

Guidance for Industry

“Computer Crossmatch” (Computerized Analysis of the Compatibility between the Donor’s Cell Type and the Recipient’s Serum or Plasma Type)

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Guidance for Industry

“Computer Crossmatch” (Computerized Analysis of the Compatibility between the Donor’s Cell Type and the Recipient’s Serum or Plasma Type)

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I. INTRODUCTION

“Computer crossmatch” is a process used to ensure that blood released for transfusion is compatible with the intended recipient.¹ We, FDA, are issuing this guidance to assist you, blood establishments that perform compatibility testing using a computer crossmatch system to perform computerized matching of blood, consistent with current good manufacturing practice (CGMP) requirements in 21 CFR Parts 210, 211 and 606. Blood establishments must have standard operating procedures (SOPs) “to demonstrate incompatibility between the donor’s cell type and the recipient’s serum or plasma type” under the compatibility testing requirements in 21 CFR 606.151(c). This guidance describes practices that we believe satisfy the requirements in 21 CFR 606.151(c) to help ensure detection of an incompatible crossmatch when using a computerized system for matching a donor’s cell type with a recipient’s serum or plasma type.

Recipient - donor compatibility may be evaluated by using either a serologic crossmatch or a computer crossmatch. We consider computer crossmatch an acceptable method of compatibility analysis when it is properly designed, validated, implemented, and monitored. However, the use of the computer crossmatch requires a high degree of testing and validation to ensure accuracy.

In addition, this guidance contains recommendations for blood establishments performing compatibility testing that intend to implement a computer crossmatch procedure. For licensed establishments, this guidance also describes how to report this manufacturing change to FDA under 21 CFR 601.12. This guidance finalizes the draft guidance entitled “Guidance for Industry: ‘Computer Crossmatch’ (Electronic Based Testing for the Compatibility between the Donor’s Cell Type and the Recipient’s Serum or Plasma Type)” dated June 2007 (June 21, 2007, 72 FR 34259).

¹ For the purpose of this document, the term “computer crossmatch” is defined as an assessment of donor and recipient blood compatibility that is done by substituting a computerized record review for the serologic crossmatch. The computerized record review follows strict decision rules to determine recipient criteria and donor blood compatibility. This procedure is also known as an “electronic crossmatch” and is defined further in section III.

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FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe 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

Before we finalized the regulation amending 21 CFR 606.151 in 2001 (Ref. 1), compatibility testing was required to be performed by serologic crossmatch. Specifically, prior to September 5, 2001, the effective date of amended 21 CFR 606.151, SOPs for compatibility testing were required to include "[t]he testing of the donor's cells with the recipient's serum (major crossmatch) by a method that will demonstrate agglutinating, coating and hemolytic antibodies, which shall include the antiglobulin method" (Ref. 2). A computer crossmatch was permitted only if we granted you written approval to use computer crossmatch as an alternative to a serologic crossmatch. Under 21 CFR 640.120, we approved requests for an alternative procedure such as a computer crossmatch when documentation of decision-making rules, validation records, and SOPs demonstrated the process was at least as safe as serologic crossmatch.

In March 1994, we approved the first alternative procedure permitting a blood establishment to use a computer crossmatch. Between that time and implementation of the new rule on September 5, 2001 (Ref. 1), we approved requests from 33 blood establishments to utilize alternative procedures permitting use of a computer crossmatch. Although 33 establishments represent only a small percentage of all blood establishments (there are over 5,000 blood establishments in the United States), these establishments have used the process for some time without reports of serious recipient-related injury or death. In addition, we believe that additional establishments have implemented computer crossmatch since the rule became effective on September 5, 2001.

The software, personnel, SOPs and hardware are all important parts of the computer crossmatch process. The use of a computer reduces the risk of human error through the use of software-controlled decision-making. Computer crossmatch systems are included within some Blood Establishment Computer Software (BECS) systems cleared by FDA.² The computer crossmatch systems include the following basic elements:

- Instead of performing a serologic crossmatch, an establishment determines the compatibility of blood for transfusion on the basis of data entered and stored in the computer;

² FDA issued a draft guidance entitled "Guidance for Industry: Blood Establishment Computer System Validation in the User's Facility" dated October 2007 (October 29, 2007, 72 FR 61171), addressing the validation of a blood establishment computer system that incorporates BECS. This draft guidance, when finalized, will represent FDA's current thinking on that topic.

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- The computer data are obtained by performing serologic tests on separate blood samples of the donor and recipient, with results stored in the computer;
- The software interprets the data using a set of precisely defined rules (software-controlled decision-making); and
- If the rule-based criteria for compatibility are not met, or if essential data are missing, the computer displays a warning message.

