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Advanced Medical Technology Association

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July 26, 2001

Dockets Management Branch (HFA –305)
Food and Drug Administration
5630 Fishers Lane - Room 1061
Rockville, MD 20857

Re: Docket No: 99D-3028 - Draft Guidance on Premarket Approval Applications for Assays Pertaining to Hepatitis C Viruses (HCV) that are indicated for Diagnosis or Monitoring of HCV Infection or Associated Disease, released for comment on April 27, 2001

Dear Dr. Dubois:

These comments are submitted by the Advanced Medical Technology Association (AdvaMed), in response to the Food and Drug Administration's (FDA's) draft document titled "Guidance on Premarket Approval Applications for Assays Pertaining to Hepatitis C Viruses (HCV) that are Indicated for Diagnosis or Monitoring of HCV Infection or Associated Disease" (HCV guidance document) dated April 27, 2001. AdvaMed is a Washington D.C. based trade association and the largest medical technology association in the world. AdvaMed represents more than 800 manufacturers of medical devices, diagnostic products, and medical information systems. AdvaMed's members manufacture more than 90 percent of the $58 billion of health care technology products purchased annually in the United States, and more than 50 percent of the 137 billion purchased annually in the world.

We note that the guidance document does not represent a significant change from the October 8, 1999 version of the document and that many of the issues raised in our February 11, 2000 comments have not been addressed. The issues remain a major concern and have been reiterated in our comments. Our specific comments have been provided in the attached table. Our general comments are the following:

- The requirements outlined in the guidance document are somewhat excessive in light of the fact that HCV assays, approved by the Center for Biologics Evaluation and Research, have been marketed without significant problems for sometime.

- Based on Microbiology Panel meetings and the Least Burdensome Guidance document recently released, it is clear that well-characterized stored samples should be acceptable to demonstrate safety and effectiveness of these products. We believe that this concept for sample bank correlation studies should be added to the next draft of the guidance, with the stipulation that each stored sample have sufficient patient clinical information so that the

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patient information can be used for discrepant resolution when the tests being compared do not give the same answer.

- A "definitions" section would add clarity to the guidance document. We are concerned that FDA's definitions may not reflect concurrence within the scientific community. FDA's use of certain terms appears inconsistent with how they are used by industry.

- In some instances, the requirements that have worked for serology assays will not work for nucleic acid testing (NAT) and has not been taken into consideration by the agency.

- Testing on each genotype can be burdensome. The reproducibility section in particular creates a reproducibility panel that can be quite onerous. The panels would include three copy levels for each genotype and anticoagulant that is claimed in the package insert. This is an infeasible solution, which is overly burdensome considering the incidence of the various genotypes in the U.S.

- Throughout the document, many studies are to be performed in each matrix to be claimed, (serum and each different type of plasma). This should only be necessary if differences in performance are demonstrated during serum/plasma equivalence studies. Where equivalent performance has been demonstrated, it would be overly burdensome and unnecessary to perform stability, analytical sensitivity, interference, reproducibility etc on each matrix type. Further serum/processed plasma based controls are state of the art and should be acceptable for use when testing matrices that have been demonstrated to give equivalent performance.

AdvaMed appreciates the opportunity to provide comments on FDA's guidance document. We again recommend that FDA vet the document with practicing clinicians knowledgeable in this area. Should you have any questions regarding our comments, please do not hesitate to contact us.

Respectfully Submitted,

Carolyn D. Jones

Carolyn D. Jones
Associate Vice President
Technology and Regulatory Affairs

(see attached table)

