



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 864

[Docket No. FDA-2016-N-0406]

Medical Devices; Hematology and Pathology Devices; Classification of Blood Establishment

Computer Software and Accessories

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is proposing to classify the blood establishment computer software (BECS) and BECS accessories into class II (special controls). FDA is identifying proposed special controls for BECS and BECS accessories that are necessary to provide a reasonable assurance of safety and effectiveness. FDA is also giving notice that the Agency does not intend to exempt BECS and BECS accessories from premarket notification requirements of the Federal Food, Drug, and Cosmetic Act (the FD&C Act). FDA is publishing in this document the recommendations of the Blood Product Advisory Committee regarding the classification of these devices. After considering public comments on the proposed classification, FDA will publish a final regulation classifying these device types.

DATES: Submit either electronic or written comments by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Please see section IV of this document for the proposed effective date of a final rule that may issue based on this proposal.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <http://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <http://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2016-N-0406 for “Medical Devices; Hematology and Pathology Devices; Classification of Blood Establishment Computer Software and Accessories.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <http://www.regulations.gov> or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <http://www.regulations.gov>. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public docket, see 80 FR 56469, September 18, 2015, or access the information at: <http://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Jessica T. Walker, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

A. Statutory and Regulatory Authorities

The FD&C Act (21 U.S.C. 301 et seq.), as amended by the Medical Device Amendments of 1976, establishes a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) establishes three categories (classes) of devices depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Class I devices are those devices for which the general controls of the FD&C Act (controls authorized by or under sections 501, 502, 510, 516, 518, 519, or 520 or any combination of such sections) are sufficient to provide reasonable assurance of safety and effectiveness; or those devices for which insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness or to establish special controls to provide such assurance, but because the devices are not purported or

represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and do not present a potential unreasonable risk of illness or injury, are to be regulated by general controls (section 513(a)(1)(A) of the FD&C Act). Class II devices are those devices for which general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but for which there is sufficient information to establish special controls to provide such assurance, including the issue of performance standards, postmarket surveillance, patient registries, development and dissemination of guidelines, recommendations, and other appropriate actions the Agency deems necessary to provide such assurance (section 513(a)(1)(B) of the FD&C Act). Class III devices are those devices for which insufficient information exists to determine that general controls and special controls would provide a reasonable assurance of safety and effectiveness, and are purported or represented for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury (section 513(a)(1)(C) of the FD&C Act).

Under section 513(d)(1) of the FD&C Act, devices that were in commercial distribution before the enactment of the Medical Device Amendments of 1976 (1976 amendments), May 28, 1976 (generally referred to as “preamendments devices”), are classified after FDA: (1) Receives a recommendation from a device classification panel (an FDA advisory committee); (2) publishes the panel’s recommendation for comment, along with a proposed regulation classifying the device; and (3) publishes a final regulation classifying the device.

FDA has classified most preamendments devices under these procedures, relying upon valid scientific evidence as described in section 513(a)(3) of the FD&C Act and 21 CFR

860.7(c), to determine that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.

Devices that were not in commercial distribution before May 28, 1976 (generally referred to as “postamendments devices”), are classified automatically by section 513(f) of the FD&C Act into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval, unless and until: (1) FDA classifies or reclassifies the device into class I or II or (2) FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval.

The Agency determines whether new devices are substantially equivalent to previously marketed devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 of the regulations (21 CFR part 807).

A person may market a preamendments device that has been classified into class III through premarket notification procedures without submission of a premarket approval application (PMA) until FDA issues a final order under section 515(b) of the FD&C Act (21 U.S.C. 360e(b)) requiring premarket approval.

B. Regulatory History of the Devices

After the enactment of the 1976 amendments, FDA began to identify and classify all preamendments devices in accordance with section 513(b) of the FD&C Act.

