Stanford Medical School
Blood Center

February 10, 2001

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

Re: Docket No. 99N-2237

Proposed rule: 21CFR Parts 606 and 610
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")

To the Docket:

I am writing in general support of the FDA's proposed rule that would extend the requirement for HCV lookback to include the prior donations from individuals identified as HCV-infected through their reactivity on the first generation HCV screening test, and extend multiantigen lookback further back in time. In fact, my institutions (a blood center and transfusion service) have already performed an extended lookback. The preliminary results of our program were presented to the PHS Advisory Committee on Blood Safety and Availability in January 1999. This presentation, I believe, was instrumental in convincing the Advisory Committee that an extended lookback was feasible. The final results of our extended HCV lookback are now published (reference 1).

I have some concerns and questions, however, about some of the specific recommendations in the proposed rule:

1. **Are the criteria for consignee notification and recipient notification different?**

   It would greatly simplify the rule if you could state in one place all the conditions that trigger quarantine and consignee notification. The rule is currently so long and complex that it is very difficult to find the relevant guidance, even with the reference chart. It appears that there are different criteria for consignee notification versus recipient notification. If this is the case, please clarify whether the requirements for consignee notification apply only to products that could still be in-dated.

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2. Inclusion of donors with S/CO less than 2.5 in the lookback process.

Proposed 21 CFR 610.48 (d) (3) states that lookback process must be initiated if the donor's reactivity on the first generation screening test showed a sample to cut-off ratio of less than 2.5 on two out of three tests. However, the PHS Advisory Committee specifically recommended that such donors be excluded from the lookback requirement. The Advisory Committee's recommendation was based on data presented at the January 1999 meeting indicating that donors with a sample to cut-off ratio of less than or equal to 2.5 had a low likelihood of HCV infection. (These data have been published, see reference 2). I suspect, therefore, that paragraph 610.48 (d) (3) was included in the proposed rule by mistake. Donors with a sample to cut-off ratio of less than or equal to 2.5 should be excluded from lookback. Paragraph 610.48 (d) (3) should be deleted from the rule.

The data presented to the PHS Advisory Committee and published in reference 2 suggest that lookback should be required for donors with sample to cut-off ratio of greater than 2.5. These are the donors described in paragraph 21 CFR (d) (4) of the proposed rule, which should be retained; however the wording should be corrected to refer to donors with S/CO "greater than 2.5" as this is how the data have been presented, not "greater than or equal to 2.5."

3. Role of unlicensed RIBA 1 results in the lookback:

21 CFR 610.48 (d) (2) as it is presently worded does not appear to allow a blood collection agency to use the results of a RIBA 1 assay to guide a first generation lookback. I request that the rule be modified to allow the use of RIBA 1 to guide lookback; specifically, to permit the exclusion from lookback donors that tested negative on an unlicensed RIBA 1 assay. The lookback program at our institution that was presented to the PHS Advisory Committee was based on RIBA 1 results. The Committee's recommendation did include an allowance for lookback to be based on such results. Many blood establishments performed unlicensed RIBA 1 or unlicensed RIBA 2 supplemental testing on donations that were reactive on the first generation HCV EIA.

In cases where RIBA 1 testing was performed, these results are more readily available to the blood collection agencies than are the values of sample to cut-off ratio. That is, many blood establishments have the results of donor supplemental testing in electronic databases. On the other hand, few if any blood establishments have the values of sample to cut off ratio available electronically. Therefore, most blood establishments would have to review individual test records to identify those donors with sample to cut off ratio of greater than 2.5. In some blood establishments, the information about the strength of reactivity may be available only on the original print-out from the EIA reader. Since the printouts from such readers are typically on thermal sensitive paper many of these records would no longer be readable. Such blood establishments would be required to perform lookback on all EIA reactive donors, which would lead to a large number of patients being notified inappropriately.

Thus, allowing blood establishments to use results of unlicensed RIBA 1 or RIBA 2 to guide lookback, where such results are available, would be of benefit both to blood establishments and transfusion recipients. Published data strongly support the option of using unlicensed RIBA 1 results to guide lookback. The published data, as presented below, indicate that a lookback guided by RIBA 1 would actually include a larger proportion of the truly infected donors than would a lookback guided by the use of sample to cut-off ratio.