Other computer crossmatch system elements that may be relevant are as follows:

- Systems may be restricted for use with Red Blood Cell (RBC) products (note that some systems also release other blood components for transfusion);
- Systems may require a serologic crossmatch for recipients exhibiting clinically significant RBC antibody(ies) (e.g., with a positive antibody screening test); or
- Systems may require antigen negative RBCs for recipients with a history of clinically significant RBC antibody(ies).

It should be noted that this guidance does not apply to those circumstances where the donor's blood has not been screened for agglutinating, coating and hemolytic antibodies. In such cases, 21 CFR 606.151(d) requires that "...the recipient's cells shall be tested with the donor's serum (minor crossmatch) by a method that will so demonstrate."

We believe that the published literature and observations of safe use over the past 16 years support the safety of properly implemented computer crossmatch systems (Refs. 3-10), and we regard computer crossmatch to be an acceptable method of compatibility demonstration when it is properly designed, validated, implemented, and monitored. However, there are many issues that could affect the safety and effectiveness of blood products when you use computer crossmatch. The quality of the process depends on careful user validation and proper quality management.

III. TERMS USED IN THIS GUIDANCE

Antibody screen - The combining of recipient serum or plasma with reagent RBCs for detection of unexpected antibodies to red blood cell antigens; also known as the antibody detection test.

Note: It is widely recognized that not all unexpected RBC antibodies are clinically significant. Furthermore, there is no single method of screening for unexpected RBC antibodies that will reliably detect all that are clinically significant. The computer crossmatch switches the emphasis for safety of the compatibility test from the serologic crossmatch to the antibody screening (in addition to correct determination of ABO and Rh (D) types) (Ref. 5). As with the immediate spin crossmatch (defined below), the absence of an antiglobulin crossmatch necessitates that your antibody screening techniques be sufficiently sensitive to detect clinically significant antibodies. You must determine how you will ensure the appropriate level of sensitivity (e.g., use of potentiators, screening cell sets that contain RBCs with homozygous expression of clinically significant antigens).

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Compatibility testing - The procedures performed to establish the matching of a donor's blood or blood components with that of a potential recipient (21 CFR 606.3(j)).

Computer crossmatch - Assessment of donor and recipient blood compatibility that is done by substituting a computerized record review for the serologic crossmatch (see below). The computerized record review follows strict decision rules (see below) to determine recipient criteria and donor blood compatibility. This procedure also is known as an "electronic crossmatch."

Crossmatch - A general term for any test that combines a sample of blood from a blood donor and a sample of blood from a recipient to determine compatibility prior to transfusion. The crossmatch is one element of the more general compatibility testing.

Decision rules - The rules applied in software-controlled decision-making. The software vendor, the user, or both, may be responsible for control of such rules.

Decision tables - Decision tables are tables included in your software system.

Immediate spin crossmatch - A serologic test of recipient serum or plasma with donor RBCs, consisting of centrifugation of samples and immediate examination for agglutination or hemolysis, which primarily detects ABO incompatibility. There is no incubation and no antiglobulin test.

Major crossmatch - A serologic test of recipient serum or plasma with donor RBCs consisting of incubation and testing with anti-human globulin to detect incompatibility. In a computer crossmatch system, a major crossmatch may be required to assess compatibility when the recipient sample demonstrates the presence of an atypical RBC antibody(ies).

Minor crossmatch - A serologic test of donor serum or plasma with recipient RBCs consisting of incubation and testing with anti-human globulin to detect incompatibility. Contrast with major crossmatch (above).

Potentiator - A reagent solution added to enhance in vitro antibody-antigen reactions.

Serologic crossmatch - A physical, in vitro laboratory test of recipient serum or plasma with donor RBCs. Contrast with computer crossmatch (above).

Note: One of the functions of a serologic crossmatch, especially the immediate spin crossmatch, has been the detection of ABO incompatibilities (Ref. 9). Adequate compatibility testing in the absence of a serologic crossmatch may rely upon the performance characteristics of the ABO reagents. For example, it is important to know how monoclonal reagents react with samples that have unusual ABO groups such as weak subgroups, acquired B antigen, and the B(A) phenomenon.

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IV. ELEMENTS OF A COMPUTER CROSSMATCH SYSTEM

The following are critical process elements of decision rules for a computer crossmatch system.

A. Data Entry Review and Acceptance

You should have a method for a user to review and verify data before it can be used in the decision process. Some examples are:

- The user enters data, reviews it on screen and then accepts the entry; or
- The user enters data twice and the system accepts the entry if there is a match; or
- Data is entered from an interfaced instrument and the user confirms information on a printed report before acceptance.

