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July 23, 2001

Dockets Management Branch (HFA –305)
Food and Drug Administration
5630 Fishers Lane - Room 1061
Rockville, MD 20852

RE: Premarket Approval Applications for In Vitro Diagnostic Devices Pertaining to Hepatitis C Viruses (HCV): Assays Intended for Diagnosis, Prognosis, or Monitoring of HCV Infection, Hepatitis C, or Other HCV-Associated Disease; Draft Guidance for Industry and FDA [Docket 99D-3028]

Dear Sir or Madam:

Abbott Laboratories submits the following comments regarding FDA draft guidance document "Premarket Approval Applications for In Vitro Diagnostic Devices Pertaining to Hepatitis C Viruses (HCV): Assays Intended for Diagnosis, Prognosis, or Monitoring of HCV Infection, Hepatitis C, or Other HCV-Associated Disease; Draft Guidance for Industry and FDA" published in the Federal Register on April 27, 2001 at 66 FR 21160.

Thank you for the opportunity to provide these comments. In general, we are concerned that many of the studies requested in the draft guidance document, although scientifically interesting, do not have a direct bearing on the safety and effectiveness of an HCV assay. Of particular concern are the assay reproducibility (precision) studies, which involve testing of multiple anticoagulants, HCV genotypes, and HCV variants, and the prevalence study of healthy individuals. Therefore, we request the Agency to reconsider this draft document in light of its recently issued draft Least Burdensome guidance document. Specific comments, including citations to the applicable portions of the Least Burdensome guidance document, follow in a tabular format.

99D-3028

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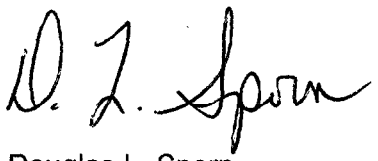
Should you have any questions, please contact April Veoukas at (847) 937-8197 or by facsimile at (847) 938-3106.

Sincerely,



Douglas L. Sporn
Divisional Vice President
Corporate Regulatory Affairs, Abbott Laboratories

Specific Comments
on
FDA's Draft Guidance Premarket Approval Applications for Assays Pertaining to Hepatitis C Viruses (HCV) that are Indicated for Diagnosis or Monitoring of HCV Infection or Associated Disease

SECTION	TEXT	COMMENT
Background Page 2 ¶ 3	Replace "immuno-coinfection" with "immunity, coinfection"	This appears to be a typographical error. The proposed modification will correct this error.
Clinical Significance and Utility Page 4 Item D	"Discussion of historical and currently accepted methods used to detect HCV and HCV infections, including approaches for detecting HCV antibodies, antigens, or RNA."	As currently written, the topic is very broad. We suggest narrowing the focus by clarifying "currently accepted methods" with examples. We recommend "currently accepted methods (e.g., clinical practice, NIH consensus statement, and CDC recommendations)."
Clinical Significance and Utility Page 4 Item F	"Description of reference ("gold standard") methods, if available, for detecting evidence of HCV infection in clinical specimens."	Because no other "gold standards" exist for HCV diagnostic tests, clarify that "gold standard" means CBER licensed products or clinically accepted practice.
Clinical Significance and Utility Page 4 Item G	"Discussion of genetic variants of HCV, their proposed clinical significance, and their known potential impact on the new assay."	As written, this item is very broad. We recommend FDA include a list of genotypes/subtypes for consideration of the known potential impact on the new assay. Without the clarification, the request is open-ended requiring discussion of items that are not relevant to the particular HCV IVD.

