Labeling of Red Blood Cell Units with Historical Antigen Typing Results

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Draft Guidance for Industry

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For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
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Contains Nonbinding Recommendations

Draft – Not for Implementation

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Draft Guidance for Industry

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I. INTRODUCTION

We, FDA, are issuing this guidance document to provide you, establishments that collect blood and blood components for transfusion, with recommendations for labeling Red Blood Cell (RBC) units with non-ABO/Rh(D) antigen typing results obtained from previous donations (historical antigen typing results). This guidance provides recommendations to transfusion services for managing RBC units labeled with historical antigen typing results. This guidance also provides licensed blood collection establishments that choose to implement labeling of RBC units with historical antigen typing results instructions regarding how to report the manufacturing and labeling changes under 21 CFR 601.12. This guidance does not apply to test results for ABO and Rh(D) antigens. For ABO and Rh(D) antigens, you must follow FDA requirements in 21 CFR 640.5(b) and (c), and 606.121(c)(9) and (13), as well as all other applicable requirements.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Non-ABO/Rh(D) Blood Group Antigens and Current Approaches for Typing RBC and Selecting Units for Transfusion

In addition to ABO and Rh(D) RBC antigens, there are over 300 antigens that have been recognized on RBCs (Ref. 1). Some individuals develop antibodies to non-ABO/Rh(D) antigens that they lack on their own RBCs (alloantibodies), following exposure to foreign

RBC antigens through blood transfusion or pregnancy. The proportion of patients with non-ABO/Rh(D) RBC alloantibodies is estimated to be 1-2 percent in the general hospital population; however, it is much higher in patients who are chronically transfused and in multiparous females (Ref. 2). Some alloantibodies may be clinically significant, causing a hemolytic transfusion reaction if the patient receives a transfusion of RBCs that have the corresponding antigen(s). Therefore, pre-transfusion testing routinely includes tests to detect clinically significant RBC alloantibodies and to select RBC units that lack the corresponding antigen(s). It is also common practice to provide RBC units that match a chronically transfused patient's non-ABO/Rh(D) antigen phenotype to prevent the development of alloantibodies.

When a prospective transfusion recipient has one or more clinically significant alloantibodies or needs antigen matched RBCs, the transfusion service obtains RBC units that lack the corresponding antigens. The ease with which such antigen negative units can be found depends on several factors, including the prevalence of the RBC antigens in the donor population, the availability of reagents and tests to detect the antigens on donor RBCs, and the availability of RBC units from donors whose non-ABO/Rh(D) antigen types have been previously determined.

Blood collection establishments and transfusion services can locate suitable RBC units by randomly testing units from their inventory; however, the process can be time consuming, labor and resource intensive, and difficult to complete in emergency situations. If records of RBC antigen typing results are retained and linked to donors, they can be used to pre-select current RBC donations for transfusion. Blood collection establishments usually confirm the historical typing results by testing samples from the current donations before labeling the units with the test results.

Blood establishments typically perform serologic testing for non-ABO/Rh(D) RBC antigens using FDA licensed typing reagents. If a licensed typing reagent for a particular antigen is not available, blood establishments might choose to use an unlicensed typing reagent with appropriate positive and negative controls (Ref. 3). Some blood establishments use FDA approved molecular tests (i.e., gene sequence based) to determine donors' likely RBC phenotypes. When an unapproved molecular test is used, the results are usually verified by testing the RBCs for selected antigens using serologic tests or an approved molecular test, when feasible.

B. Current Approaches for Labeling RBC Units with Previously Determined (Historical) Non-ABO/Rh(D) Typing Results

Blood collection establishments routinely provide historical RBC antigen typing results associated with current donations to transfusion services. Providing historical RBC antigen typing results may expedite the process for finding acceptable units, especially in emergency situations.

To convey historical RBC antigen typing results, blood collection establishments use either a separate document included with the shipment of RBC units or a tie-tag attached to each unit that lists the historical RBC typing results and associates them with the current donations. A statement on the document or the tie-tag may indicate that the results are historical (obtained on one or more previous donations made by the donor).

When historical RBC antigen typing results associated with a current donation are provided by a blood collection establishment, some transfusion services confirm the results by repeating the testing on the current donation. In addition, the transfusion service performs a compatibility test to confirm that, at least by in vitro testing, the donor RBCs are compatible with the intended recipient's plasma.

C. Previous Discussions about Historical RBC Antigen Typing

At the AABB-FDA Liaison Meeting held on April 12, 2012 (Ref. 4), AABB stated that it is the practice of some blood collection establishments to provide historical RBC antigen typing results to transfusion services using a tie-tag attached to the RBC unit. AABB asked for recommendations from FDA regarding labeling of RBC units with historical RBC antigen typing results.

