Guidance for Industry

Variances for Blood Collection from Individuals with Hereditary Hemochromatosis

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This guidance document represents FDA's current thinking on the distribution of blood and blood components from individuals with hereditary hemochromatosis without disease labeling, and collecting blood more frequently than every eight weeks without a physical examination on the day of donation. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. PURPOSE

This guidance document provides recommendations to you, blood establishments, that wish to distribute blood and blood components collected from individuals with diagnosed hereditary hemochromatosis without indicating the donor's disorder on the container label. This guidance also provides recommendations if you wish to collect blood from such individuals more frequently than every eight weeks without a physical examination and certification of the donor's health by a physician on the day of donation. This document identifies conditions under which we, FDA, will consider approving the above as alternative procedures, or variances, to the current regulations, under the provisions of Title 21, Code of Federal Regulations, Section 640.120 (21 CFR 640.120). It also provides guidance on what you should submit to us when requesting these variances. These recommendations apply to all blood establishments, whether or not you hold a U.S. License for the manufacture of blood and blood components.

II. INTRODUCTION

Hereditary hemochromatosis (HH) is an inherited disorder of iron metabolism, with an estimated prevalence of 0.25-0.50% among Caucasians. An epidemiologic study is currently underway to determine the prevalence, as well as the genetic and environmental determinants, of iron overload related to hereditary hemochromatosis in a multiethnic population. This iron metabolism disorder often results in the deposition of excess iron in body tissues that can reach toxic levels leading to organ damage. The toxicity can affect most tissues and organs, but particularly the liver, endocrine organs, and the heart. Early initiation of therapeutic phlebotomy before organ damage occurs may restore a normal life expectancy and improve symptoms. (Ref. 1, 2)

Treatment of HH typically has two phases. First, the patient undergoes iron depletion therapy, in which excess iron is removed. In one study of current practices, two to three units of blood were withdrawn per month, for approximately one year. In the second phase, maintenance therapy, an average of one unit was withdrawn every two months. In the same study, 76% of respondents

reported full or partial insurance coverage of therapeutic phlebotomy charges. Charges ranged from a mean of $48 for home phlebotomy, $52 for blood centers, $69 for physician's offices, to $90 for hospitals. (Ref. 3)

On the basis of the currently understood molecular mechanisms of disease, there is no evidence that blood from HH patients would carry any added risk for transfusion recipients from HH. In addition, there is no evidence to support a transfer of a genetic disorder by transfusion. Blood from HH patients has been used for transfusion in other countries without reports of adverse reactions in recipients. (Ref. 2)

Currently, FDA does not prohibit the use of blood from therapeutic bleedings, but requires that blood intended for transfusion be labeled with the donor's disease (21 CFR 640.3(d)). In addition, the regulations state that a person may donate a unit of blood more than once in eight weeks only after a physical examination and certification of health by a physician (21 CFR 640.3(f)).

Many blood establishments that collect blood during a therapeutic phlebotomy have not routinely distributed this blood for transfusion, because consignees have refused to accept blood that is labeled with a disease. Thus, the labeling requirement is considered to be a barrier to the use of blood from HH donors for transfusion, despite evidence that this blood is safe.

There have been several studies that have shown an increase in the prevalence of bloodborne viral pathogens in blood obtained from paid donors as compared to volunteer donors. Therefore, there is concern about creating an incentive for HH patients to donate blood for free, rather than pay for a therapeutic phlebotomy. If a blood establishment charged a fee for therapeutic phlebotomy, but not for a blood donation for transfusion, the HH donor would have an incentive to deny risk conditions that might preclude cost-free donation. In this circumstance, blood donation provides indirect compensation for medical phlebotomy. (Ref. 4)

III. BACKGROUND

On April 29, 1999, the Public Health Service Advisory Committee on Blood Safety and Availability (ACBSA) recommended that the Department of Health and Human Services (DHHS) "create policies that eliminate incentives to seek [blood] donation for purposes of phlebotomy" from patients with diagnosed hemochromatosis who require phlebotomy as therapy for their disorder. Further, ACBSA recommended that DHHS "create policies that eliminate barriers to using this resource" to augment the country's blood supply. (Ref. 5)

On August 10, 1999, the Commissioner of Food and Drugs made a commitment to consider case-by-case exemptions to existing blood labeling and donor suitability regulations for blood establishments that can verify that therapeutic phlebotomy for hemochromatosis is performed at no expense to the patient (Ref. 6). The Commissioner wrote that as part of any exemption, we would request that safety data be collected and submitted to the Agency and that this data would be compared with data gathered on the general donor pool.