SECTION	TEXT	COMMENT
Clinical Significance and Utility Page 4 Items E, F, and G	E. "Comparison between the new assay and any previously licensed or approved device (i.e., similarities and differences). F. "Discussion of historical and currently accepted methods used to detect HCV and HCV infections, including approaches for detecting HCV antibodies, antigens, or RNA." G. "Discussion of genetic variants of HCV, their proposed clinical significance, and their known potential impact on the new assay."	For each of these items scientific literature and device package inserts could be used to aid the discussion. Similar to items B-D, we suggest FDA clarify that this information may be derived from and referenced to scientific literature and other device package inserts.
Indications Page 5 Items 3 -6	"Aid in the detecting asymptomatic acute infection with HCV... chronic HCV infection, . . .diagnosis of acute hepatitis C and... diagnosis of chronic hepatitis C."	The guidance document provides for 12 different device indications, which includes the 5 sub-indications listed under item 8. We are concerned that this list of indications micro-dissects the disease in such a manner that it does not add value, especially since there is no clear reason for so many indications. We suggest modifying the list of indications to: 1) screening (CBER) and 2) diagnostic.
Indications Page 6 Item 8	"Monitoring HCV Infection includes at least several important indications . . . "	FDA should clarify how it defines monitoring. We suggest defining monitoring as changing concentrations of the virus. In addition, we suggest that FDA delete the text in this section and replace it with the following: "Monitoring HCV (i.e., HCV RNA or HCV antibody) infection to aid in the management of patients diagnosed with HCV infection."
Indications Page 6 Item 8(a)	"Prognosis of chronic HCV infection without antiviral therapy."	We are concerned with the ethical considerations of denying chronic HCV patients with anti-viral therapy if appropriate. We suggest the use of current peer-reviewed scientific literature to discuss this indication or a protocol considering chronic HCV patients not on anti-viral therapy as those that refused treatment, discontinued treatment due to adverse events, non-responders, or those determined not to be candidates for therapy.

SECTION	TEXT	COMMENT
Performance Characteristics Page 9 ¶ 3	"Any cutoff changes, however . . .may need to be tested in subsequent clinical or reproducibility studies."	Clinical studies are not needed for a change in cutoff value. A determination of a specimen as positive or negative is based on the reference test method, not the test device. Therefore, the clinical population has not changed. The clinical data can be re-analyzed with the new cutoff without the need to conduct an additional clinical trial. We suggest the following revision: "Any cutoff changes, however . . .may need to be tested in subsequent reproducibility studies."
Preclinical Laboratory Studies Page 11 ¶ 1	"Several possible approaches to determining analytical sensitivity include . . . for assays that detect HCV antigen or RNA, establishing limits of detection (LOD) or endpoints by determining the minimum detectable number of analyte molecules and, if possible, a minimum number of 50% chimpanzee (or, if available, cell-culture) infectious doses of HCV."	To establish an analytical sensitivity claim one would base the claim on the number of analyte molecules. Experiments designed to evaluate chimpanzee infections doses or cell-culture would not serve as the basis of the analytical sensitivity claim. Therefore, we recommend the following revision: " . . . for assays that detect HCV antigen or RNA, establishing limits of detection (LOD) or endpoints by determining the minimum detectable number of analyte molecules."
Preclinical Laboratory Studies Page 10 Item 3 d	"Approximate interpretations should be established for results that represent different concentrations of analyte (analogous to setting cutoffs: please refer to section IV.A.1, above)."	HCV is chronic or acute. However, concentration values can change for various reasons (e.g., treatment). For antibody assays, a correlation between concentration value and infection status is not well-established in the literature. Therefore, we recommend deleting the proposed text.
Preclinical Laboratory Studies Page 11 Item 4	"Specificity for detecting HCV RNA"	To clarify that this section is addressing target amplification we recommend the following revision: "Specificity for detecting HCV RNA **using Target Amplification Methods**."
Preclinical Laboratory Studies Page 11 Item 5 b	Exogenous substances (e.g., glove powder or the effect of different drugs) that may have been introduced to individual specimens or an archived collection.	We would like to thank FDA for responding to previous comments to clarify the types of exogenous substance by providing examples. Please clarify the intent of "different drugs." Therapeutic or illegal drugs are assessed as endogenous substances.

