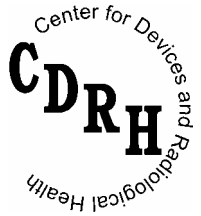
Guidance for Industry and FDA Staff

Review Criteria for Assessment of C-Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP) and Cardiac C-Reactive Protein (cCRP) Assays

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This document supersedes:
"In Vitro Diagnostic C-Reactive Protein Immunological Test System"
Issued on July 20, 1998

For questions regarding this document contact James V. Callaghan 240-276-0443 or by email james.callaghan@fda.hhs.gov



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostic Device Evaluation and Safety
Division of Chemistry and Toxicology Devices

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Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, 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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Table of Contents

1. INTRODUCTION 4

2. BACKGROUND 5

3. CONTENT AND FORMAT OF AN ABBREVIATED 510(K) SUBMISSION 6

4. SCOPE 7

5. TYPES OF CRP ASSAYS 8

6. RISKS TO HEALTH 10

7. DEVICE DESCRIPTION 11

8. ANALYTICAL PERFORMANCE CHARACTERISTICS 11

9. METHOD COMPARISON 15

10. CLINICAL INFORMATION 17

11. LABELING 18

12. REFERENCES 21

Contains Nonbinding Recommendations

Guidance for Industry and FDA Staff

Review Criteria for Assessment of C-Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP) and Cardiac C-Reactive Protein (cCRP) Assays

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

This guidance is intended to provide device manufacturers and FDA staff with updated recommendations concerning 510(k) submissions for various types of assays for C-Reactive Protein (CRP). The document is a revision of "Guidance for Industry: In Vitro Diagnostic C-Reactive Protein Immunological Test System," issued on July 20, 1998. It is updated to address issues associated with the development of hsCRP (high sensitivity CRP) and cCRP (cardiac CRP) assays. These types of CRP assays have significantly lower limits of detection, and functional sensitivities that may be used to support new clinical uses of CRP quantitation. This document now includes discussion of how you should support indications for use claims of cCRP *"for the evaluation of patients with coronary disease and coronary syndromes"* in premarket submissions, including how you should assess different ranges of measurement, based on indications for use. Additionally, we provide recommendations for limitations of CRP test interpretation based on the non-specific nature of CRP elevations in blood.

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 should 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 burden that may be incurred in your attempt to follow 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 CRP test system should conform to the general controls of the Federal Food, Drug and Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR 807 Subpart E, and obtain a substantial equivalence determination from FDA prior to marketing the device.

This guidance document identifies the classification regulations and product codes for various types of CRP tests. (Refer to Section 4 – **Scope.)** In addition, other sections of this guidance document list the risks to health identified by FDA from the various CRP tests and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these kinds of CRP tests and lead to a timely [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

As explained in "**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**[1]," a manufacturer may submit a Traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k), when appropriate. 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).

[1] http://www.fda.gov/cdrh/ode/parad510.html

3. 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 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 describe the methods or tests used and a summary of the test data, description of the acceptance criteria applied to address the risks identified in this document, and 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 generally 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 11 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 the following:

- A 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.[2]
- A description of device design and its 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.)
- A 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.

[2] Refer to http://www.fda.gov/cdrh/ode/indicate.html for the recommended format.

- A description of the test method(s) you used to address each performance aspect identified in Sections 8-9 (and 10, if appropriate) 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) present the data resulting from the test in clear form, such as a table, **or** (2) describe the acceptance criteria that you apply to your test results.[3] (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

- If you choose to rely on a recognized standard for any part of the device design or testing, you may include either: (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.[4] Because a declaration of conformity is based on results from testing, we believe you cannot properly submit a declaration of conformity until you have completed the testing the standard describes.

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 your data, as well as methods, acceptance criteria, and conclusions. Manufacturers considering modifications to their own cleared devices should consider submitting Special 510(k)s.

4. Scope

The scope of this document is limited to the following devices as described in 21 CFR 866.5270, C-reactive protein immunological test system.