Proposed 21 CFR 610.48 (d) (2) indicates that the agency would permit the use of RIBA 2 results to guide first generation lookback. Specifically, in cases where RIBA 2 results are available, lookback would be required if the donor were positive or indeterminate on RIBA 2, and would NOT be required if the donor were negative on RIBA 2. We believe that published data support the application of the same criteria to RIBA 1 results, i.e., to require lookback in cases where RIBA 1 results are positive or indeterminate, and to permit no lookback in cases where RIBA 1 is negative. This recommendation is based on two large studies that correlate the results of RIBA 1 and RIBA 2 on blood donor samples (references 3 and 4). Table 1 shows the results of one study that compares RIBA 1 and RIBA 2 results in samples from 367 U.S. blood donors that were reactive on HCV first generation EIA (reference 3). Table 2 shows the results of a similar study performed on 732 French blood donors (reference 4). Table 3 combines the results of both studies.

Table 1: Comparison of RIBA 1 and RIBA 2 results in U.S. blood donors (from Evans et al., reference 3)

		RIBA 2 results			
		Pos	**Indeterm**	**Neg**	**Total**
RIBA 1 Results	**Pos**	168	1	0	169
	Indeterm	22	29	23	74
	Neg	4	3	117	124
	Total	194	33	140	367

Table 2: Comparison of RIBA 1 and RIBA 2 results in French blood donors (from Courouce et al., reference 4)

		RIBA 2 results			
		Pos	**Indeterm**	**Neg**	**Total**
RIBA 1 Results	**Pos**	205	9	10	224
	Indeterm	40	64	97	201
	Neg	7	3	297	307
	Total	252	76	404	732

Table 3: Summary, comparison of RIBA 1 and RIBA 2 results (combination of results in Tables 1 and 2)

		RIBA 2 results			
		Pos	**Indeterm**	**Neg**	**Total**
RIBA 1 Results	**Pos**	373	10	10	393
	Indeterm	62	93	120	275
	Neg	11	6	414	431
	Total	446	109	544	1,099

As shown in Table 3, if lookback were to be performed on all RIBA 1 positive or indeterminate donors, this lookback would include 538/555 = 97% of donors who would have been reactive (positive or indeterminate) on RIBA 2.

In comparision, Table 4 shows the correlation of S/CO ratio with RIBA 2 reactivity. As shown in Table 4, a lookback triggered by S/CO > 2.5 would include only 1277/1500 = 85% of donors that are RIBA 2 reactive (positive or indeterminate).

Table 4: comparison of S/CO ratio with RIBA 2 reactivity (from Tobler et al., reference 2)

		RIBA 2 results			
		Pos	**Indeterm**	**Neg**	**Total**
S/CO ratio	**≤ 2.5**	146	77	1954	2177
	> 2.5	1180	97	299	1576
	Total	1326	174	2253	3753

Assuming that the agency's intent is to include in lookback donors that would have been reactive (pos or indeterminate) on RIBA 2 and to exclude from lookback donors who would have been negative on RIBA 2, we can compare the relative sensitivity and specificity of lookbacks guided by S/CO vs. RIBA 1 (Table 5)

Table 5: Comparison of the effects of using S/CO > 2.5 vs RIBA 1 reactivity (positive or indeterminate) to guide first generation lookback

	Donors To Be Included In The Lookback	
	S/CO > 2.5	**RIBA 1 pos or indet**
Percentage of total EIA 1 reactive donors that would be included in lookback	1576/3753=42%	668/1099=61%
Proportion of RIBA 2 positive donors that would be included in lookback	1180/1326=89%	435/446=98%
Proportion of RIBA 2 indeterminate donors that would be included in lookback	97/174=56%	103/109=94%
Proportion of RIBA 2 (positive or indeterminate) donors that would be included in lookback	1277/1500=85%	538/555=97%
Percentage of donors included in lookback who are negative by RIBA 2	299/1576=19%	130/668=19%

As shown in Table 5, a RIBA 1-guided lookback would include in the lookback program larger proportions of both RIBA 2 positive and RIBA 2 indeterminate donors than would a lookback guided by S/CO ratio. A RIBA 1-guided lookback program would not contain a larger proportion of RIBA 2 negative donors. In other words, when compared to the S/CO ratio method, the RIBA 1 method has better sensitivity and similar specificity. Therefore, blood establishments should be permitted to use RIBA 1 results to guide a first generation lookback where such results are available.

With regard to the remainder of the proposed rule, I have some additional comments/questions:

4. **Incorrect reference in 610.48(b) to a requirement for supplemental testing?**

   The section referred to, 610.40(c) does not seem to apply. Is this the wrong reference?

5. Timeframe for quarantine and consignee notifications triggered by review of historical test records

In 610.48 (e) and (f) the specified timeframe of 3 calendar days is confusing; it should probably not apply to this category of donors. The one-year timeframe should apply.