SECTION	TEXT	COMMENT
Preclinical Laboratory Studies Page 12 Item 7	"Real-time stability studies should determine optimal and permissible conditions for each proposed matrix (and each anticoagulant, if plasma would be used). These studies should evaluate effects of specimen collection, transport, and storage effects on assay results, particularly with regard to inhibition of HCV RNA detection."	The guidance document recommends real-time stability studies for each anti-coagulant. Under a least burdensome approach, scientifically sound alternative approaches should be considered (The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Draft Guidance for FDA and Industry, page 4). Demonstration of equivalent assay performance between anticoagulants and real-time stability testing of a representative plasma matrix would negate the need to conduct real-time stability studies on each anti-coagulant. We recommend the following revision:" Stability studies should determine optimal and permissible conditions for each proposed matrix. These studies should evaluate effects of specimen collection, transport, and storage effects on assay results."
Preclinical Laboratory Studies Page 13 Item 8	"Include data from testing, the human-derived reagents using FDA approved methods to demonstrate that there are no infectious agents such as human immunodeficiency virus and hepatitis B virus (HBV)."	We request deletion of this item as recent FDA regulation requires medical devices containing human blood or a blood component as a component of the final device that have been manufactured from reactive blood contain a warning statement (see 21 CFR 610.42(a), published June 11, 2001 at 66 FR 31164).
Preclinical Laboratory Studies Page 13 Item 9	"**Validation of reagent stability:** Real-time studies should determine if expiration dates are accurate. Studies should also evaluate performance of any indicators that are provided for evidence of improper storage."	For clarity we recommend the following revision: "**Validation of whole kit stability:** Real-time studies should be used to determine expiration dating. A stability protocol may be submitted with the PMA and when approved by the FDA, expiration date extended as data is accumulated. Studies should also evaluate performance of any indicators that are provided for evidence of improper storage."

SECTION	TEXT	COMMENT
Preclinical Laboratory Studies Page 13 Item 10 d	"A different group, or panel, of specimens should be studied for each type of specimen matrix to be used with the assay."	Under a least burdensome approach, scientifically sound alternative approaches should be considered (The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Draft Guidance for FDA and Industry, page 4). Where equivalence has been demonstrated between specimen matrices there is no need to demonstrate assay reproducibility (precision) for each matrix. We recommend the following addition: "**If the specimen matrices are not equivalent**, a different group, or panel, of specimens . . . "
Preclinical Laboratory Studies Page 13 Item 10 e	"A different group of specimens should be studied to represent (in the form of antibody, antigen, or RNA) each HCV genotype or variant that the assay is intended to detect."	Under a least burdensome approach, scientifically sound alternative approaches should be considered (The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Draft Guidance for FDA and Industry, page 4). First, this issue is already addressed as part of the analytical sensitivity and clinical sensitivity sections of the guidance document. There is no need to repeat it in the reproducibility section. Second, if equivalent detection of genotypes has been demonstrated, testing with a single genotype to demonstrate assay reproducibility is sufficient. Therefore, we suggest FDA delete it from this section.
Preclinical Laboratory Studies Page 14 Item 10 f Top of page	For quantitative assays, at least two additional specimens should be studied. These specimens should represent upper and lower thresholds for clinical decisions that pertain to each indication for use. One specimen should contain a high concentration of analyte... The other specimen should contain a low concentration of analyte..."	Consistent with how other products are currently being assessed we suggest the following revision: "For quantitative assays**, analyte concentrations should include specimens that challenge the entire dynamic range of the assay**." This modification is consistent with the least burdensome approach to new issues that affect all devices of a type, "it is important to deal with all of the devices that present that concern rather than hold up a specific application," (here, HCV diagnostic assay applications) [The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Draft Guidance for FDA and Industry, page 9].