Additionally, we made a commitment to work with the Health Care Financing Administration (HCFA) in ensuring that the financial incentives for persons with HH to donate blood for transfusion are removed. This issue was further discussed at the FDA Blood Products Advisory Committee meeting on September 16, 1999. For the foreseeable future, if you wish to distribute blood collected from donors with HH without disease labeling, you will have the responsibility of removing financial incentives for these donors. You will have to evaluate the advantages of entering these donors into your donor pool. (Ref. 7, 8)

IV. CONTENT OF VARIANCE REQUESTS

We will consider requests for variances to the labeling and physician examination regulations. We believe that variances incorporating the following provisions would be acceptable.

A. Blood donors with HH would meet the same suitability requirements as other donors (21 CFR 640.3(d)).

B. To collect blood products from a donor with HH more frequently than every eight weeks you would:
   1. collect blood products from a donor who has presented a physician's prescription (bearing instructions regarding frequency of phlebotomy and heamtocrit/hemoglobin limits) for therapeutic phlebotomy for HH; or,
   2. have your physician examine and certify the good health of the donor on the day of donation in accordance with 21 CFR 640.3(f) if you do not have a prescription on file for the donor's therapeutic phlebotomy for HH.

C. You would not charge a fee for phlebotomies performed on any individuals with HH, including those who do not meet allogeneic donor suitability requirements at the initial or subsequent donations. At the initial donation, you would obtain the donor's written acknowledgement that the donor understands that you are providing therapeutic phlebotomy free of charge even if the donor is ineligible as an allogeneic blood donor. We note that you are required to maintain health history records of donors (21 CFR 606.160(b)(1)), and we would expect this health history to include diagnoses of HH.

V. SUBMISSION OF VARIANCE REQUESTS

A. In accordance with 21 CFR 640.120, you must not implement changes at variance to the regulations prior to receiving approval from us.

B. To obtain approval for a variance to 21 CFR 640.3(d) (labeling with the donor's disease) under the provisions of 21 CFR 640.120, you must submit a written request to us to omit HH labeling. You should include a statement that HH individuals whose blood will be used for transfusion will meet your allogeneic donor suitability criteria. You should also include a copy of the donor acknowledgement form (informed consent or other written statement), to be signed by the donor, that she/he will not be charged a fee for the phlebotomy even if found to be ineligible as an allogeneic blood donor.

C. To obtain approval for a variance to 21 CFR 640.3(f) (physician examination) under the provisions of 21 CFR 640.120, you must submit a written request to collect blood products from donors with HH more frequently than every 8 weeks without examination by a physician at the time of donation. The submission should include statements that you are requiring a physician's prescription for therapeutic phlebotomy for HH, and that your physician would examine previously diagnosed HH donors without a prescription on the day of donation if less than 8 weeks have elapsed since the last donation.

D. You may request these variances concurrently.

E. If you hold a U.S License, you must submit variance requests as major changes (prior approval supplements) pursuant to 21 CFR 601.12(b). If you do not hold a U.S. License, you are not subject to 21 CFR 601.12, but are still required to obtain approval of variance requests before implementing changes at variance with the regulations.

F. If you discontinue operating under the terms of the approved variance (e.g., start charging a fee for therapeutic phlebotomies for HH donors who do or do not meet allogeneic donor suitability criteria), the variance is no longer in effect and you must comply with the current regulations. You should notify us of this change in writing. If you hold a U.S. License, include this notification in your Annual Report.

VI. REFERENCES

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