

POST-DONATION INFORMATION AFFECTING SAFETY OF PLASMA DERIVATIVES: REVISED ALGORITHM

Committee Update

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Update on the Post-Donation Information Algorithm

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Blood Products Advisory Committee,
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As you know, we have been discussing at BPAC since 1997, the topic of what previously was called "Inadvertent Contamination," now called "Post-Donation Information." Let me remind you that, so far, these discussions have involved only those viruses for which serologic tests exist and which can be inactivated or removed by procedures applied during the manufacturing process for plasma derivatives, namely, HBV, HCV, and HIV. In summary, BPAC voted in March 1999 in favor of the "Test Positive" algorithm; in May 1999 BPAC voted in favor of the "Risk Factor" algorithm, with the proviso that Footnote "i" be shortened. A copy of the "Risk Factor" algorithm has been given to you today for reference (Document A). Shortening of Footnote "i" was requested by BPAC because the number of risk factors that could activate the algorithm was so large that post-donation information would affect every lot of every plasma derivative.

A major effort was made by FDA to shorten Footnote "i". Document B is a copy of the original Footnote "i", annotated with a list of the number of post-donation information reports for each risk factor received by FDA during FY98. I will not take the time now to go through this list with you, although you are welcome to ask questions at the conclusion of this update. The main purpose in showing this to you is to remind you of the extent of the problem of post-donation

information.

We then tried to reduce the number of listed risk factors based on several approaches. Some were eliminated based on lack of evidence of a significant risk for HBV, HCV, or HIV. Some were eliminated because they were "secondary risk factors," whose risk only reflected the risk associated with other high risk activities; in these cases, it seemed more reasonable to limit the algorithm to the "primary risk factor," since potential donors with it should include all donors with the "secondary risk factor" who were truly at risk.

Document C lists the risk factors that we removed from Footnote "i" and the reasons they were removed. I will go through each of these with you now, briefly. [Discussion of Document C.]

There remained four risk factors in Footnote "i," as shown in Document D. Although we do not yet know the precise number of reported events associated with the first two risk factors (because we limited them to "within 12 months" and our currently available data is for "ever" having had the risk factor), and although we do not yet have the number of events for HBV alone in the third risk factor, these numbers currently are being obtained from the original reports and will be available at a later date. Nevertheless, Document D clearly shows that, even when Footnote "i" is reduced to these four risk factors, the number of events is almost certainly so large that nearly every lot of every product would have to be quarantined, and life-threatening shortages would occur.

It seemed as if the algorithm could not be made usable by reducing the number of risk factors that would activate it. We therefore decided to reconsider the algorithm in view of this and in view of two other developments, namely:

1. Nucleic acid amplification tests (NAT) on minipools for HCV have been applied under IND to almost all units of plasma collected in the U.S. since 1998, and NATs on minipools for HIV will be similarly applied to all units by the end of 1999.
2. An industry association, the IPPIA, has developed a set of GMP enhancements that it says will do the GMP evaluation in the algorithm before the products are released. They will be presenting a summary of this in the open session today. It should be noted, however, that their plan has not yet been submitted to or reviewed by FDA.