The product codes are:

DCH - System, Test, C-Reactive Protein, Rhodamine
DCK - C-Reactive Protein, Antigen, Antiserum
DCN - System, Test, C-Reactive Protein

[3] 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.
[4] 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.

NQD - Cardiac C-Reactive Protein, Antigen, Antiserum

(a) Identification. A C-reactive protein immunological test system is a device that consists of the reagents used to measure by immunochemical techniques the C-reactive protein in serum and other body fluids. Measurement of C-reactive protein aids in evaluation of the amount of injury to body tissues.
(b) Classification. Class II (performance standards).

The devices addressed in this guidance document are for prescription use.

5. Types of CRP Assays

The following types of CRP assays have been cleared:

- Conventional C-Reactive Protein (CRP)
- High sensitivity CRP (hsCRP)
- Cardiac C-Reactive Protein (cCRP)

Conventional CRP

Conventional CRP assays include qualitative, semi-quantitative and quantitative assays, with indications for use ***for evaluation of infection, tissue injury, and inflammatory disorders.*** These assays provide information for the diagnosis, therapy, and monitoring of inflammatory diseases. CRP is one of the cytokine-induced "acute-phase" proteins [1] whose blood levels rise during a general, unspecific response to infections and non-infectious inflammatory processes [2]. For conventional CRP assays, test values are typically considered to be clinically significant at levels above 10 mg/L. In apparently healthy persons blood CRP levels are below 5 mg/L, while in various conditions this threshold is often exceeded within four to eight hours after an acute inflammatory event, with CRP values reaching approximately 20 to 500 mg/L. [3]

CRP is a more sensitive and more reliable indicator of acute inflammatory processes than the erythrocyte sedimentation rate (ESR) and leukocyte count. Blood CRP levels rise more rapidly than ESR, and after the disease has subsided CRP values rapidly fall and reach the reference interval often days before ESR has returned to normal. [4, 5]

High sensitivity CRP (hsCRP)

High sensitivity CRP assays have a range of measurement that extends below the measurement range typical of most conventional CRP assays. This lower range of measurement may expand the indications for use to include ***the evaluation of conditions thought to be associated with inflammation in otherwise healthy individuals.*** Increases in CRP values are non-specific and should not be interpreted without a complete clinical evaluation. Indications for hsCRP assays are general and not associated with specific diseases or risks for disease.

Cardiac C-Reactive Protein (cCRP)

Cardiac CRP assays are indicated ***for use as an aid in the identification and stratification of individuals at risk for future cardiovascular disease. When used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes, cCRP may be useful as an independent marker of prognosis for recurrent events in patients with stable coronary disease or acute coronary syndrome.*** Cardiac CRP assays, like hsCRP assays, have measurement ranges that extend below the measurement range typical of most conventional CRP assays. The difference between hsCRP and cCRP is not the analyte itself, but is due to the additional performance validation to support the expanded intended use in the evaluation of coronary disease discussed below. For cCRP, the validity of the indications related to cardiovascular disease should be demonstrated in clinical studies. You may use literature based on a predicate device to support a cCRP claim for your device if you present bridging studies, showing comparability of values across devices, to support transfer of clinical findings to the new cCRP device. Bridging studies should demonstrate comparability of devices in terms of method comparison study results, precision, and interference. In addition, to enable comparison of cCRP assay results to each other, cCRP assays should be standardized to IFCC/BCR/CAP CRM 470, a certified reference material for the acute-phase reactants [6]. Manufacturers of cCRP assays should always emphasize in the device labeling that increases in CRP values are non-specific and should not be interpreted without a complete clinical evaluation.

The table below outlines similarities and differences between these 3 types of assays, in terms of intended use and performance features that you should demonstrate in a 510(k).

