GEN-PROBE

9928 '01 JUL -3 10:08

June 29, 2001

Woody Dubois, Ph.D.
Branch Chief, Virology
Division of Clinical Laboratory Devices
Food and Drug Administration
Room 1061 (HFA-305)
2098 Gaither Road
Rockville, MD 20850

Re: "Draft Guidance on Premarket Approval Applications for Assays Pertaining to Hepatitis C Viruses (HCV) that are indicated for Diagnosis or Monitoring of HCV Infection or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 Gen-Probe Incorporated 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.

Gen-Probe Incorporated appreciates the opportunity to comment on this document. 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. Gen-Probe Incorporated believes 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 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

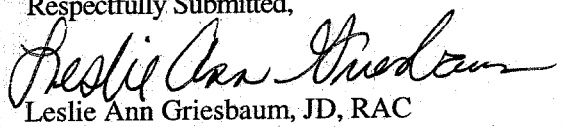
99D-3028

C2

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.

Gen-Probe Incorporated sincerely appreciates DCLD's attempt to recognize the needs of the industry, and the requirements of the FDAMA, in seeking least burdensome means to demonstrate Safety and Effectiveness.

Respectfully Submitted,



Leslie Ann Griesbaum, JD, RAC
Regulatory Affairs Specialist

cc: Steve Gutman, DCLD; Carolyn Jones, AdvaMed

(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
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 than the ones specifically referred to in the guidance. By specifically mentioned creates a bias that these two are the only methods in the industry. It indicates 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 C	"Description of epidemiology, including prevalence and groups at risk for infection and disease."	This information is not assay specific and every manufacturer should not be required to repeat it. It is usually contained in the published literature reference in the bibliography.
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."	These statements have not been required for serology assays and should not be apart of intended use for any future intended use statements. Allowing statements such as these in the draft guidance gives an impressing that the FDA is biased against new technologies.
Detailed Principle Page 7 Items 5-6	"Cutoff value(s) or reporting threshold, for qualitative assays." "Limit of detection and limit of quantitation, for quantitative assays."	FDA should define the following terms in the guidance or provide references to generally accepted definitions: "reporting threshold"," limit of detection" and " limit of quantitation."
Performance Characteristics Page 8 ¶ 5 bullet 2	"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. We suggest the following revision: "Any cutoff changes, however . . .may need to be tested in subsequent reproducibility and/or validation studies."

SECTION	TEXT	COMMENT
Preclinical Laboratory Studies Page 9 Item 1 b	"For a qualitative assay, FDA strongly 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." "NB: Traditional microtiter-plate EIAs for anti-HCV essentially designate all values above a cutoff as equivocal; i.e., specimens that yield "initial" positive results are retested in duplicate before reportable results are interpreted. At this time, ALL ASSAYS INDICATED FOR SAFETY OF BLOOD OR BLOOD PRODUCTS SHOULD BE DESIGNED TO ADHERE TO SUCH A REPEAT-TESTING ALGORITHM. Manufacturers should contact CBER for specific and updated recommendations. While there is no requirement for such an algorithm when an assay would be used for diagnostic or monitoring indications, a different type of testing and interpretation algorithm should be extensively supported by data and analysis from the manufacturer."	We suggest the following revision: "For qualitative assays, describe the basis for equivocal zone, if applicable." We recommend FDA delete this text; it is unnecessary
Preclinical Laboratory Studies Page 10 Item 2 c	"FOR EXAMPLE, THE OUTSIDE OF THE KIT SHOULD INDICATE THIS CONTRAINDICATION IN BOLD LETTERS THAT CONTRAST WITH OTHERS. THE MANUFACTURER SHOULD USE A DIFFERENT COLOR FOR LABELING (KIT, VIALS, PACKAGE INSERT, ETC) THAN THOSE FOR OTHER ASSAYS IT DISTRIBUTES." "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 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. 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 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**."

SECTION	TEXT	COMMENT
Preclinical Laboratory Studies Page 11 Item 4 a	"Search Genbank or other comprehensive nucleic-acid databases for similarity between sequences of the assay's an....."	This can be a burdensome task, if there are specific diseases than 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.
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. We suggest the following revision: "Endogenous substances likely to be present in specimens (e.g., triglycerides, bilirubin, hemoglobin, proteins, or therapeutic drugs.)" We are very curious as to why the FDA would change commonly accepted practices for this document. There are also privacy issues surrounding getting actual specimens in regards to illegal drug users. To recreate these specimens it creates a undue burden on finding a lab and set up a lab for controlled substances.
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 the types of exogenous substance by providing examples.
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. The cost of such studies is not justified. 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 12 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."	This can be burdensome. A representative approach may be more feasible option.

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."	These are tested as part of analytical sensitivity. Reproducibility should be claimed on the most sensitive and most divergent. The statement should be changed to clearly allow for this least burdensome concept.
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.	This analysis does not distinguish between serology and amplified NAT testing. This approach does not work for both. Since there is approved quantitative assay to get those results with a certainty can't be done with amplified NAT testing. If a claim of 50 c/mL is made, the 1.2 and 0.8 of those cut-offs are well within the range of the quantitative assays at these lower copy levels.
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."
Design and Protocols: General Considerations Page 20 Item 6 b(2) (3)	stipulates that multiple specimens from the same individual should be tested. Such a series of (at least 4) specimens should be initially antibody negative and later specimens, antibody positive. Also, page 20, section (3), two or more specimens per individual during a period of at least 6 months should be tested to establish chronic infection.	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.

GEN-PROBE

Gen-Probe Incorporated
10210 Genetic Center Drive
San Diego, CA 92121-4362

SAN DIEGO CA JUN 29 '01
0.55
U.S. POSTAGE
8215214

Woody Dubois, Ph.D.
Branch Chief, Virology
Division of Clinical Laboratory Devices
Food and Drug Administration
Room 1061 (HFA-305)
2098 Gaither Road
Rockville, MD 20850