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February 12, 2001

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

Re: ***Docket No. 99N-2337 Current Good Manufacturing Practice for Blood and Blood Components; Notification of Consignees and Transfusion Recipients Receiving Blood and Blood Components at Increased Risk of Transmitting HCV Infection (''Lookback''); Proposed Rule***

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Dear Sir:

Thank you for the opportunity ro comment on the proposed rule for hepatitis C virus (HCV) "Lookback" noted above.

The regulations you have proposed are far-reaching. They go beyond those currently in effect, based upon prior guidance issued by the Food and Drug Administration (FDA). I trust, therefore, that you will revise the proposed rules to make them more appropriate, up-do-date, and efficient for those impacted by "Lookback."

As noted on **page 69379, under Section B., Existing Donor Screening and Testing Requirements,** the extant HIV lookback regulations also need modification. I agree. Currently, nucleic acid testing (NAT) is being performed for HIV RNA on virtually all units of blood collected in the United States, albeit, under Investigational New Drug (IND) protocols. Despite the fact that HIV NAT is not licensed, the use of this type of assay is still considered to be the "gold standard" of whether or not an individual is carrying HIV and, thus, capable of transmitting this infection. Therefore, present recommendations, as well as proposed regulations, should take this fact into account. If an individual, e.g., a donor, has a reactive anti-HIV EIA test, and is positive for HIV RNA by NAT, then lookback should proceed forthwith. However, if HIV NAT is non-reactive, then the donor is not infected with HIV, and is most likely a false positive; therefore, lookback should <u>not</u> proceed. The same should hold true for HCV RNA testing by NAT. Thus, if a blood donor has a repeatedly reactive anti-HCV test by EIA, and a reactive NAT for HCV RNA, lookback should proceed, irrespective of other "confirmatory" testing, e.g., by the recombinant immunoblot assay (RIBA). On the other hand, if the HCV RNA NAT is non-reactive, then, the donor is almost certainly not infectious. Section 610.40(c) of the Proposed Rule should permit donations found to be repeatedly reactive by screening tests to be further tested with <u>either</u> a licensed or an investigational supplemental test to determine if the donor is truly, not falsely, reactive in the screening test.

On **page 69381**, the consignee must notify the recipients' attending physician, or the recipient, that they may have received a unit of blood infectious for HCV based upon just a repeatedly reactive test for antibody to HCV. By the time an individual is actually notified, some type of licensed, or investigational confirmatory, assay could have been

performed, which would either make the notification necessary, or unnecessary. In the case of the investigational NAT, which is being concurrently performed (certainly within 3 calendar days of serologic testing), its result would be known along with the repeatedly reactive test for antibody to HCV. Thus, it would make more sense to notify, or not notify, based upon this immediately available test which is considered by most to be the "gold standard" of whether or not someone is infected (and infectious). Therefore, the HCV proposed rule should be modified to take into account NAT; also, the HIV lookback process should be similarly modified. At the bottom of this page, there appears to be a typographical error, in that "1998" should probably be "1988."

At the **top of page 69382**, it is noted that the proposed rules would not require quarantine of products that have already been pooled for further processing into plasma derivatives, since fractionation, along with attendant processes, inactivates or removes HCV. I applaud this proposed rule!

Under **Section C., Proposed Revisions to Section 606.160,** it is noted that increasing the required retention period to no less than 10 years will modify Section 606.160(d). Thus, since the prior transfusions will have taken place months to years in the past, and cannot be interdicted, this is another reason to wait for some type of "confirmatory" testing to be done before notification, whether the "confirmatory" testing is licensed or investigational.

On **page 69383**, under **Section F., Proposed Section 610.48(a) Quarantine and Consignee Notification,** blood establishments would be required to take appropriate action within 3 calendar days after the date on which a donor returns to donate, and is found to have a repeatedly reactive test for "evidence of HCV infection on a required test..." If this is meant only to apply to in-date components to prevent transfusion, this should be carried out in this time frame. But, if it is meant to start the patient notification, it is inappropriate and too short. As noted in the previous paragraph, most prior donations would have been transfused months, if not years before, so there is no urgency, certainly within 3 calendar days, to attempt to notify them, plus it is unlikely they would be found within 3 days. Therefore, the blood establishment should be permitted to perform confirmatory testing, or base notification on NAT, which should be available in 3 working days, to determine whether or not a donor is capable of transmitting HCV. It may be appropriate to quarantine any components not transfused, but it is definitely not appropriate to begin consignee notification so soon, and without taking into account all testing which is performed, whether licensed or investigational, e.g., NAT. I am glad to see that, later on the page, the FDA recognizes that, if there are no in-date prior collections, there is no need to quarantine or trace products.

Section 610.46(a) of the HIV lookback should be modified to conform to the current guidelines for HCV lookback; both should permit the use of NAT results to determine consignee notification. The majority of anti-HIV and anti-HCV tests, when performed on

asymptomatic blood donors are falsely positive; therefore, much notification, based upon just a repeatedly reactive EIA test, would be unwarranted. If on the other hand, the results of NAT were positive for either HIV RNA or HCV RNA, this should trigger a lookback; conversely, if the tests for HIV RNA and HCV RNA were non-reactive by NAT, then, lookback should not be carried out irrespective of even a licensed, confirmatory test, e.g., the Western blot, or the RIBA.