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
Introduction Page 1 Item B	"This type of device . . . quantify HCV antibodies, antigens or RNA in clinical specimens."	This document is intended to address requirements for antigen tests as well as antibody and RNA tests yet; it is inconsistent with respect to referencing requirements for HCV antigen tests. This should be better addressed throughout the document.
Introduction Page 2 Item C	"When an HCV IVD is indicated only for safety of blood and blood products, a pre-license application (PLA) should not be submitted to CDRH."	Change to: Biologic License Application (BLA).
Background Page 3 ¶ 3	"These HCV-RNA assays, none of which are currently approved or licensed by FDA, use target amplification methods such a polymerase chain reaction (PCR) or direct hybridization techniques such as branched DNA (bDNA)."	There are other target amplification technologies other than those referred to in the guidance. Specific mention of technologies creates a bias that the two mentioned are the only methods in the industry. It suggests a bias towards the ones mentioned over the omitted technologies. The term of choice should be Nucleic Acid Testing (NAT).
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."	Clarify the meaning of the phrase "currently accepted methods" by providing 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 assays. Without 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.
Contraindications Page 4 ¶ 2	"FOR SAFETY REASONS THIS CONTRAINDICATION SHOULD BE DISPLAYED ON PACKAGE LABELS AND THE PACKAGE INSERT IN WAYS TOMINIMIZE THE POSSIBILITY THA THE ASSAY COULD BE USEDS, INADVERTANTLY OR INTENTIONALLY, FOR DONOR INDICATIONS."	We recommend that the guidance follow established precedent for PMA approved HBsAg assays with respect to location of warnings and wording to be used. Contraindications are not currently required on package labels for these tests.
Indications for Use Page 5 Item 1 ¶ 1	"Qualitative assays should demonstrate performance for at least this indication. FDA believes this indication is not appropriate for assays that quantify HCV antigens for RNA."	We recommend the following revision: "Qualitative assays and quantitative assays, that make a claim for a general indication, should demonstrate performance for this indication. In the diagnostic field, there are many quantitative markers that have diagnostic utility when above a defined concentration or detectable level, i.e., total bHCG). Therefore quantitative assays should not be excluded from claiming this "general" indication, but it should not be a requirement
Indications for Use Page 5 Item 1 ¶ 3	"A negative result does not exclude active HCV replication. It is not known if performance is affected by the state (acute or chronic) of infection. It is not know if performance is affected by the presence or absence of disease."	We suggest that the statement if required can be added to the "Limitations" section of the package insert and revised as follows: **HCV results should only be used and interpreted in the context of the overall clinical picture. A negative result does not exclude the possibility of exposure to or infection with hepatitis C virus.** This is also in alignment with the comment below that "aid in diagnosis" not standalone.

SECTION	TEXT	COMMENT
Indications for Use Page 5 Item 1 ¶ 4	" It was not considered appropriate to indicate the use of such test for individuals without evidence of liver disease."	We recommend that the sentence be deleted. Patients infected with HCV often present with no signs or symptoms for a number of years. Further, testing is recommended for defined risk groups such as IV drug users, etc.
Indications Page 6 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."	We recommend that these indications for use be deleted and replaced with a general statement of intended use such as, "Aid in the diagnosis of HCV infection."
Indications Page 6 Item 8	"Monitoring HCV Infection includes at least several important indications . . . "	FDA should clarify how it defines monitoring. We suggest monitoring be defined as 1) 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 or HCV antigen) 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, those not a candidate for therapy, or non-responders.
Device Methodology Page 7 Item D. 3. b.	"You should also include the upper positive range after which a 'prozone' effect may cause a false negative result."	Remove from this section, as it does not pertain to controls. High dose hook studies should be performed and results provided in the labeling when appropriate.

SECTION	TEXT	COMMENT
Device Methodology Page 8 Item D. 3. d.	"Matrices of controls and specimens should be identical."	This puts undue burden on clinical laboratories and manufacturers. Unless established otherwise by serum/plasma equivalence studies, serum and plasma should not be considered different matrices. Both are protein based which is the critical factor. An aqueous control for example, when testing serum plasma sample would not typically be appropriate, but a serum control used when testing plasma specimens is common lab practice. Propose wording: " Matrices of controls should mimic insofar as possible the specimens to be tested."