During that Liaison meeting, FDA voiced the following concerns about placing historical RBC antigen typing results directly on the container label of the unit:

- Assurance of the quality of the historical RBC antigen typing results based on the reagents or the type of tests that were used at the time.
- Linkage of the historical RBC antigen typing results to the donor and current donation. The donor should be positively identified so that historical RBC antigen typing results can be accurately associated with the current donation.
- The feasibility of confirming the historical RBC antigen test results on the current donation.
- The methods used to communicate historical RBC antigen typing results to the transfusion service.

AABB created a workgroup composed of representatives from the blood industry and liaison members from FDA. The workgroup addressed options for labeling RBC units with historical RBC antigen typing results and provided its suggestions to FDA.

FDA's Blood Products Advisory Committee (the Committee) discussed this topic on December 4, 2012. Following presentations that described current practices in the United States, the Canadian experience labeling RBC units with historical RBC antigen typing results, the AABB workgroup suggestions and RBC antigen typing using molecular tests, the Committee supported the concept of using historical RBC antigen typing results to label RBC units (Ref. 5).

The Committee agreed that current processes to ensure donor identification and accurate linkage of sequential donations with the donor were adequate to allow the labeling of current donations with historical RBC antigen typing results. The Committee recommended that labeling with historical RBC antigen typing results should occur only if results from two previous donations were available. Most Committee members did not think that confirmation of historical RBC antigen typing results on the current donations prior to transfusion was necessary, and agreed that serologic or molecular tests were acceptable to determine non-ABO/Rh(D) RBC antigen types.

AABB has revised its standards to include accommodations for labeling RBC units with historical RBC typing results. According to the 30th Edition of the AABB Standards for Blood Banks and Transfusion Services (Ref. 6), RBC units may be labeled as RBC antigen negative without testing the current donation if two previous separate donations were tested by the collection facility and results of RBC typing were found to be concordant. The Standards indicate that facilities have the option to put the non-ABO/Rh(D) historical antigen typing results on a tie-tag or directly on the container label.

III. RECOMMENDATIONS

A. RBC Antigen Typing

When typing RBC units for non-ABO/Rh(D) antigens, you should perform RBC antigen typing using FDA licensed serologic reagents or FDA approved molecular tests when such reagents or tests are available. If such reagents or tests are not available and you choose to use an unlicensed reagent or unapproved molecular test:

1. Unlicensed RBC typing reagents, including serum/plasma prepared for in-house use as RBC typing reagents, expired licensed RBC antigen typing reagents and unapproved molecular tests should be used only with the approval of the responsible physician (Ref. 3).

    a. Unlicensed RBC typing reagents, including serum/plasma prepared for in-house use as RBC typing reagents, and expired licensed RBC antigen typing reagents should be used only with appropriate positive and negative controls. You must maintain laboratory control procedures that include adequate provisions for monitoring the reliability, accuracy, precision and performance of test procedures and instruments, and records of such tests must be maintained consistent with 21 CFR 606.140(b) and 606.160.

    b. Unapproved molecular tests for in-house use in RBC antigen typing should be used only with appropriate positive and negative controls. You must maintain laboratory control procedures that include adequate provisions for monitoring the reliability, accuracy, precision and

performance of test procedures and instruments, and records of such tests must be maintained consistent with 21 CFR 606.140(b) and 606.160. Historical RBC antigen typing results obtained using molecular test kits that were for research use only (RUO) or for investigational use only (IUO) at the time the testing was performed are considered as having been obtained using an unapproved test.

2. You must have written Standard Operating Procedures (SOPs) (21 CFR 606.100(b)) that describe your non-ABO/Rh(D) RBC antigen typing. The SOPs should describe how your non-ABO/Rh(D) RBC antigen typing will be performed and documented and how reagents and tests will be evaluated for their capacity to perform as expected. You must use reagents and tests in a manner consistent with instructions provided by the manufacturer, in accordance with 21 CFR 606.65(e). You must maintain records of non-ABO/Rh(D) antigen typing results in accordance with 21 CFR 606.160(b).

B. Labeling RBC Units with Historical RBC Antigen Typing Results

When blood establishments use historical non-ABO/Rh(D) RBC antigen typing results for a subsequent donation by the same donor, the labeling of the RBC unit should indicate that the results are historical and whether the results were obtained using an unlicensed reagent or unapproved test. The transfusion service receiving the unit may use this information to determine whether additional confirmation of the typing is warranted.

We recommend the use of the container label or a tie-tag to convey historical RBC typing results, based on whether the historical testing was performed using licensed reagents/approved tests or unlicensed reagents/unapproved tests, respectively. See recommendations 2 and 3 below. In addition, FDA recommends the following for blood collection establishments to label RBC units with non-ABO/Rh(D) historical RBC antigen typing results:

1. You should use historical antigen typing results to label a unit only if two previous separate donations from the donor were tested by your blood collection establishment and antigen typing results were found to be concordant.

2. You should place historical RBC typing results directly on the container label only if two concordant test results were obtained using licensed reagents or approved tests. If RBC antigen typing results are printed directly on the container label, you should use a standard labeling format such as ISBT 128 or another format accepted by FDA to display the results in eye-readable text. The labeling format used should indicate that the typing results are historical.