Re **page 69384, Section G., Proposed Section 610.48(b) Further Testing and Consignee Notification of Results.** As noted, it would be appropriate to do further testing of an individual found to be repeatedly reactive for evidence of HCV infection, and to notify consignees within a 45-day calendar period after the day on which the donor tested repeatedly reactive. This is what really should be done, and not the initial notification less than 3 calendar days without some type of confirmatory tests being completed first. In most of America today, NAT is being performed for HCV RNA, so could be the confirmatory test, even if it is not licensed at the moment. As noted in the second paragraph, this could also be true for HIV, both in terms of lengthening the period to 45 days, and using NAT as the "confirmatory test."

Section H., Proposed Section 610.48(c), Review of Historical Testing Records and Identification of Donors Tested Using a Multiantigen Screening Test Prior to the Effective Date of this Regulation. It is noted that the FDA would "take into account the use of unlicensed tests, under specific circumstances." Certainly, NAT would qualify here, and should be used as part of the process of deciding whether or not a donor is infected with hepatitis C virus. However, this paragraph ends up with the comment that there must be "use of a currently licensed test, as specified." Please note: if the only result we have on a donor is a validated NAT result for HCV RNA, along with a negative EIA for anti-HCV, and the donor does not return, there would be no requirement to do lookback.

Under **proposed Section 610.48(c)**, the dating should not go back "indefinitely," even for computerized, electronic records. It should be 10 years maximum; it is likely there would be no records beyond this, and patients would be difficult to find beyond this time period, anyway. As noted on **page 69385**, it is reasonable to restrict the lookback to "prior collections dating back to the last 12 months prior to the donor's most recent negative multiantigen screening test for HCV."

In the **second full paragraph on page 69385**, the FDA describes a number of situations where there is an increased risk of transmitting HCV from the donor's prior collections. Certainly, this is a place where NAT results for HCV RNA should be taken into account, or other unlicensed tests, which show increased risk of infectivity. As written, however, the RIBA 3.0 must be used to avoid lookback; this locks blood and plasma collectors into a single test from one manufacturer to determine lookback.

In the **paragraph which begins at the end of this page, and continues over to page 69386**, it is not clear, in fact, it is confusing, what do to if the S/CO is less than 2.5 with an HCV 1.0 EIA test. When the results are less than 2.5 S/CO for a 1.0 EIA screening test, there should be no lookback of patients, since the vast majority of these results are falsely positive. It would be appropriate if the results were equal to or greater than 2.5 S/CO to do lookback, if there were no confirmatory testing of the sample.

Section J. on page 69386 entitled, Proposed Section 610.48(e), Quarantine and Consignee Notification... Since proposed Section 610.48(e)(2) would require notification within 3 calendar days, the use of test results from NAT should be employed here. If the sample were NAT negative for HCV RNA, then, this should end the lookback and quarantine of prior units. If this section is to remain 3 days, then it should really be 3 working days, because of holidays and other time periods that may not be feasible to perform supplemental testing and/or notification.

Page 69387: proposed **Section 610.48(f)(2)** is academic, since no 1.0 tests are left, and any testing by this first generation EIA would have been performed from 1990 to 1992. Thus, there is no need to require blood establishments to notify consignees of the test results within 3 calendar days!

In proposed **Section 610.48(g)(1)(ii)**, there should be an allowance for nucleic acid testing for HCV RNA. Unnecessary notification could be done with harm to the recipient, due to a notification for a falsely reactive EIA test. Note: HCV is not as transmissible to contacts as HIV; so, the HIV rules should not apply here.

On **page 69389**, the FDA discusses the results of testing by the polymerase chain reaction (PCR), a test, which uses nucleic acid technology to determine whether or not a person has HCV RNA. Since the FDA discusses the importance of PCR here, it should acknowledge the role of this test in conjunction with EIA testing for anti-HCV; both are being currently performed on almost all blood and plasma units being collected in the U.S. By citing the importance of PCR testing to validate results of the RIBA supplemental test, the FDA has acknowledged the importance of PCR for detecting HCV RNA, irrespective of the fact that PCR is an unlicensed assay.

On **page 69390, Section O., Proposed Section 610.48(j), Release from Quarantine,** it is not clear here what to do if the result is indeterminate by the RIBA 3.0, especially if there is a negative result by PCR. What would be the purpose of notifying prior recipients in this case, since all the data would indicate that the anti-HCV EIA is falsely positive?