	Conventional CRP	**hsCRP**	**cCRP**
Intended use	For evaluation of infection, tissue injury, and inflammatory disorders. Provides information for the diagnosis, therapy, and monitoring of inflammatory disorders.	For evaluation of conditions thought to be associated with inflammation, in otherwise healthy individuals.	For aid in identification and stratification of individuals at risk for cardiovascular disease. When used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes, cCRP may be useful as an independent marker of prognosis for recurrent events, in patients with stable coronary disease or acute coronary syndrome.

Typical clinical cutoff concentrations	Cutoff: approximately 10 mg/L. Apparently healthy individuals: ≤ 5 mg/L Acute range: 20-500 mg/L	Cutoff: ≤ 1.0 mg/L	Cutoff: ≤ 1.0 mg/L
Appropriate assay measuring range	≥ 5mg/L to upper range of the assay	< 1.0 mg/L to ≤ 10.0 mg/L	< 1.0 mg/L to ≤ 10.0 mg/L
Analytical sensitivity information	Describe performance at the low end of claimed assay range	Determine limit of quantitation (functional sensitivity)	Determine limit of quantitation (functional sensitivity)
Clinical or method comparison information	Comparison of new device to a predicate device	Comparison of new device to a predicate device	Comparison of new device to a predicate device whose clinical utility and cutoff has been demonstrated or Presentation of results from literature describing clinical utility of the new device or Clinical studies for the new device.
Standardization of new device	Describe assay standardization or traceability	Describe assay standardization or traceability. Assay should at a minimum be traceable to IFCC/BCR/CAP CRM 470	Describe assay standardization. Assay should be standardized to IFCC/BCR/CAP CRM 470

6. Risks to Health

Failure of a CRP assay to perform as indicated may lead to improper patient management. A falsely low or falsely high measurement could contribute to improper risk assessment or improper differentiation of tissue injury and inflammatory processes, from non-inflammatory processes. A false result for a cCRP assay could result in assignment of inappropriate risk stratification for individuals thought to be at risk for cardiac events. In addition, an error in

interpretation of results, such as use of assay results to adjust a treatment regimen without consideration of other clinical factors, may also lead to improper patient management.

In the table below, FDA has identified the risks to health generally associated with the use of CRP tests 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:	
Due to failure of the device to perform as indicated	Sections 8-9 (and 10, if appropriate)
Due to misdiagnosis based on incorrect use	Section 11

7. Device Description

You should identify your device by regulation and product code in your 510(k).
For any CRP test, you should fully describe the principle method of the assay in the 510(k). For new technologies or methods, you should also provide details on how this new method for CRP relates to predicate CRP assays, cleared with the same indications for use as your assay.

8. Analytical Performance Characteristics

General Study Recommendations

Whenever possible, we recommend that you include patient samples or sample pools, derived from the intended use population (i.e., apparently healthy individuals suspected to be at risk of the specific inflammatory associated condition or disease) for the various analytical protocols described below. If sufficient samples at the low end of the assay range cannot be obtained from such samples, then we recommend supplementing with patient samples or sample pools derived from healthy individuals, at low risk of inflammatory conditions or disease.

Although spiked samples can be used to supplement the analytical 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 in the analytical studies because these specimens may not test the effects of all preparatory steps on test performance.

So that acceptance criteria or results 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 CLSI (Clinical Laboratory Standards Institute)/NCCLS protocols or guidelines, we recommend that you indicate which specific aspects of the protocols or guidelines you followed, and describe any modifications.

Generally, we recommend that performance be assessed in the testing environment where the device will ultimately be used (i.e., central laboratory or point of care), by the types of individuals who will use the test in clinical practice (e.g., trained technologists, nurses). 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 may be able to 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. You may contact OIVD before initiating a clinical study.

The intended use of your device should be compatible with the performance characteristics of the assay; for example, assays that do not meet high sensitivity performance criteria should not claim use for evaluation or stratification of patients for diseases associated with inflammation. Additionally, claims for cardiac risk stratification should be supported with clinical data, whether from new studies, peer-reviewed literature sources using the same device for which clearance is sought, or literature together with device-specific bridging studies.