3. You should use a tie-tag to convey historical RBC typing results if:

    a. two (or more) historical RBC antigen typing results were obtained using unlicensed reagents or unapproved tests with concordant results; or

    b. one historical RBC antigen typing result was obtained using a licensed reagent or approved test and one historical result was obtained using an unlicensed reagent/unapproved test.

    The tie-tag should provide the current donation identification number of the unit and indicate that the typing results are historical.

Notes:

1. We recommend that you use a validated process to confirm the donor's identification and accurate linkage that relates the current donation to the non-ABO/Rh(D) typing results from previous donations.

2. Blood establishments may choose to use a tie-tag rather than the container label to convey historical typing results when two concordant test results were obtained using licensed reagents or approved tests.

C. Additional Procedures for Managing Units with Historical RBC Antigen Typing Results

We note the following additional procedures for managing the process of selecting and labeling RBC units with historical RBC antigen typing results:

1. You should initiate an investigation whenever any of the following occurs:

    a. Historical RBC antigen typing results are not concordant.

    b. The transfusion service receiving an RBC unit labeled with historical RBC typing results repeats an antigen typing test and reports a discordant result.

    c. The recipient has a transfusion reaction because of an RBC antibody and the transfused unit was labeled as negative for the corresponding antigen.

    d. The transfusion service reports that a recipient developed an alloantibody to an RBC antigen and the transfused unit was labeled as negative for that antigen.

If applicable, you must submit a Biological Product Deviation Report according to 21 CFR 606.171. For further information, see "Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments" dated October 2006 (Ref. 7).

The transfusion service must document in its SOPs any procedures it uses to confirm relevant historical RBC typing results prior to transfusion, in accordance with 21 CFR 606.100(b).

2. The transfusion service's SOPs must include procedures to demonstrate incompatibility between the donor's cell type and recipient's serum or plasma type, consistent with 21 CFR 606.151(c). If the intended recipient has or has had a clinically significant alloantibody, the transfusion service's SOPs should include using appropriate serologic tests to demonstrate compatibility between the intended recipient's plasma/serum and donor RBCs (Ref. 8).

IV. REPORTING IMPLEMENTATION: CHANGES TO AN APPROVED APPLICATION

Accurate testing and labeling of RBC units with historical RBC antigen typing results is important to ensure the distribution of products that are safe for transfusion. Changes in procedures for testing and labeling have a substantial potential to have an adverse effect on the safety or effectiveness of the product. Therefore, the revision of procedures to implement recommendations contained within this guidance is considered a major change. Licensed blood collection establishments must report such changes to procedures, and related labeling changes, as a Prior Approval Supplement (PAS) under 21 CFR 601.12(b) and 601.12(f)(1).

The PAS submission must include a description of the proposed changes. We recommend this description be included in a cover letter or other narrative. The submission should also include:

A. Form FDA 356h, "Application to Market a New or Abbreviated New Drug or Biologic for Human Use."

B. Written SOP(s) incorporating the details of your process for labeling RBC units with historical non-ABO/Rh(D) RBC antigen typing results as described in this guidance document.

C. The proposed container labeling and/or tie-tag that you will use to convey historical RBC typing results to the transfusion service. If historical RBC typing results will be printed directly on container labels, the submission should include examples of labels showing the format that will be used to distinguish the various RBC antigens, such as C and c and Jk^a and Jk^b.

For assistance in preparing your supplement and for the completion of the Form FDA 356h, see FDA's guidance document entitled "Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h 'Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use,'" dated May 1999 (Ref. 9).

For assistance in using FDA's eSubmitter program, see "Guidance for Industry: Availability of FDA's e-Submitter Program for Regulatory Submissions from Licensed Blood Establishments," dated August 2011 (Ref. 10).

V. REFERENCES

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2. Poole J, Daniels G. Blood group antibodies and their significance in transfusion medicine. Transfus Med Rev 2007;21:58-71.

3. Compliance Program Guidance Manual, Chapter 42 – Blood and Blood Components, Inspection of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories, and Contractors – 7342.001, dated June 1, 2016. http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-bio-gen/documents/document/ucm337001.pdf

4. AABB-FDA Liaison Meeting April 12, 2012. http://www.aabb.org/advocacy/government/fdaliaison/bloodcomponents/Pages/flm041212.aspx

5. Blood Products Advisory Committee Meeting Transcripts – December 4, 2012. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm344648.htm

6. AABB, Standards for Blood Banks and Transfusion Services, 30th edition.

7. FDA "Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments," October 2006. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm073455.htm

8. FDA "Guidance for Industry: 'Computer Crossmatch' (Computerized Analysis of the Compatibility between the Donor's Cell Type and the Recipient's Serum or Plasma Type)," April 2011. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm252829.htm

9. FDA "Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h 'Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use,'" May 1999. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm077087.htm

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