6. Further testing of donors identified through review of historical records:

Further testing of donors identified through the review of historical test records should be permitted but not required, i.e., the wording in 610.48(h)(1) and 610.48(i)(1) should be changed to "may" rather than "shall." Blood centers should be permitted the option of initiating lookback immediately, based on EIA reactivity, rather than trying to locate donors and trying to obtain a follow-up specimen for supplemental testing. Further testing should be presented simply as an option that could eliminate the need for lookback if certain results were obtained.

7. Is it permissible to use unlicensed RIBA 2 to guide lookback?

610.48(d) (1) and (2) do not include the word "licensed", suggesting that unlicensed RIBA 2 results may be used. However, 610.48(j) and 610.49 appear to state that only the results of a licensed supplemental assay may be used to guide lookback. It is my understanding that the unlicensed RIBA 2 kit was exactly the same formulation as that which was ultimately licensed; therefore, blood centers should be allowed to apply the results of unlicensed RIBA 2 testing in exactly the same way as the results of the licensed RIBA 2 assay.

8. Is recipient notification for prior donations required if the donor is RIBA 2 or RIBA 3 indeterminate?

Section 610.48 appears to require quarantine and consignee notification regarding prior donations if RIBA 2 or 3 are indeterminate. However, Section 610.49 appears to state that transfusion services need not notify recipients of prior donations if RIBA 3 is indeterminate, or under some circumstances if RIBA 2 is indeterminate (see 610.49(a)(6)(iii)). Please clarify. It appears that some indeterminate results might trigger consignee notification but not recipient notification?

In order to clarify the circumstances in which recipient notification is required, it would be much better if you could just state explicitly what test results DO trigger a recipient notification, e.g.,

- any repeatedly reactive EIA with no further supplemental testing (except in the case of first generation EIA where recipient notification is not required if the S/CO of the EIA was less than or equal to 2.5),

- any positive supplemental test result, and
- any indeterminate supplemental test result unless a later generation EIA or supplemental test is negative.

(Is this correct?)

9. Is lookback required if the donor is EIA 3.0 reactive, RIBA 2 negative?

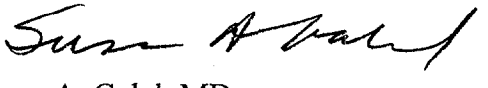
The proposed rule indicates that consignee notification and recipient notification would not be required if a donor is EIA 2.0 reactive/RIBA 2 negative. However, the rule does seem to suggest that these notifications are required if the donor is EIA 3.0 reactive/ RIBA 2 negative (610.48(c)(3)). If the sensitivity of RIBA 2 is adequate to guide lookback for EIA 2 reactive donors, why then is it insufficient to guide lookback for EIA 3 reactive donors? While it is clear that EIA 3 has improved sensitivity in comparison to EIA 2, it is also true that the overwhelming majority of EIA 3 reactive, RIBA 2 negative donors are not infectious. Recipients of prior donations from such donors will not be at a measurably increased risk of HCV in comparison to the general population. Therefore, it does not seem reasonable or appropriate to notify recipients of prior donations from such donors.

10. Can the rule be presented in a flow chart or table format?

This is a very complex rule. Similar information is presented in multiple sections of the rule, however, there do appear to be discrepancies between the sections. The reference charts are not particularly helpful, since they list paragraph numbers that are very difficult to locate and which themselves refer to other numbered sections. The rule would be much easier to follow if the instructions themselves could be presented in a table format. I believe that this would dramatically increase the likelihood that the rule would be followed correctly; it would also be much easier for blood establishments to identify and keep track of the different criteria that appear to apply to different parts of the process (e.g., consignee notification vs. recipient notification).

Thank you for the opportunity to submit these comments. I have listed below and attached a copy of each cited reference. The Agency should be commended for its work in putting together such a thoughtful and thorough proposal.

Sincerely,



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References:

1. Menozzi D, Udulutch T, Llosa AE, and Galel SA. HCV lookback in the United States: effectiveness of an extended lookback program. Transfusion 2000; 40:1393-1398.

2. Tobler LH, Tegtmeier G, Stramer SL, Quan S et al. Lookback on donors who are repeatedly reactive on first-generation hepatitis C virus assays: justification and rational implementation. Transfusion 2000; 40:15-24.

3. Evans CE, Tobler L, Polito A, Stewart J, et al. Comparative evaluation of supplemental hepatitis C virus antibody test systems. Transfusion 1992; 32:408-414.

4. Courouce A-M, Janot C, and the Hepatitis Study Group of the French Society of Blood Transfusion. Recombinant Immunoblot Assay First and Second Generations on 732 Blood Donors Reactive for Antibodies to Hepatitis C virus by ELISA. VOX Sang 1991; 61:177-180.

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