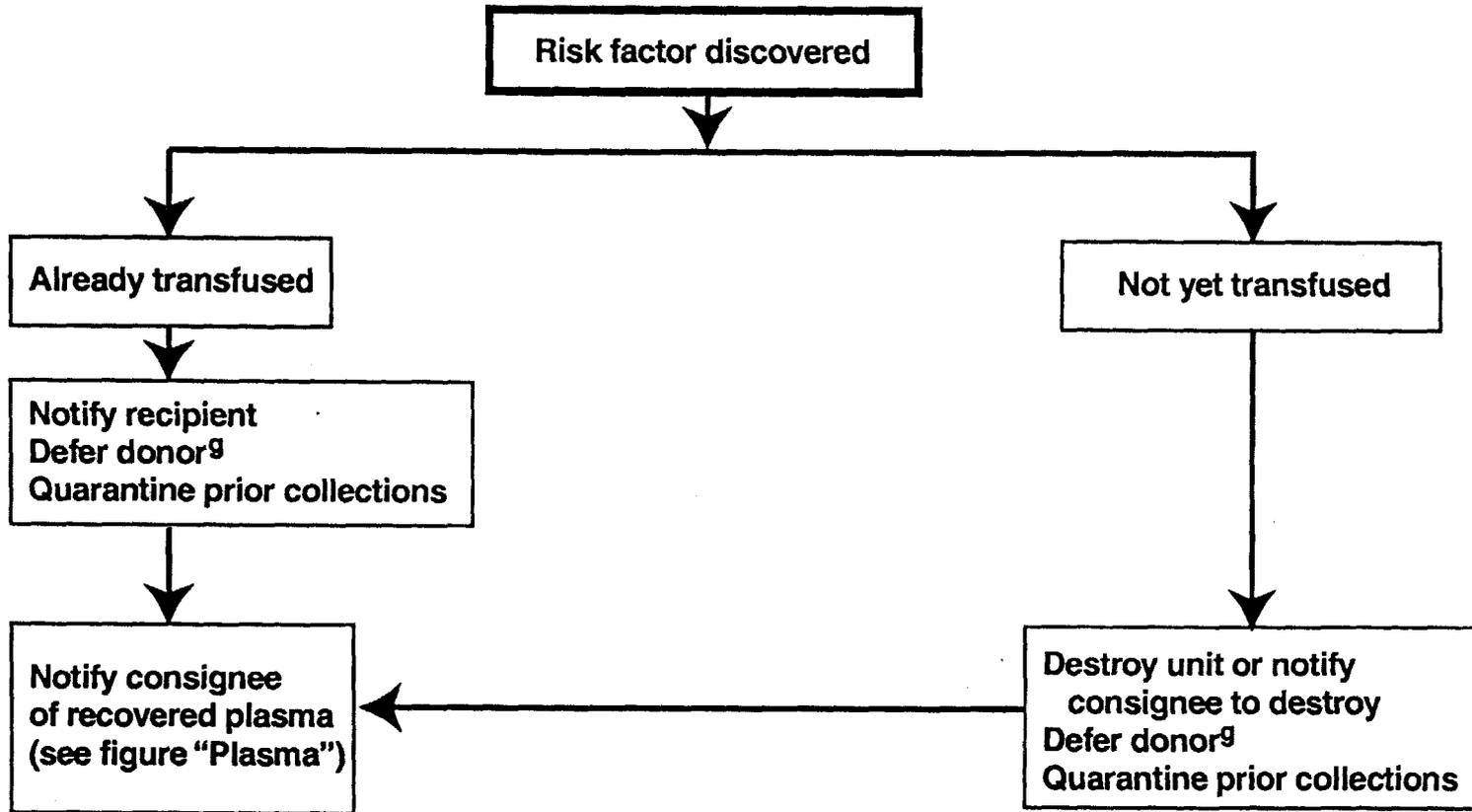
Based on these considerations, FDA plans to modify this algorithm. This is an "update" session; our intent is to inform BPAC of what we are doing with an issue that has been actively discussed at numerous prior meetings. We will bring a further revised algorithm to you for discussion and, most likely, for a vote, at a subsequent BPAC meeting. One concept under consideration would be to make the following change to the algorithm:

All units entering the plasma pool will have been found to be negative for HCV and HIV in minipool testing prior to pooling. If post-donation information is received that a donor is in a listed risk group, we could suggest that the pool itself be tested, as a precaution, for HCV and