SECTION	TEXT	COMMENT
Specimen collection, transport . . . Page 8 Item E. 2.	"Types and recommended volumes of all appropriate specimens for testing. Discuss the effects of testing inadequate or inappropriate specimens types and applicable volumes of all appropriate specimens for testing. Additionally, discuss the effects of testing inadequate or inappropriate specimens"	The terms inadequate or inappropriate are open-ended and need to be better defined. We recommend the following revision: "Types and applicable volumes of all appropriate specimens for testing."
Specimen collection, transport . . . Page 8 Item E. 3.	"Appropriate processing and transport conditions (e.g., time and temperature) for each type of specimen and the effect(s) of inappropriate processing and transport"	The term inappropriate is open-ended and needs to be better defined. We recommend the following revision: "Appropriate processing and transport conditions (e.g., time and temperature) for each type of specimen."
Specimen collection, transport . . . Page 8 E.4	"Recommended storage time and temperature and the effect(s) of inappropriate storage time and temperature."	The term inappropriate is open-ended and needs to be better defined. We recommend the following revision: "Recommended storage time and temperature."
Performance Characteristics Page 9 ¶ 4	"Any cutoff changes . . . may need to be tested in subsequent clinical or reproducibility studies."	Clinical studies are not needed for a change in cutoff value. We suggest the following revision: "Any cutoff changes, however . . .may need to be tested in subsequent reproducibility and/or validation studies."
Preclinical Laboratory Studies Page 10 Item 1 b ¶ 1	"FDA recommends that the manufacturer describe the basis for and then establish a least one equivocal (gray) zone; different equivocal zones might be appropriate for different indications for use."	We suggest the following revision: "For qualitative assays, describe the basis for equivocal zone, if applicable."
Preclinical Laboratory Studies Page 10 Item 1 b ¶ 2	Traditional microtiter-plate EIAs for anti-HCV essentially designate . . . a different type of testing and interpretation algorithm should be extensively supported by data and analysis from the manufacturer."	We recommend FDA delete this text; it is unnecessary

SECTION	TEXT	COMMENT
Preclinical Lab Studies Page 10 Item A.2.a	" ***Analytical sensitivity*** should be determined for: a. Each of the specimen matrices and diluents that would be used."	Where equivalence has been demonstrated between specimen matrices or diluents there is no need to demonstrate analytical sensitivity for each matrix or diluent used. Proposed wording: "Each specimen matrix where differences in performance during equivalence studies has been established."
Preclinical Laboratory Studies Page 11 Item 2	"FOR EXAMPLE, THE OUTSIDE OF THE KIT SHOULD INDICATE THIS CONTRAINDICATION IN BOLD LETTERS THAT CONTRAST WITH OTHERS.	We agree that assays that have not been licensed by CBER should be clearly labeled as such. How this will be done is a style issue. We recommend deleting this text.
Preclinical Laboratory Studies Page 11 Item 2 ¶1 Bullet 5	"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."	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 11 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 either chronic or acute. Concentration values can change for various reasons (e.g., treatment). A correlation between concentration value and infection status is not 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 4 a	"Search Genbank or other comprehensive nucleic-acid databases for similarity between sequences of the assay's analye-specific reagents and those of other entities.	This can be a burdensome task; if there are specific diseases then those should be stated. At the rate this technology is moving, any results presented would likely be outdated when published. Those interested in this area should conduct their own research when it is relevant.

SECTION	TEXT	COMMENT
Preclinical Laboratory Studies Page 12 Item 5 a	"Endogenous substances likely to be present in specimens (e.g., triglycerides, bilirubin, hemoglobin, proteins, therapeutic drugs or illegal drugs). For studies, the source of such endogenous substances should be actual human specimens (that will contain the range of metabolic permutations of each substance) rather than purified products."	By requiring that the source of endogenous substances used in interference studies be from actual human specimens, FDA is imposing requirements not imposed on other tests. There is nothing special about HCV tests that would require this. The use of human samples containing natural levels of endogenous substances and appropriate levels of the analyte under test is overly burdensome and not always possible. Obtaining samples from individuals containing these substances would be extremely difficult particularly at clinically meaningful or therapeutic levels. Evaluating potentially interfering endogenous substances (triglycerides, bilirubin, hemoglobin) can be performed following NCCLS EP-7P. These prepared samples can be tested with analyte spiked into them at levels close to the decision point(s) of the assay. Further, there are also privacy issues surrounding getting actual specimens in regards to illegal drug users. To recreate these specimens, creates an undue burden on finding a lab and setting up a lab for controlled substances. We recommend that the second sentence is deleted leaving the following text: Endogenous substances likely to be present in specimens (e.g., triglycerides, bilirubin, hemoglobin, proteins, therapeutic drugs). In addition FDA should clarify that it would be acceptable to spike HCV from a reactive specimen into human specimens containing the endogenous substances to conduct these studies.
Preclinical Laboratory Studies Page 12 Item 5 b	Exogenous substances . . . that may have been introduced to individual specimens or an archived collection.	FDA should clarify "different drugs". Therapeutic or illegal drugs are assessed under 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. Where equivalence has been demonstrated between specimen matrices and anticoagulants there is no need to conduct real-time stability studies on each matrix or anti-coagulant used. 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." There is no valid scientific basis for the requirement.
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)."	This should be deleted. FDA regulation requires that medical devices containing human blood or a blood component as a component of the final device and that are 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."
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."	Where equivalence has been demonstrated between specimen matrices or diluents there is no need to demonstrate reproducibility for each matrix. Under these circumstances, this would be overly burdensome. A representative approach is a more feasible option. 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). We recommend the following revision: A different group, or panel of specimens should be studied unless matrix comparisons have demonstrated no bias between results of the matrices being considered."