On **page 69392, Section S., Proposed Section 610.49(b)**, it states that: "The transfusion service is ultimately responsible for ensuring that the notification takes place." Actually, the patient's physician should be ultimately responsible; only if the physician is unavailable or defers to the transfusion service, should the transfusion service, then, take

over the notification process. If, however, the physician decides that notification is inappropriate, or not justified, this decision should not be overridden by a transfusion service. Further, the transfusion service is usually not in a position to provide to the recipient counseling and further testing. The notification should be by the physician responsible for the patient, and the transfusion service should only take this over if requested to do so by the physician. Further, as noted on **page 69393**, the requirement for three attempts should be changed to one. If one documented attempt is unsuccessful, e.g., a return receipt requested letter, are there any data that two more attempts would be any more successful? In the only studies to date, which we carried out, looking at the impact of lookback notification, almost half of the patients impacted did not wish to be notified. What would be the purpose of trying to notify them three times, if after the first one they indicated they did not wish to be notified? (See Aoki, et al. *Evidence of hepatitis in patients transfused with blood components containing antibody to hepatitis C.* Blood 1993;82:000-1005; and, Aoki, et al. *Evidence that use of a second generation hepatitis C antibody assay prevents additional cases of transfusion-transmitted hepatitis.* Journal of Viral Hepatitis, 1994;1:73-77).

Page 69393, Section T., Proposed Section 610.49(c), Notification of Legal Representative or Relative. The proposed section 610.49(c) requiring the transfusion service or the physician to notify a legal representative designated in accordance with State law, if the recipient has been adjudged incompetent or, subsequently, found to be dead, is both inappropriate and unnecessary. The risk of secondary transmission of hepatitis C is slim, and little purpose would be gained by notification of a legal representative for a patient who is either incompetent, or dead. Further, much wasted effort might be spent trying to determine the legal representative who should be notified. This is especially incongruous if the recipient is deceased.

On **page 69397, under Section B., Benefits of the Proposed Rule, Item 1., Individual Benefits of HCV "look-back,"** it is stated that there is a "medical and ethical imperative to inform identified transfusion recipients of their HCV risk." If FDA believes this to be true, it should apply to those infected with HCV not related to transfusion, the vast majority of HCV-infected individuals. Further, those who have acquired HCV, not by transfusion, are more likely to live long enough to get complications of HCV. Thus, the ethical imperative should be extended to those individuals who have acquired HCV by any routes, not just to the estimated 7% who have acquired HCV via transfusions in the past. In addition, since there is no CDC recommendation to take any sexual precautions to avoid HCV infection, why should "infected patients identified through the proposed lookback procedures [be told they] could take steps to protect sexual partners from the risk of infection"? Finally, health care providers (HCP) should treat patients no differently, whether they are known to be infected with hepatitis C, or not. In fact, knowing a patient is infected with hepatitis C might make HCP unusually cautious and more prone to stick themselves than if they used universal precautions for all patients because of a risk of any infection, identified or not. Most infected patients, whether by

transfusions or the more usual route, IV drug use, would not qualify as blood donors, so need not be informed that they must not donate blood. Further, with the multiple testing we have in place today, even if they attempted to donate and passed the donation process, they should be picked up by the current HCV antibody test and the concomitant use of NAT for HCV RNA.

On **page 69398**, what is the basis for the FDA's assumption that 48% of notifications would be successful? The data show that only 50% of people are alive six months after a transfusion; of these, many may not be locatable, or do not wish to be notified (see Aoki et al., 1993). In fact, the targeted lookback efforts to date have been incredibly ineffective, identifying only a few percent of those at risk from HCV infection by transfusions.

Further, on **page 69398, under Section 2. Societal Benefits of HCV Lookback,** the FDA has ignored the fact that 93% of individuals with HCV did not acquire this infection by transfusions. If it is so important to notify individuals with HCV from transfusions, why is it not even more important to get at the 93% of HCV acquired by other means?

On **page 69399, under Item 3.a., Alternatives Considered for HCV Lookback**, the FDA raises issues about the risk of litigation. Does the FDA have any idea of how many HCV cases have been filed because of lookback? We have one already, based on a false positive HCV test (shown by follow-up testing on the donor). Defending against unwarranted lawsuits is costly, and time-consuming, plus further erodes the resources of a blood center.

On **page 69400,** the FDA describes data from Canada regarding lookback efforts. These data are not generally applicable to the United States. In Canada, the cost of medical care is borne by the government, as opposed to the United States, where it is not. However, even in Canada, the efficacy of targeted lookback has been marginal. Further, there was no provision in Canada for not wanting to be notified (see prior references).

In sum, I would like to re-emphasize some of the points, which I believe are problematic in the proposed rules. The urgency and significance of HCV lookback are not the same as those for HIV. If anything, the HIV rules should be changed to the HCV guidelines currently in place. Most importantly, there is time to wait for some kind of supplemental, or confirmatory, testing beyond just 3 calendar days. In most cases, nucleic acid testing for HCV RNA will be available in this time frame; this "gold standard" test should be taken into account in the notification process. Even when the only licensed, supplemental test is performed and found to be positive after a reactive anti-HCV by EIA, a nucleic acid test, e.g., PCR for HCV RNA, is used to determine the need for therapy and to help counsel the patient. Why then do we not use the same "investigational test" to help determine HCV lookback? One valid, documented attempt

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should be sufficient to notify a recipient, instead of 3 times. Finally, there should be no need to notify the legal representative of a deceased patient.

Thank you for your consideration of these comments.

Sincerely,

Paul Holland

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Medical Director/Chief Executive Officer

PVH:rc 33.01

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