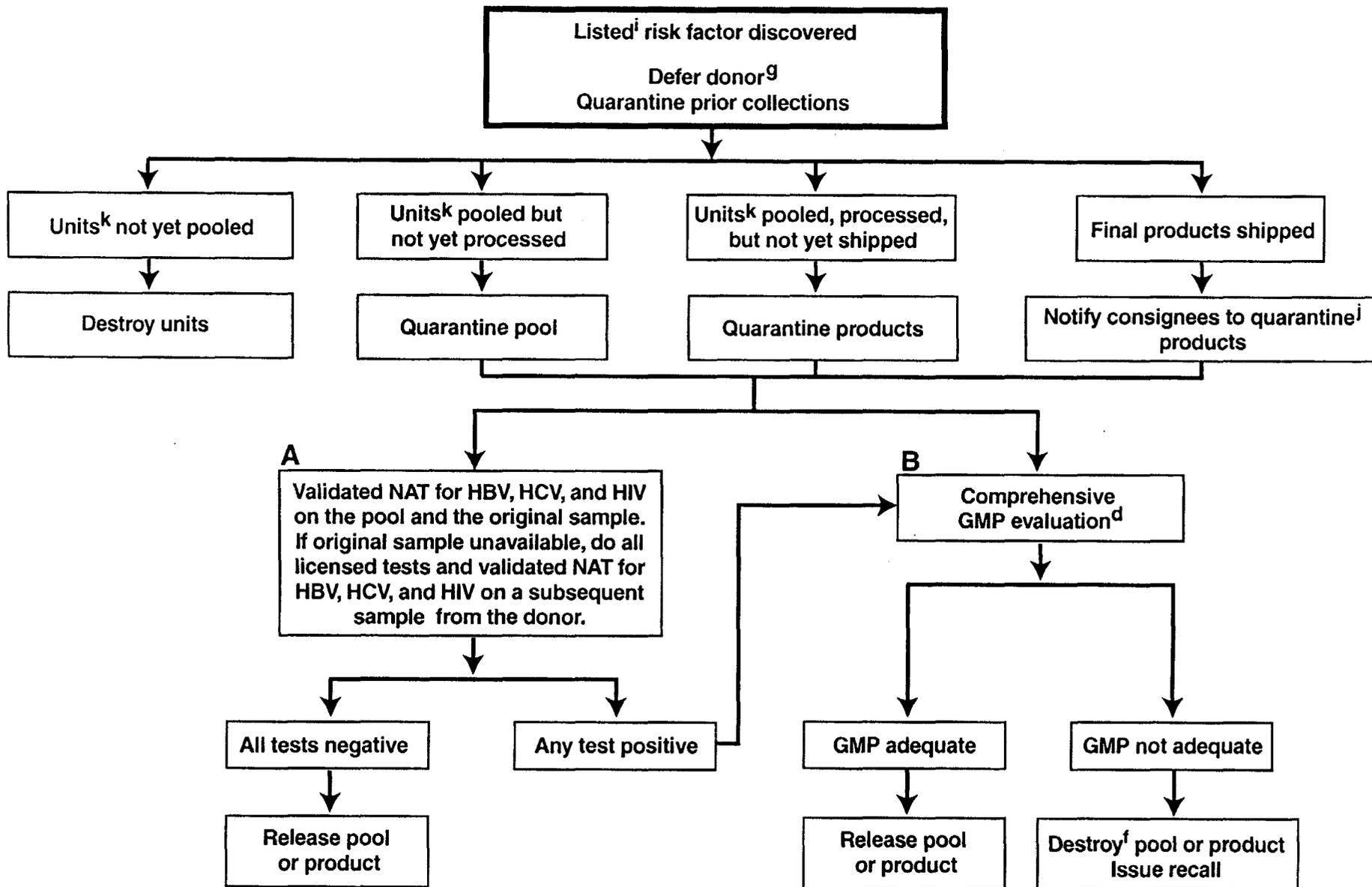
HIV by a NAT test under an IND, and for HBV DNA by a NAT test validated by the manufacturer under an IND. If all of these tests are negative, the pool or products would be releasable, without the need for quarantine and further GMP review. A positive test would trigger quarantine and, most likely, a further GMP assessment.

We welcome comments now. However, I want to emphasize that a formal modification of the algorithm will be developed and brought to a future BPAC meeting.