Specific Performance Characteristics

Precision of Quantitative C-Reactive Protein Assays

For quantitative assays, we recommend that you characterize within-run, and total precision using patient samples or sample pools. We recommend that you follow guidelines provided in "Evaluation of Precision Performance of Quantitative Measurement Methods"; Approved Guideline –Second edition (2004) CLSI (Clinical Laboratory Standards Institute)/NCCLS, EP5-A2. That document includes guidelines for experimental design, computations, and a format for stating performance claims.

You should evaluate precision at relevant CRP concentrations, including near medical decision points, and concentrations near the limits of reportable range. We recommend that for hsCRP and cCRP assays, one level should be at the American Heart Association/Centers for Disease Control and Prevention (AHA/CDC) clinical cutoff for low risk category (1.0 mg/L) [7] and should have a C.V.$\leq$ 10%, another should be at a mid-point of the assay range and the third should be at or near the upper limit of the assay. We recommend that you describe the following items in your 510(k):

- sample types (e.g., serum, plasma, or whole blood) and preparation, or origin
- sites at which the protocol was run
- number of days, runs, and observations
- target concentrations
- mean and standard deviations for within-run and total precision

We recommend that you describe which factors (e.g., instrument calibration, reagent lots, operators) were held constant, and which were varied during the evaluation, as well as the computational methods, if they are different from that described in CLSI/NCCLS EP5-A2.

Precision studies for a point of care setting should be conducted at three sites by intended users such as nurses, technicians, doctors, etc.

Precision of Qualitative/Semi Quantitative CRP Assays

For qualitative assays, we recommend you follow "User Protocol for Evaluation of Qualitative Test Performance"; Approved Guideline (2002), CLSI/NCCLS, EP12-A, to establish an estimate of precision. You should test negative and positive samples at concentrations within 20% of the cutoff, since evaluation of low-negative or high-positive samples would not challenge the assay. We recommend that you test 20 replicates of each sample and calculate percent agreement for the negative samples and also the positive samples.

In your 510(k), you should describe your study design, including sample types, study sites, and factors varied (e.g., days, operators).

Interference

We recommend that you characterize the effects of potential interferents on assay performance. Examples of experimental designs, including guidelines for selecting interferents for testing, are described in "Interference Testing in Clinical Chemistry; Approved Guideline" (2002) CLSI/NCCLS, EP7-A.

Typically, interference studies involve adding the potential interferent to a serum sample and determining any bias in the recovery of CRP relative to a control sample (to which no interferent has been added).

We recommend that you describe the following concerning your study design:

- types and levels of interferents tested
- a description of the samples tested (e.g., matrix, preparation, origin)
- concentrations of CRP in the sample
- definition or method for computing interference (including replicates tested)

We recommend that you identify any observed trends in bias (i.e., negative or positive) and indicate the range of observed recoveries in the presence of the particular interferent. This approach is more informative than listing average recoveries alone.

We recommend that you state the criteria on which non-interference is determined. For example: "Inaccuracies due to bilirubin are less than x% at CRP concentrations of 1.0 mg/L".

You may not need to perform additional interference testing with interferents identified in literature or by other sources. However, you should identify these interferents in your instructions for use.

Sensitivity

For CRP assays claiming high sensitivity (hsCRP or cCRP), you should calculate and report the limit of quantitation (LOQ) of the assay, (sometimes also referred to as functional sensitivity). We use this term to mean the lowest concentration at which assay bias and precision are within acceptance criteria, under your stated experimental conditions. Acceptance criteria for precision should be %CV $\leq$ 20%. The LOQ should be significantly below the clinical cut-off of the assay (1.0 mg/L in the case of cardiovascular risk assessment with cCRP tests). In determining the LOQ, we recommend that you follow "Protocols for determination of Limits of Detection and Limits of Quantitation; Approved Guideline (2004), CLSI/NCCLS, EP-17A.

You may also wish to report the limit of blank, also discussed in further detail in CLSI/NCCLS, EP-17A . This is often determined as the highest measurement results likely to be observed for a blank sample. Typically, manufacturers determine two or more standard deviations (SD) above the mean of the zero standard or calibrator, by repeated measurements of one or more blank samples, such as the zero calibrator.