B. Recipient Data Elements

The electronic database should include these data elements:

- Unique identification number;
- RBC antibody assessment;
- ABO group/Rh (D) type and interpretation;
- Recipient Sample; and
- Special transfusion requirements (i.e., leukocyte reduced, CMV antibody negative).

1. Recipient RBC Antibody Assessment

You must have procedures to demonstrate incompatibility between the donor's cell type and the recipient's serum or plasma type (21 CFR 606.151(c)). These procedures usually include instructions to perform an antibody screening test. You must use fresh recipient serum or plasma samples less than 3 days old for all pretransfusion testing if the recipient has been pregnant or transfused within the previous 3 months (21 CFR 606.151(b)). The acceptable sample age should be determined with the collection of the specimen at day 0 and the sample expiring at midnight on day 3. You must follow the specimen requirements described in the instructions for use provided by the manufacturer of the antibody screening cells (21 CFR 606.65(e)). If testing of the recipient's specimen shows that the recipient has clinically significant RBC antibodies (antibodies known to cause transfusion reactions) or records show a history of clinically significant RBC antibodies, you should not rely on a computer crossmatch. Under those circumstances, your procedures should provide for compatibility testing using serologic crossmatch techniques.

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2. Recipient ABO/Rh (D) Type and Interpretation

You should determine a recipient's ABO and Rh (D) antigens (Ref. 11). You should either perform or maintain a record of a second test, confirming the recipient's ABO/Rh (D). For example, this second test may be a record of a test performed previously, or a repeat test on a second, separately drawn specimen. Repeating ABO and Rh (D) tests on the same specimen is not recommended, as the major cause of ABO errors is "wrong blood in tube" (WBIT). Performing tests on two separately drawn specimens is preferred, as this lessens the likelihood of errors because specimens have been drawn in error. In certain situations, however, only one specimen may be available for testing, such as in emergencies or when only one sample is received for home transfusion. At those times, repeat testing may be performed on the same specimen, but the repeat test should be performed either by a different technologist or by the same technologist using different reagents.

If ABO typing discrepancies exist, you should not rely on a computer crossmatch. This is particularly important if there is mixed field red cell reactivity, missing serum reactivity, or apparent change in blood type following hematopoietic stem cell transplantation. Under those circumstances, your procedures should provide for compatibility testing using serologic crossmatch techniques.

3. Recipient Sample

Our regulations do not specify a specimen age restriction for a recipient who has not been transfused or pregnant within the last three months. Based on your ability to obtain a reliable recipient history and to store positively identified recipient specimens, you should define appropriate specimen age limits. Your procedures must be consistent with any limitations described in the reagent manufacturers' directions for use (21 CFR 606.65(e)).

C. Donor Data Elements

The electronic database should include:

- Unique identification number;
- Component name;
- ABO group/Rh (D) type and interpretation;
- Special manufacturing requirements (e.g., leukocyte reduced, CMV antibody negative, irradiation); and
- Donor RBC antibody assessment.

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D. Donor RBC Antibody Assessment

If tests for unexpected antibodies are positive, blood and blood components intended for transfusion must be labeled by the blood collecting facility with the name of the antibody (21 CFR 606.121(e)(1)(iii), (e)(2)(ii) and (e)(4)). Using this information, you should determine if the donor has clinically significant RBC antibodies. If the donor has clinically significant RBC antibodies, you should not rely on a computer crossmatch. Under those circumstances, your procedures should provide for compatibility testing using serologic crossmatch techniques capable of detecting such clinically significant antibodies.

E. Decision Tables

Your written procedures should explain where the decision tables are located and how to populate or configure them with the specific decision rules used to determine donor/recipient compatibility for the computer crossmatch. The software manufacturer's documentation, e.g., User's Manual(s), usually provides this information. The decision rules are usually defined by you. However, they may be pre-defined by the software manufacturer in the programming code (this situation is referred to as "hardcoding") and cannot be modified by you. After you clearly understand the rules - whether defined by you or the manufacturer - you should verify that the decision rules are appropriate for your practices by checking the results of data entry. Once you verify that the rules for software controlled decision-making are appropriate, you should validate the performance of the computer crossmatch process in your establishment, as recommended in this guidance.

Identification of the product to be transfused is important for software-controlled decisions. For example, if you issue Whole Blood using the computer crossmatch, the decision table should include ABO compatibility definitions for minor crossmatches. Alternatively, you may limit the use of computer crossmatch to those situations where you release only RBC components.

