

Labeling of Red Blood Cell Units with Historical Antigen Typing Results

Guidance for Industry

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Table of Contents

I.	INTRODUCTION.....	1
II.	BACKGROUND	1
A.	Non-ABO/Rh(D) Blood Group Antigens and Current Approaches for Typing RBC and Selecting Units for Transfusion	1
B.	Current Approaches for Labeling RBC Units with Previously Determined (Historical) Non-ABO/Rh(D) Typing Results	2
C.	Previous Discussions about Historical RBC Antigen Typing	3
III.	RECOMMENDATIONS.....	3
A.	RBC Antigen Typing for Non-ABO/Rh(D) Antigens	3
B.	Labeling RBC Units with Historical RBC Antigen Typing Results.....	4
C.	Additional Procedures for Managing Units with Historical RBC Antigen Typing Results	6
IV.	REPORTING IMPLEMENTATION: CHANGES TO AN APPROVED APPLICATION.....	6
V.	REFERENCES.....	8
VI.	PAPERWORK REDUCTION ACT OF 1995.....	9

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

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 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

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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 antigen negative 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, historical typing results can be used to select current antigen negative units in inventory that match the types needed by the recipient. Blood collection establishments may 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' predicted 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 approved molecular tests, when feasible.

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

To convey historical RBC antigen typing results to transfusion services, blood collection establishments have traditionally used 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. Statements on the document or the tie-tag may indicate that the results are historical, whether they were obtained on one or more previous donations, and whether the results were confirmed by testing the current donation prior to labeling.

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Some transfusion services confirm historical antigen typing results provided by the blood collection establishment by repeating the testing on the current donations. The practice of a transfusion service may be to confirm results regardless of whether they were obtained on previous donations or the current donation, or to confirm only historic results. The ability of a transfusion service to repeat the typing depends on whether an intended recipient's condition allows time for the testing to be performed and whether the necessary reagents/tests are available.

C. Previous Discussions about Historical RBC Antigen Typing

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, and 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. 4).

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 (Standards) (Ref. 5), 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 for Non-ABO/Rh(D) Antigens

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. If you choose to use an unlicensed reagent or unapproved molecular test, for example, because a licensed reagent for a rare antigen is not available, we recommend the following:

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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). The responsible physician may choose to approve the use of unlicensed reagents or unapproved tests on a case by case basis or the responsible physician may choose to approve standard operating procedures that describe the conditions under which unlicensed reagents or unapproved tests may be used. The procedures should include testing of subsequent donations for each RBC antigen using a licensed reagent or approved test, when feasible.
2. 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.
3. 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.
4. 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.
5. Your Standard Operating Procedures (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. We note that under 21 CFR 606.100(b), you must have written SOPs that describe your non-ABO/Rh(D) RBC antigen typing process. 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

The following recommendations apply to blood establishments that wish to label RBC units with historical non-ABO/Rh(D) RBC antigen typing results.

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1. You should convey to transfusion services your practices for repeating historical RBC typing results on current donations and for labeling RBC units with historical RBC antigen typing results.
2. 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. The two concordant antigen typing results may be obtained using serological or molecular tests or a combination thereof.
3. 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 in sections a. and b. below:
 - a. 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.

If the results were obtained using licensed reagents or approved tests, the container label need not indicate that the typing results are historical. Blood establishments that want to distinguish historical RBC typing results from the results obtained on the current donation may include this information on the container label or other labeling, such as shipping documents.

- b. You should use a tie-tag to convey historical RBC typing results if one or more than one historical RBC antigen typing result was obtained using an unlicensed reagent or unapproved test. The tie-tag should provide the current donation identification number of the unit. The tie-tag should indicate that the typing results are historical and that the results were obtained using unlicensed reagents or unapproved tests. The transfusion service receiving the unit may use this information to determine whether additional confirmation of the typing is warranted.

Notes:

1. You should 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. If the results were obtained using

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licensed reagents or approved tests, the tie-tag does not need to indicate that the typing results are historical.

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

We recommend or require the following additional procedures to for managing RBC units labeled 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 antigen 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.
2. The transfusion service must include in its SOPs any procedures used to confirm relevant historical RBC typing results prior to transfusion, in accordance with 21 CFR 606.100(b).
3. The transfusion services 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 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. 6).

IV. REPORTING IMPLEMENTATION: CHANGES TO AN APPROVED APPLICATION

Licensed blood establishments must report changes in accordance with 21 CFR 601.12. The following is intended to assist such establishments in reporting changes in testing procedures and changes in labeling of RBC units with historical RBC antigen typing results:

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1. FDA considers changes made to implement the recommendations in this guidance to be minor.¹ Report such changes in your annual report under 21 CFR 601.12(d), noting the date the process was implemented.
2. Changes made to implement different procedures than those described in this guidance are considered to have a moderate potential to adversely affect the safety or effectiveness of the product. Report such changes to FDA as a Changes Being Effected (CBE) supplement under 21 CFR 601.12(c)(5). You should include the following in your CBE submission:
 - a. Cover letter, describing the change or procedures that you will use.
 - b. Form FDA 356h, “Application to Market a New or Abbreviated New Drug or Biologic for Human Use.”
 - c. Written SOP(s) incorporating the details of your process for labeling RBC units with historical non-ABO/Rh(D) RBC antigen typing results and any related documents.
 - d. The container labels and/or tie-tags that you will use to convey historical RBC typing results to transfusion services. 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 completing 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. 7).

For assistance in using FDA’s eSubmitter program, see guidance document entitled “Guidance for Industry: Availability of FDA’s eSubmitter Program for Regulatory Submissions from Licensed Blood Establishments,” dated August 2011 (Ref. 8).

¹ See 21 CFR 601.12(a)(3).

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V. REFERENCES

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VI. PAPERWORK REDUCTION ACT OF 1995

The guidance document contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520). The guidance refers to the collections of information for putting the non-ABO/Rh(D) historical antigen typing results on a tie-tag or directly on the container label. These collections of information have been approved under OMB control number 0910-0862.

The guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR part 601 and Form FDA 356h have been approved under OMB control number 0910-0338; and the collections of information in 21 CFR part 606 have been approved under OMB control number 0910-116. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0862 (expires 11/30/2018).