The determination of the limit of the blank for conventional CRP assays may be clinically irrelevant, if that limit is considerably below the clinical cutoff. In such cases, you may choose not to state this value in the label. However, you should describe assay performance (e.g. linearity, precision) at the low end of the claimed assay range or clinical cutoff.

In the description of your sensitivity evaluation, we recommend that you describe your study design, calculations, and definition of your measures of sensitivity. You should also provide results, acceptance criteria, and clarification of how measurements below the level of sensitivity are reported to the user.

Linearity

For quantitative or semi-quantitative tests, 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 Measurement Procedures, A Statistical Approach; Approved Guideline (2003), CLSI/NCCLS, EP6-A 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 statistical methods or calculations used (including replicates tested). When describing

your acceptance criteria or summary data, we recommend that you include the slope and intercept with confidence intervals, the estimated regression 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. We recommend that you list observed or acceptable values relative to the expected values for each level you evaluated.

Specimen collection and handling conditions

You should 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 your criteria for an acceptable range of recoveries under the recommended storage and handling conditions.

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. FDA recommends that cCRP assays should be standardized to IFCC/BCR/CAP CRM 470 and hsCRP assay should at a minimum be traceable this standard.
- 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.

9. Method Comparison

General Recommendations

You should compare results obtained with your device to those obtained with a predicate device with similar indications for use and similar assay range. Banked (retrospective) samples may be appropriate for the studies as long as appropriate information concerning sample characterization is available.

You should evaluate patient samples with CRP concentrations distributed across the reportable range of the assay. Regardless of whether prospective or retrospectively collected

samples are used, we recommend 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 risk profiles pertinent to indications for either conventional CRP assays or hsCRP or cCRP assays.

We recommend that you follow guidelines provided in "Method Comparison and Bias Estimation Using Patient Samples"; Approved guideline (2002) CLSI/NCCLS, EP9-A2, concerning experimental guidelines and statement of performance characteristics. 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.

Method comparison studies for a point of care setting should be conducted at three sites by intended users such as nurses, technicians, doctors, etc. At least 40 samples at each site should be tested with a minimum of 25 percent of the samples having values near the cut-off concentration. You may be able to 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.

You may contact OIVD for input on your study plan prior to initiating the studies.

Additional considerations for hsCRP and cCRP method comparison evaluations

For cCRP assays, you should compare your new assay directly to a predicate device for which clinical studies are available to support clinical utility of the specific device. Results of your study should support transferability between the assays.

In order to fully evaluate the clinically relevant range for accuracy for a hsCRP assay, your method comparison to the predicate or reference assay should encompass the entire assay range starting from less than 1.0 mg/L. The rationale for this is that CRP levels less than 1.0 mg/L are generally considered below the clinical cut-off for hsCRP measurements. (For this reason, we believe the analytical cutoff should also be significantly less than 1.0 mg/L.) The evaluation should extend to 5.0 mg/L or greater, but not more than 10.0 mg/L. Patient samples should be evenly distributed throughout this range. Your study should demonstrate that the assay can accurately measure values between the LOQ and 5.0 mg/L, in order to encompass the clinically meaningful stratification values recommended by the AHA/CDC [7].

Considerations for qualitative conventional CRP assays

Qualitative conventional CRP assays are usually devices with a titration format, e.g., latex particle agglutination assays. These assays are generally not sensitive in the low range of measurement, and are not able to differentiate degree of disease state, but are intended to evaluate qualitatively for disease versus non-disease states. The clinical cut-off for conventional CRP assays is frequently between 5.0 and 10.0 mg/L. For such tests we

recommend that you follow guidelines provided in the document "User Protocol for Evaluation of Qualitative Test Performance"; Approved Guideline (2002), CLSI/NCCLS, EP12-A concerning experimental guidelines and statement of performance characteristics.