Unless the manufacturer has hardcoded the decision rules, you may usually modify software-controlled decision rules to include procedures appropriate for you (e.g., by including other recipient criteria or compatibility elements in your donor/recipient compatibility decision tables).

F. Warning Messages

A warning message is a software-generated message that is displayed to notify you when an action does not conform to the decision rules. We believe that a warning message is adequate if it is obtrusive enough to assure that the operator will notice and heed it. Your software should also document warning messages and the circumstances surrounding their display (e.g., date, time, name of operator). You should decide what alert level is

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necessary at each decision point in order to provide an acceptable margin of safety. You should use different levels appropriate for the importance of each situation. Some possible alert levels would include displaying a warning message and:

- Allowing the user to proceed; or
- Requiring the user to enter a code before proceeding; or
- Requiring a supervisor's code before the user can proceed; or
- Not allowing the user to proceed under any circumstances.

G. Computer Downtime

In the event you need to make compatibility determinations when the computer system is down, you must have written procedures explaining how to perform compatibility testing and release blood during computer downtime (21 CFR 606.100(b) and 606.151(c)). Your downtime SOP should address recovery after the computer is again operational (e.g., entry of test results completed during the downtime, including sample date and time).

V. VALIDATION AND RE-VALIDATION

A. Validation

User validation is testing new equipment or a new process in the environment where it will be used to ensure that it will reliably produce a product that meets predetermined qualifications and quality standards (Refs. 12, 13, and 14). Electronic equipment, including computer systems, must be routinely checked according to a written program designed to assure proper performance (21 CFR 211.68(a)). In addition, input to and output from the computer or other records or data must be checked for accuracy (21 CFR 211.68(b)). Therefore, before you start user validation, you must develop a validation protocol and acceptance criteria to ensure the system is performing properly (21 CFR 211.68(a)). The validation protocol is your plan for the testing, evaluation, and final acceptance of the process. You should perform validation testing at your location using the same software, hardware, SOPs, and personnel who will perform the process after it is formally implemented (Refs. 12 and 13). You should perform the validation tests in a software partition set aside for such tests, and not on your live system where actual recipient and inventory records are in use.

When you plan your validation protocol, you should address:

- Routine functions – the most common circumstances of daily work;
- At-risk functions – the riskiest parts of the operation, such as the release of ABO incompatible blood or the release of blood when the recipient has a history of clinically significant antibody(ies);
- Strategies or test methods you will use to test each function;

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- Decision values – the quantitative decisions made by the computer, such as evaluating the number of days of a sample age. You should test at just below, and just above, the decision value;
- Unexpected outcomes and events – test issues which you do not expect to occur but which may occur, such as the release of Whole Blood, even though you rarely stock Whole Blood or the simultaneous entry of conflicting results;
- Security and authority levels – if your system allows override of a warning only by those assigned a particular level of authority, you should challenge the system to document that the authority limitations are enforced;
- Predetermined acceptance and completion criteria;
- Criteria for failure investigation, corrective action and follow-up, including criteria for re-testing; and
- Final review or sign-off authority.

Under the regulations, you must inspect and routinely validate your computer crossmatch process according to a written program designed to assure proper performance (21 CFR 211.68(a)). See also 21 CFR 211.100(a), 606.100(b)(14), and 606.151(c). A written program is not “designed to assure proper performance” unless it requires user validation prior to routine use, on a routine basis, and any time a change is made to the program that has the potential to affect the computer crossmatch process. Therefore, you must perform user validation of any new computer system or functionality prior to routine use by testing and documenting the new system or functionality in your facility (21 CFR 211.68(a), 211.100(a), 606.100(b)(14), and 606.151(c)).

In addition, as discussed in greater detail below, you must inspect and routinely validate all of the critical elements of your computer crossmatch process (21 CFR 211.68(a)), including:

- Hardware (including bar code readers and printers);
- Software (including interfaces with other systems); and
- User performance, including a mechanism to test the ability of the user to understand and correctly interface with the computer system.

The key issues that should be covered during your user validation of a computer crossmatch process are presented below. You must check according to a written program designed to assure proper performance (21 CFR 211.68(a)). Accordingly, you should develop your own test cases based on your system, its intended use and functionality, and your work environment.

As discussed above, you must routinely check or validate all of the critical elements of your crossmatch process (21 CFR 211.68(a) and (b)). These validation activities should include:

- On-site validation: Validate the computer crossmatch process at your location using the same hardware, software, SOPs and personnel that will be routinely used.