Risk Factor: Whole Blood (Recovered Plasma)



Risk Factor: Plasma



Footnotes

- ^a Anytime a confirmed positive test result is belatedly found on an individual unit, the unit must be destroyed if it has not yet been pooled.**
- ^b If the positive is a result from testing a pool, the result should be repeated to verify that it is correct.**
- ^c Disposition of unit and donor status should occur as defined in each IND.**
- ^d Comprehensive GMP evaluation by fractionator to verify virus removal and inactivation. GMP inspection by FDA as needed. Fractionators will send reports to FDA listing all GMP evaluations conducted because of inadvertent contamination.**

- e Tests for virus in question only.**
- f In some cases, pools or products can be reprocessed if under an approved protocol.**
- g Donor must be deferred. In addition, if donor can be located, all licensed tests for markers of HCV and HIV should be done on a newly obtained sample. If any tests for HCV or HIV are positive or indeterminate, lookback should be conducted.**
- h “Lookback” here indicates both product retrieval and recipient notification.**

ⁱ Risk factors for HBV, HCV, or HIV to be used for the Inadvertent Contamination Risk Factor algorithm (postdonation information)

Needlestick or transfusion (within 12 months)

Tattoo (within 12 months) (unless presumed sterile)

Body piercing other than earpiercing (within 12 months)

IV drug use (ever)

Male to male sex (within 12 months)

Sex with an IV drug user (within 12 months)

Sex partner tests positive for current HBV infection or HIV

Exchanged sex for drugs or money (within 12 months)

History of incarceration greater than 72 hours (within 12 months)

AIDS-related signs or symptoms (currently)

Female had sex (within 12 months) with male who had sex with a male

Sexually transmitted disease (within 12 months)

Travel to or immigration from HIV Group O areas

j Quarantine is not necessary if additional testing is negative (point A) or comprehensive GMP evaluation is adequate (point B) and either of these is completed within 72 hours of the discovery that a unit in the pool came from a donor with a listed risk factor (postdonation information)

k Postdonation information typically is found to apply to multiple collections from the same donor

ⁱ Risk factors for HBV, HCV, or HIV to be used for the Inadvertent Contamination Risk Factor algorithm (postdonation information)

	<u>Number of reports in FY98</u>
Needlestick or transfusion (within 12 months)	1,161 events, including earpiercing (25%). Mostly tattoos.
Tattoo (within 12 months) (unless presumed sterile)	
Body piercing other than earpiercing (within 12 months)	
IV drug use (ever) - - - - -	388 events
Male to male sex (within 12 months) - - - - -	263 events
Sex with an IV drug user (within 12 months) - - - - -	194 events
Sex partner tests positive for current HBV infection or HIV - - - - -	384 events (HCV & HBV); 82 events (HIV)
Exchanged sex for drugs or money (within 12 months) - - - - -	58 events
History of incarceration greater than 72 hours (within 12 months) - - - - -	187 events
AIDS-related signs or symptoms (currently) - - - - -	<27 events
Female had sex (within 12 months) with male who had sex with a male - - -	46 events
Sexually transmitted disease (within 12 months) - - - - -	24 events
Travel to or immigration from HIV Group O areas - - - - -	196 events

Document C

<u>Risk Factor Removed</u>	<u>Reason Removed</u>
Needlestick, transfusion	Rarely transmit HBV, HCV, HIV
Tattoo	No data to support transmission risk (CDC) except 1 or 2 reports of HBV
Body piercing	No data to support transmission risk unless drug use (CDC)
Sex with IVDU	A "secondary risk"
Hx. incarceration >72 hrs.	"Surrogate" for IVDU and MSM
AIDS related signs, symptoms	Not markers of acute infection (27 reports in FY98)
Female had sex with MSM	A "secondary risk"
Sexually transmitted disease	"Surrogate" (24 reports in FY98)
Travel/immigration, Group O area	Remote risk

Document D

Revision of Footnote "i"

Risk factors for HBV, HCV, or HIV to be used for the Risk Factor Algorithm (Postdonation Information)

	Number of Events Reported to FDA in <u>FY98</u>
IV drug use (within 12 months)‡	388 (ever)*
Male to male sex (within 12 months)‡	263 (ever)*
Sex partner tests positive for current HBV infection or HIV	384 (HBV** & HCV); 82 (HIV)
Exchanged sex for drugs or money (within 12 months)‡	58

‡Because the history accompanying this risk factor may not always be available with regard to "the last 12 months," the algorithm will only be used if the possible exposure is known to have occurred within 12 months and an effort is made to ascertain this.

*Number of reports affected by 12 month cut-off being reviewed currently by FDA

**HBV and HCV separation of number of cases in progress