Presentation of results

We recommend that you conduct a separate analysis of data for each group. Specifically, for hsCRP, it may be appropriate to separately analyze apparently healthy individuals referred for risk evaluation for a condition related to inflammation and individuals known to be at risk or to have inflammatory disorders. For conventional CRP, you should analyze patients with non-inflammatory processes versus inflammatory processes. When providing the results of the method comparison study, we recommend that you include the following information:

- Quantitative or semi-quantitative tests: plots of results from the new assay (y-axis) versus the reference method (x-axis) or predicate, including all of the data points, the estimated regression line and the line of identity. Data points should represent individual measurements. If a predicate device is used for comparison, we recommend that you employ Deming regression, or another method that accounts for variability in both test systems. You should provide 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 coefficient of determination and an estimate of systematic bias at medical decision points.
- Qualitative tests: a 2 X 2 table showing agreement between the new assay (rows) versus the reference method or predicate device (columns), and calculations of the percent positive, percent negative, and overall agreement between the methods, including the 95% confidence intervals or other measure of robustness where appropriate.

10. Clinical Information

Based on the studies described above, you should demonstrate transferability of reference intervals, between the new device and a predicate, for which clinical utility has already been demonstrated. We recommend using guidelines in "How to Define and Determine Reference Intervals in the Clinical Laboratory"; Approved Guideline, Second Edition 2000, CLSI/NCCLS C28-A2. Specifically, if the new test system has similar imprecision and known interferences, comparable standards and calibrators, and is acceptably comparable in absolute values to a predicate device previously cleared for the same indication, then the reference interval can generally be transferred, and further clinical studies will generally not be needed.

In accordance with the least burdensome provisions, the agency will rely upon well-designed bench (and/or animal testing) rather than requiring clinical studies for new devices unless there is a specific justification for asking for clinical information to support a determination of substantial equivalence. However, we may request clinical studies in the following instances:

- The indications for use are dissimilar from CRP assays of the same type.
- The performance of the new CRP assay does not allow for reference interval transfer previously determined in clinical studies used in support of the indication.

We will consider alternatives to clinical testing when the proposed alternatives are supported by an adequate scientific rationale.

Data to support clinical utility can be based on clinical studies you conduct. You should conduct these studies (e.g. method comparison studies, precision studies) in two or more external sites, in addition to that of the manufacturer. Your support for clinical utility can also be based on literature, when available, for example, a meta-analysis of information derived from the literature using the new device. If you are conducting a clinical study to demonstrate substantial equivalence, refer to Blue Book Memorandum entitled "Significant Risk and Nonsignificant Risk Medical Device Studies" http://www.fda.gov/cdrh/d861.html.

11. Labeling

The premarket notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). Although final labeling is not required for 510(k) clearance, final labeling must also comply with the requirements of 21 CFR 809.10 before a medical device is introduced into interstate commerce. The following suggestions are aimed at assisting you in preparing labeling that satisfies the requirements of 21 CFR 807.87(e) and 21 CFR 809.10.

Directions for use

You should include clear and concise instructions that delineate the technological features of your device and how it 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.

Intended Use

As discussed above, the intended use should be compatible with the performance characteristics of the assay. Assays that do not meet high sensitivity performance criteria, and are not supported by bridging studies or literature should not claim use for evaluating patients for specific diseases associated with inflammation; rather, the intended use of such assays should be limited to the general use in the detection and evaluation of infection, tissue injury, and inflammatory disorders.

Summary and Explanation

You should explain that CRP is an "acute phase" protein and rises non-specifically in response to inflammation. You should also clarify that intra-individual variation is a major limitation of the assay when the assay is used for directing therapies and include recommendations such as the following:

- Intra-individual variations of the CRP levels are from 30 to 60%. Serial measurements may be required to estimate true mean of CRP depending on the intended use in any specific individual.