SECTION	TEXT	COMMENT
Preclinical Laboratory Studies Page 15 Item 12(c)	"Description, explanation, and validation supporting the effectiveness of error messages."	The guidance document requires validation that proves the effectiveness of any error messages. This is a part of design validation and should not be required here. In accordance with the least burdensome approach, "FDA should generally avoid using premarket review to ensure compliance with FDA statutes or regulations unrelated to the regulatory decision (e.g., ...QS Regulation)" [The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Draft Guidance for FDA and Industry, page 7]. We recommend the following revision: "Description and explanation supporting the effectiveness of error messages."
Design and Protocols for Clinical Studies: General Considerations Page 15 Item 3	"The protocol should be identical for each type of laboratory in which the assay will be studied. Any site-to-site variables should be explained."	Please clarify the phrase "site-to-site variables" by providing examples such as type of site, specimen type, and patient population. It is important to receive clarification on this item as it impacts drafting the clinical study design. We feel that additional clarification in the guidance document will promote efficiency at subsequent early collaboration meetings because industry will be able to provide a study design that meets FDA's intent.
Design and Protocols: General Considerations Page 16 Item 4, ¶ 1	"A prospective study, following a design to determine performance for a particular indication for use in a particular population, is the optimal type of study. If the specimens have been properly maintained (see below, V.B.7) and no biases were introduced by selecting certain specimens, it does not matter that the study was performed in the past."	This section is biased toward prospective studies. We suggest the following revision: " A prospective study, following a design to determine performance for a particular indication for use in a particular population, is the optimal type of study. **However, a study using previously collected and well characterized banked specimens (i.e., a retrospective study) may be acceptable as long as the specimens have been properly maintained (see section V.B.7). When designing a retrospective study, it is important to consider and then minimize the potential for introducing bias through the specimen selection process."**

SECTION	TEXT	COMMENT
Design and Protocols: General Considerations Page 17 Table 1	"Comparative-assay results as evidence of HCV infection, per package insert instructions: interpretation for categorizing specimens or individuals in studies"	As this table provides interpretation instruction for specimen categorization, we suggest FDA review the table with practicing clinicians. This can be accomplished through a professional society or public forum. In addition, please provide instruction on table usage when assay package inserts define terms differently from the table.
Design and Protocols: General Considerations Page 18 Item 5 b	"Other appropriate lab findings should be documented from line data for each individual or specimen."	We recommend that FDA clarify this sentence by adding lab findings come from source documents (e.g.., case report forms), and that such lab findings can be document alongside raw data, specimen identification, etc., which is typically printed in a format referred to as "line data" or "line listing."
Design and Protocols: General Considerations Page 18 Item 6 ¶ 1	"You should supply information from studies to support all indications for use except for, possibly, the indication "evidence of HCV infection, where the state of infection or associated disease is not specified. FDA also recommends supplying information about the individuals in the studies, except for the indication 'evidence of HCV infection, state of infection or associated disease not specified' (Indication 1)." "A physician's diagnosis, without the objective data to support it is not an acceptable criterion for categorizing patients."	We request that FDA delete the word "possibly" to provide industry clearer instructions regarding the information required for the indication "evidence of HCV infection, where the state of infection or associated disease is not specified." In addition, we request that FDA clarify that HCV serology is sufficient objective data to support indications. HCV serology is well-established.
Design and Protocols: General Considerations Page 19 Item 6 b (1) ¶ 2	"If more than one assay is used, at different labs or because historical data is cited, the PMA should contain sufficient information to enable interpretation of results from each HCV RNA assay (e.g., data from quantified reference materials)."	It is not feasible to test a designated reference material or panel on historical assays. We recommend the use of literature to enable the interpretation of results for such assays. Additionally, we request deletion of the use of a "qualified reference material," as there is no standard to develop such reference material. A "gold" standard does not exist.