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- Elements of the decision rules: Challenge the system using combinations of concordant and discordant or missing results; acceptable and unacceptable specimens; and acceptable and unacceptable selections of components. Challenge these elements to evaluate:
 - Specimen acceptability;
 - Donor and recipient ABO/Rh (D) confirmation;
 - Antibody screen;
 - Donor/recipient compatibility; and
 - Component selection.
- Warnings: Challenge the system with all combinations to demonstrate that unacceptable situations will trigger appropriate warning messages.

B. Re-Validation

As discussed above, the regulations require that you inspect and routinely validate your computer crossmatch process according to a written program designed to assure proper performance (21 CFR 211.68(a)). See also 21 CFR 211.100(a), 606.100(b)(14), and 606.151(c). A written program is not “designed to assure proper performance” unless it specifically requires user validation prior to routine use, on a routine basis, and any time a change is made to the program that has the potential to affect the computer crossmatch process. Therefore, you must also perform re-validation any time you make a change that might affect the computer crossmatch process. This would include such things as software upgrades, changes in decision tables, revised SOPs, or new hardware. Validation in these cases is usually focused on the specific performance characteristics, which may have been altered by the particular change (21 CFR 211.68(a) and (b)).

VI. RECORDS

You must maintain documentation of all significant activities, including compatibility testing, concurrently with the performance of each significant step (21 CFR 606.160(a)(1)). Under 21 CFR 606.160(b)(4), you must also maintain records of all compatibility tests, including crossmatching, testing of patient samples, antibody screening and identification, and the results of confirmatory testing.

Under 21 CFR 606.160(b)(5), you must maintain quality control records relating to calibration and standardization of equipment, and performance checks of equipment and reagents. These records should include your validation protocol, test results, evaluation of the results, any follow-up changes or corrections made in response to the testing, results of the re-testing of the system following the corrections and final approval/acceptance of the system. After the initial validation, when you make changes, you must also keep records of your process change and re-validation (21 CFR 211.68(a) and (b)).

You must keep such records for no less than 10 years after the records of processing are completed (e.g., the date of the last computer crossmatch), or until six months after the latest expiration date for the individual product, whichever is the later date (21 CFR 606.160(d)).

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Records may be kept electronically as long as you comply with the appropriate requirements of 21 CFR Part 11, as further described in previous FDA guidance (Ref. 15).

VII. IMPLEMENTATION

A. Following this Guidance

If you hold a biologics license and are implementing a computer crossmatch procedure for the first time, or are changing a computer crossmatch procedure that is already approved under your license, you must report the change to FDA under 21 CFR 601.12. The regulation provides that manufacturing changes must be reported to FDA by means of different mechanisms, depending on the degree to which the change has the potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product, as they may relate to the safety or effectiveness of the product. We believe that a computer crossmatch procedure that follows the recommendations in this guidance meets the standard for reporting in an annual report (21 CFR 601.12(d)) (Ref. 16).

We believe that changes regarding computer crossmatch procedures that do not follow the recommendations in this guidance present a moderate or substantial potential to have an adverse affect on the identity, strength, quality, purity, or potency of the product, as they may relate to the product's safety and effectiveness, and therefore require the submission of a preapproval or other supplement submission, depending on the nature of the change (21 CFR 601.12(b) and (c)).

If you plan to implement a computer crossmatch procedure and have questions about how to report the change to FDA, contact the Division of Blood Applications at (301) 827-3543. Unlicensed manufacturers are not required to report manufacturing changes to FDA under 21 CFR 601.12.

We believe that the procedures described in this guidance are consistent with CGMP requirements and may be used to satisfy the requirement in 21 CFR 606.151(c) that you have procedures to address compatibility determinations.

B. Computer Crossmatch Systems in Use

1. Validated Computer Crossmatch System

Before September 5, 2001, we approved prior approval supplement requests for alternative procedures for the use of a computer crossmatch system that included a manual check of some records, such as a check of recipient records for a history of an antibody. We now believe that the adoption of a validated computer crossmatch system with manual enforcement of some decision rules that has been fully and properly validated and is consistent with the recommendations in this guidance would have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of blood products as they relate to the safety or effectiveness of the

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product. Accordingly, if licensed establishments choose to implement a computer crossmatch procedure in a manner that is consistent with the recommendations in this guidance, they must report this change in their annual report (21 CFR 601.12(d)).

2. Unvalidated Computer Crossmatch System

If your computer crossmatch process has not been fully and properly validated, you should perform serologic testing to satisfy the compatibility testing requirements in 21 CFR 606.151(c), until you complete your user validation following this guidance. If you have been using an unvalidated computer crossmatch process, your history of use does not substitute for a proper validation. Although you may analyze your routine records of use as part of your validation, the validation should be a planned activity that challenges your process in both routine and unusual circumstances.

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