If a claim is made for use in coronary disease evaluation, or for the evaluation of other inflammatory associated conditions, you should further emphasize the non-specific nature of CRP and include clear recommendations that CRP values should not be interpreted without a complete clinical evaluation. Additionally, you should recommend follow up-testing of patients with elevated values in order to help rule out a recent response to undetected infection or tissue injury.

Principle of the Method

If you used literature to support clearance of the new device, you should discuss how your method is traceable to the method used in the supportive literature, as discussed above. For cCRP, methods should be standardized to IFCC/BCR/CAP CRM 470.

Limitations

You should thoroughly discuss the limitations of the assay. You should also discuss any recommended practice or other expert recommendations concerning the limitations of CRP for the intended use.

As an example, an AHA/CDC Scientific Statement, [7] based on investigation of the use of hsCRP and cardiovascular disease, made several recommendations for limitations on the use of Cardiac C-Reactive Protein (cCRP). These recommendations are highlighted below, and should be included in the labeling of all assays seeking cCRP indications for cardiac risk evaluation:

- Screening the entire adult population is not recommended.
- CRP is not a substitute for traditional cardiovascular risk factors.
- Acute coronary syndrome management should not depend on CRP measurements.
- When being used for risk assessment, patients with persistently unexplained CRP levels above 10 mg/L should be evaluated for other non-cardiovascular origins.
- Testing for any risk assessment should not be performed while there is indication of infection, systemic inflammation, or trauma.
- Secondary prevention measures should be based on global risk assessment and not depend on CRP.
- Serial testing of CRP should not be used to monitor effects of treatment.
- The average of CRP results repeated optimally two weeks apart should be used in performing risk assessment on metabolically stable patients.

Interpretation of Results

You should include the following, with your interpretation of results:

- Express CRP, hsCRP, and cCRP measurements in mg/L.

- Clarify that results below the lower limit of detection should be reported as less than that of the value of the lower limit of detection.
- Emphasize the need for detailed clinical evaluation and follow-up testing of elevated hsCRP and cCRP results.
- Indicate the imprecision at the 99th percentile of the reference population. This value should be ≤ 10% C.V.
- Intra-individual variations of CRP are significant and should be taken into account when interpreting values.

Performance Characteristics

You should summarize all study designs and describe performance characteristics as discussed in Sections 8-9 (and 10, if appropriate) of this document.

Precision

You should describe within-run and total precision, determined at three levels. As discussed in the precision section above, one level should be at the clinical cutoff of normal, another should be a mid-point of the assay range from the cutoff and the third should be at or near the upper limit of the assay.

Sensitivity

For high sensitivity assays, you should report functional sensitivity (limit of detection), as well as limit of blank. You may also wish to report sensitivity based on the measurements of blank samples (e.g., zero calibrator). (See the Sensitivity section, above.)

Assays with multiple ranges

It is possible that a CRP assay may offer two ranges of measurement (full range). In these instances, performance of the hsCRP or cCRP range of measurement should be characterized and presented independently from the performance of the conventional CRP range of measurement.

Method Comparison

You should present the method comparison results evenly distributed across the assay range appropriate for the intended use of your assay. For example, in cardiovascular and peripheral vascular disease risk assessment, the clinically relevant range is from values of < 1.0 mg/L to 5.0 mg/L, but not more than 10 mg/L. You should summarize the study design and results of your analyses, including the slope and intercept, with 95% confidence intervals, standard error, and coefficient of determination. We recommend that you display the data in a scatter plot.

12. References

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4. Dixon JS, Bird HA, Sitton NG. C-reactive protein in the serial assessment of disease activity in rheumatoid arthritis. Scand J Rheum 1984;13:39-44.
5. Gambino R. C-Reactive Protein: An Underutilized Test. Lab Report for Physicians 1989; 11:41.
6. Kimberly MM, Vesper HW, Caudill SP, Cooper GR, Rifai N, Dati F, Myers GL. Standardization of Immunoassays for Measurement of High-Sensitivity C-reactive Protein. Phase I: Evaluation of Secondary Reference Materials. Clinical Chemistry., 2003; 49(4) 611–616
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