SECTION	TEXT	COMMENT
Design and Protocols: General Considerations Page 21 Item 6 c (1)	" In a group not treated with anti-HCV therapy."	Please clarify that "a group not treated with anti-HCV therapy" means those that refused treatment, discontinued treatment due to adverse events, non-responders, or those determined not to be candidates for therapy.
Design and Protocols: General Considerations Page 21 Item 6 d	"Different types of populations should be studied for determining specificity and for estimating prevalence ("Expected Values") as detected by the manufacturer's new assay . . ."	We request deletion of the portion of this section requiring a study estimating HCV prevalence in healthy populations. Prevalence studies are conducted to understand the disease itself. Such a study has no bearing on the safety and effectiveness, performance, or intended use of the device. Applying the least burdensome principle to PMAs, FDA states "FDA and industry should focus on the statutory criteria for approval of the PMA, i.e., the determination of reasonable safety and effectiveness...this determination should be based on valid scientific evidence, and information unrelated to the approval decision should not be submitted to, nor requested by the Agency" (The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Draft Guidance for FDA and Industry, page 4). As prevalence is not related to the approval decision, we request the Agency delete this item from the guidance document.
Design and Protocols: General Considerations Page 21 Item 7	"Inclusion and exclusion criteria for specimens should include conditions for collection, handling, and storage. Protocols should indicate how these criteria will be met and documented . . . for inclusion in the archive, number of individuals represented (e.g., each "seroconversion panel" should represent only one individual), criteria and introduced biases for selecting certain specimens to study, and how the archive has been stored (including criteria for and documentation of monitoring during storage)."	This section is redundant. Consistent with the June 1, 1998 Presidential Memorandum on Plain Language, we recommend shortening the section as follows: " Inclusion and exclusion criteria for specimens should include **selection criteria** and conditions for collection, handling, and storage. Protocols should indicate how these criteria will be met and documented." Shorting this section will enhance understanding of the guidance document by the intended audience.

SECTION	TEXT	COMMENT
Design and Protocols: General Considerations Page 22 Item 9 b (1)	"For characteristics that pertain to qualitative diagnostic indications, performance should be expressed in terms of % new-assay results that are "correct," where correct refers to the category to which individuals or specimens have been assigned, according to criteria in the clinical protocol."	We recommend changing the word "correct" to "concordant." Concordant is a scientific, statistically defined word with a readily recognizable meaning by the intended audience of this document. Therefore, we recommend the following revision: "For characteristics that pertain to qualitative diagnostic indications, performance should be expressed in terms of % new-assay results that are **concordant** with the category to which individuals or specimens have been assigned, according to criteria in the clinical protocol.
Design and Protocols: General Considerations Page 22 Item 9 b (2)	"Performance for diagnostic indications with qualitative assays should also include validation of cutoff(s). The manufacturer should present data to demonstrate that each cutoff is appropriate, as determined from clinical studies of well-characterized individuals or specimens. Such presentation typically includes a graphic representation of data, in such forms as a ROC curve or a histogram (number of new-assay results versus new-assay values, with the cutoff marked on the horizontal axis). It is not appropriate to validate a cutoff by using results from two different populations (e.g., positive results primarily from patients with hepatitis C and negative results primarily from blood donors)."	We disagree with FDA's recommended use of the ROC analysis. It is inconsistent with how ROC analysis is typically performed. ROC analysis requires two different populations to validate cut-off. A receiver operating characteristic (ROC) plot is defined as "a graphical description of test performance representing the relationship between the true-positive fraction (sensitivity) and the false positive fraction (1-specificity); customarily, the true-positive fraction is plotted on the vertical axis and the false-positive rate (or, alternatively, the true-negative fraction) is plotted on the horizontal axis" [NCCLS "Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristics (ROC) Plots; Approved Guideline," GP10-A, Dec. 1995 page 1]. We recommend the following changes to this section: " Performance for diagnostic indications with qualitative assays should also include validation of **cutoffs**. The manufacturer should present data to demonstrate that **the** cutoff is appropriate, as determined from clinical studies of well-characterized individuals or specimens. Such presentation typically includes a graphic representation of data, in such forms as a ROC curve or a histogram (number of new-assay results versus new-assay values, with the cutoff marked on the horizontal axis)."