SECTION	TEXT	COMMENT
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). 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. Finally, due to the rarity of some genotypes/variants it will not be possible to undertake reproducibility studies on all genotypes or variants. Therefore, we suggest FDA delete it from this section.
Preclinical Laboratory Studies Page 13 Item 10 f	"For qualitative assays, it if often useful to include specimens that yield the cut-off value, 1.2 x cutoff, and 0.8 x the cutoff value."	The proposed approach will not work for both immunodiagnostic tests an amplified NAT tests. The guidance needs to address the differing concerns raised depending on what type of assay is under investigation. 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].

SECTION	TEXT	COMMENT
Instrument Performance Page 15 Item 12. b and c	FDA recommends you provide the following: b. Studies demonstrating the absence of sample or reagent carryover. c. Description, explanation and validation supporting the effectiveness of error messages.	Data requirements as specified in the Guidance document on Software controlled Medical devices (May 1998) should be sufficient to respond to these items and reference should be made to that Guidance document in item 12. What is currently written here is too subjective. Suggest replacing the present wording with reference to following that Guidance at a "Moderate" level of concern. The requirements and level of detail are more clearly specified for this particular item. It has been sufficient guidance for recently PMA approved HBV assays
Design and Protocols for Clinical Studies 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 documented and explained."	Please clarify the phrase "site-to-site variables" by providing examples, particularly as it relates to clinical design.
Design and Protocols for Clinical Studies 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."
Design and Protocols for Clinical Studies Page 16 Item 4, ¶ 2 Bullet 3	"However, without additional information about and individual, it would not be known if testing was ordered for pre or post vaccination assessment."	Delete or modify indicating that there is currently no vaccine available.

SECTION	TEXT	COMMENT
Design and Protocols for Clinical Studies Page 16 Item 5. a (1)	"Examples of such off-label deviations are "initial" (single aliquot) testing only for a currently licensed anti-HCV EIA that specifies, "repeat" triple-aliquot testing . . ."	Delete "triple aliquot", if an initial reactive is obtained and a second aliquot is tested and found to be reactive, it is not necessary and of no value to test a third aliquot, this should be permissible.
Design and Protocols for Clinical Studies Page 17 Table 1		We suggest that the table be reviewed by practicing clinicians. In addition, definitions should be checked against current package inserts. For example, requirement to repeat triple aliquot testing, definition of indeterminate, definition of not HCV infected and collection of an additional specimen within 3 months.
Design and Protocols for Clinical Studies Page 18 Item 5 b	"Other appropriate lab findings should be documented from line data provided for each individual or specimen."	We recommend that FDA clarify its definition of line data. It would be helpful to know whether the term has the same meaning for industry and FDA. We suggest that it be added to the definitions.
Design and Protocols for Clinical Studies 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."	To clarify this item we suggest FDA provide examples of "information about individuals" mean Also, please delete "possibly" This deletion will provide industry clearer instructions. FDA should specify the level of data needed to support a physician's diagnosis.
Design and Protocols for Clinical Studies Page 19 Item 6 b	"Active Infection"	Please clarify the intent of this section. Does it refer to testing a new RNA test, or using an RNA test to validate infection status indicated by a new EIA test. If it is the latter, the bulleted data are likely to be impossible to obtain.

SECTION	TEXT	COMMENT
Design and Protocols for Clinical 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)."	FDA has recommended that reference materials be quantified. Are reference materials available? If so, how should they be quantified?
Design and Protocols for Clinical Page 20 Item 6 b(2), (3)	"Acute infection should be demonstrated by testing multiple specimens from the same individual . . . FDA recommends testing at least four specimens (two successive specimens yielding negative results via comparative anti-HCV testing, followed by two successive specimens yielding positive results." Chronic infection should be demonstrated by testing two or more specimens collected from the same individual during an interval of at least 6 months. Approved comparative testing should be used to detect anti-HCV or HCV-RNA after this 6-month interval.	In both situations, this is not practical since it typically is not done clinically, and, it is burdensome for an IVD clinical trial as both the logistics of collecting of specimens over time and the cost to do so would be very difficult if not impossible to collect. Subject compliance would be a major issue to accomplish this. If an indication is sought by a study sponsor/manufacturer for a test as an "aid in diagnosis of active" HCV, or, "as an aid in diagnosis of chronic " HCV, it should be not expected that test results on multiple specimens per individual be a minimum requirement for safety and effectiveness data to support such an indication. To repeat, to do so is burdensome and not necessarily consistent with current clinical practice.
Design and Protocols for Clinical Studies 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, or non-responders.
Design and Protocols for Clinical Studies 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 recommend that the requirement to conduct a prevalence study on a healthy population be deleted. Although relevant to the disease itself, such a study does not impact the safety and effectiveness of the device.

