perform prothrombin time testing include a warning label that explains how to use the International Sensitivity Index (ISI) values, such as:

“Warning: ISI values for prothrombin time assays must be entered directly as they appear on the current reagent package insert. Any changes of reagent lot,

⁶ Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR 801 [IF IVD DEVICE INSERT: or 21 CFR 809.10] before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of part 801 801 and section 809.10.

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software upgrades, major servicing, etc., require verification of the ISI value. Failure to enter the correct ISI value will cause incorrect International Normalization Ratio (INR) results.”

We recommend that warning be in bold or with high contrast against its background.