SECTION	TEXT	COMMENT
Design and Protocols: General Considerations Page 23 Item 9 c	"Discrepancy resolution"	We recommend the text in the section be deleted. Resolution of discrepant results is not specific to HCV tests and, therefore, should be addressed in a much broader way by FDA (i.c., guidance on resolution of discrepant results). Deletion of this text is consistent with the least burdensome approach to new issues that affect all devices of a type, "it is important to deal with all of the devices that present that concern rather than hold up a specific application," (here, HCV diagnostic assay applications) [The Least Burdensome Provisions of thc FDA Modernization Act of 1997: Concept and Principles; Draft Guidance for FDA and Industry, page 9].
Design and Protocols: Additional Recommendations Page 24 Table 2 A	New assay for presumptive (1st-step) or stand-alone (only-step) detection of anti-HCV (e.g., EIA New assay for presumptive (1st-step) or stand-alone (only-step) detection of anti-HCV (e.g., EIA)" "These performance characteristics should not be referred to as "clinical" sensitivity or specificity nor should the manufacturer calculate predictive values, because *evidence of HCV infection, not specified with regard to state of infection or associated disease* is not a clinical indication for use."	Please define presumptive detection and presumptive assay. We believe that this change in terms should be reviewed by laboratory heads via a professional organization or through a public forum.
Design and Protocols: Additional Recommendations Page 25 Table 2 B	"This performance characteristic should not be referred to as "clinical" sensitivity because *evidence of HCV infection, not specified with regard to state of infection or associated disease* is not a clinical indication for use"	We request clarification of this item. As written, it is not understandable. Consistent with the June 1, 1998 Presidential Memorandum on Plain Language, re-writing this item will provide greater clarity, which will be more useful to industry in performing data analysis, and will create greater efficiency for FDA and industry.
Design and Protocols: Additional Recommendations Page 26 Table 3 B	"HCV infection, state of infection or associated disease not determined category: sensitivity suggested."	We do not believe this information is appropriate for the package insert. Therefore, we request deletion of this item.

SECTION	TEXT	COMMENT
Design and Protocols: Additional Recommendations Pages 27-29 Items 2-6	"Aid in detecting acute asymptomatic HCV infection; Aid in detecting chronic asymptomatic HCV infection; Aid in diagnosis of acute hepatitis C; Aid in diagnosis of chronic hepatitis C; Aiding diagnosing hepatitis C (indiscriminate between acute and chronic)"	We commend FDA for being forward thinking regarding possible future uses for HCV tests. However, when we consider how tests are currently being used, these intended use statements add very little to document. We recommend our position be confirmed by having these sections reviewed by practicing clinicians.
Design and Protocols: Additional Recommendations Page 29 Items 7 Bullet 1	"HCV-RNA concentrations, per the new assay, that correspond to clinical-decision points. When the new assay is qualitative, this consideration pertains to selection of one or more cutoffs."	These tests are aids in management of HCV treatment. They are part of the over-all clinical profiles. They are not likely to be used alone to determine the clinical decision points.
Design and Protocols: Additional Recommendations Page 29 Items 7 Bullet 3	"The manufacturer of a new quantitative assay should determine values that correspond to clinically significant change(s) in HCV RNA concentration."	We recommend the following change: "The manufacturer of a new quantitative assay should determine values that correspond to **statistically** significant change(s) in HCV RNA concentration." It is important to know when there is a real change in HCV concentration rather than a change that may be due to another factor, such as assay variability.
Design and Protocols: Additional Recommendations Page 29 Items 7 Bullet 3 ¶ 3	Length of study period, premarket or postmarket – the manufacturer should consider if the new assay's utility pertains to short terms (months to a few years) or for longer periods during which the most serious complications of HCV infection may develop.	Study design must support claims. There should be no limitation in the intended use based on the length of the study. We are not aware of tests where the limitations have been based on the length of the study. Deletion of this text is consistent with the least burdensome approach to new issues that affect all devices of a type, "it is important to deal with all of the devices that present that concern rather than hold up a specific application," (here, HCV diagnostic assay applications) [The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Draft Guidance for FDA and Industry, page 9].

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