SECTION	TEXT	COMMENT
Design and Protocols for Clinical Page 21 Item 6 d (2) ¶ 1-2	"Healthy individuals are appropriate for studying specificity with regard to indications that pertain to asymptomatic HCV infection . . . and for determining prevalence . . . To interpret a prevalence study for a new anti-HCV assay, results should be presented as % new-assay-positive . . . Comparative testing results should not be used to interpret the specificity of new-assay results, unless comparative testing has been applied to statistically appropriate subsets of specimens that yielded positive and negative results with the new assay."	This section implies that blood donors would not be considered an acceptable population. Examples of what FDA considers acceptable healthy populations would be helpful. We recommend the following revision: " Healthy individuals are appropriate for studying specificity with regard to indications that pertain to asymptomatic HCV infection. "
Design and Protocols for Clinical Studies 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. 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."
Design and Protocols for Clinical Studies Page 22 Item 8.a.	"Specimens should be masked. Personnel who perform the studies and interpret the data should not know any characteristics about the specimens, including results from comparative or other assays."	This is burdensome as usually 2 technologists are assigned to study. Practical considerations such as vacation, illness, etc. may render it impossible for an individual not to have previously performed the comparative assay. Revise to "Personnel...should not have immediate access to characteristics...when performing the study." Besides, for automated tests, an operator's knowledge of the specimen tested isn't likely to influence the assay's outcome. There is no subjective interpretation of results. Thus, masking Would provide little added benefit.
Design and Protocols for Clinical Studies Page 22 Item 9.a.	"Analysis should be masked. Personnel who assign individuals or specimens into categories should not know assay results."	Revise to "Personnel...should not have access to investigational assay results when assigning categories."

SECTION	TEXT	COMMENT
Design and Protocols for Clinical Studies 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 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 for Clinical Page 22 Item 9 b (2)	"Performance for diagnostic indications with qualitative assays should also include validation of cutoff(s). You 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 to challenge the assigned cutoff or data from a specific population. 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 ROC analysis performed. ROC analysis requires two different populations. 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)."
Design and Protocols for Clinical Studies 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.e., 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 the FDA Modernization Act of 1997: Concept and Principles; Draft Guidance for FDA and Industry].

SECTION	TEXT	COMMENT
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. This proposed change in use of these terms is a significant one and should be reviewed by laboratory community.
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 disagree with this statement. This change in terms should be address by practicing clinicians. Supplemental testing is not needed in the diagnostic arena.
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 that this is relevant to practicing clinicians. Goes back to intended use and what we say the intended uses should be
Design and Protocols: Additional Recommendations Page 27 Items 2, 3 & 4	b. "Case Report Forms should be submitted, with entries to for data to demonstrate absence of symptoms and biochemical abnormalities."	Data from case report forms (CRFs) are generally provided as raw data line listings in SAS, Excel or other similar formats. There is nothing unique about HCV premarket submissions that would warrant deviation from common practice. CRFs are available for review during both site and sponsor BIMO inspections. We recommend changing "Case report forms" to read "Raw data line listings***" submitting summary information that describes the study populations but not CRF's.***

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 28 Figure 1 Footnote e	"Definition of "inactive HCV infection": please refer to V.B.5.c"	The footnote reference V.B.5.c. is a typographical error. The reference should be V.B.6.c.
Design and Protocols: Additional Recommendations Page 29 Item 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 there are not likely to be alone to determine the clinical decision points.
Design and Protocols: Additional Recommendations Page 29 Item 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 biological or assay variability.

SECTION	TEXT	COMMENT
Design and Protocols: Additional Recommendations Page 29 Item 7 Bullet 4 ¶ 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].