The first BECS 510(k) premarket notification was cleared by FDA on August 26, 1996. Information Data Management, Inc., submitted premarket notifications for their Components & Distribution Information System and Donor Management Information System. These devices were compared to systems marketed prior to the 1976 medical device amendments, including the

Blood Inventory Management System by Computer Sciences Corporation and the Donor Deferral Registry developed by the American National Red Cross. Between 1996 and December 2015, FDA has cleared 220 BECS and BECS accessories under the 510(k) program.

In 1998, FDA sought recommendations from the Blood Product Advisory Committee (BPAC) serving as a Device Classification Panel on the classification of BECS. The Device Classification Panel recommended regulating BECS as a class II device with premarket review (Ref. 1). The classification of BECS was not finalized following the Device Classification Panel's recommendation in 1998 because of competing priorities.

On December 3, 2014, the BPAC, serving as a Device Classification Panel (the Panel), again convened to discuss the classification of BECS and BECS accessories (Ref. 2). The Panel discussed the risks to health associated with BECS and BECS accessories, the classification of BECS and BECS accessories, and if classified as class II devices, the special controls that would be required for these devices. The Panel agreed that general controls were not sufficient to provide a reasonable assurance of safety and effectiveness of BECS and BECS accessories. The Panel believed that BECS and BECS accessories presented a potential unreasonable risk of illness, injury, or death, and that sufficient information exists to establish special controls for these devices. Consequently, the Panel recommended that these devices be classified into class II (special controls) with premarket review. FDA is not aware of new information that has arisen since this Panel meeting that would provide a basis for different recommendations or findings. The recommendations of the Panel are summarized in Section II.

II. Panel Recommendation

This section summarizes the Panel's deliberations on December 3, 2014.

A. Identification

FDA proposed the following definition of BECS and BECS accessory to the Panel for their consideration: BECS and BECS accessories are devices used in the manufacture of blood and blood components to assist in the prevention of disease in humans by identifying unsuitable blood donors by: (1) Preventing the release of unsuitable blood and blood components for transfusion or for further manufacturing into products for human treatment or diagnosis; (2) performing compatibility testing between donor and recipient; and (3) performing positive identification of patients and blood components. A BECS accessory expands or modifies the function of the BECS and/or indications for use of the BECS device. These devices are intended for use with or capable of functioning with BECS for the purpose of augmenting or supplementing the BECS performance.

B. Recommended Classification of the Panel

The Panel recommended that BECS and BECS accessories be classified into class II (special controls) with premarket review, and that FDA revise the proposed definition of a BECS accessory. The consensus of the Panel was that class II classification (special controls) and premarket review would provide reasonable assurance of safety and effectiveness of these devices and that there is sufficient information to establish special controls to provide such assurance for BECS and BECS accessories.

The Panel considered the following valid scientific evidence to make their recommendations regarding the safety and effectiveness of the device under its conditions of use. Specifically, the Panel considered the history of safety and effectiveness of BECS and BECS accessories over many years of use in blood establishments; the results of an FDA review of the scientific literature; medical device reports (MDRs) of adverse events or malfunctions; device

recalls; and a summary of FDA's extensive inspectional and regulatory experiences with BECS and BECS accessories.

The Panel also commented on the proposed definition of BECS accessories: "A BECS accessory expands or modifies the function of the BECS and/or indications for use of the BECS device." These devices are intended for use with or capable of functioning with BECS for the purpose of augmenting or supplementing the BECS performance. The Panel recommended that FDA clarify which added functionalities would be considered a BECS accessory and, therefore, subject to regulations as a class II device with special controls.

C. Risks to Health and Special Controls

As required by section 513(f)(1)(A) of the FD&C Act, FDA provided to the Panel the following summary of valid scientific evidence regarding the benefits and risks of BECS and BECS accessories. In the 1990s, during establishment inspections, FDA investigators observed numerous problems with BECS, including software programs that posed significant risks to health, such as the potential for release for transfusion of blood and blood components found to be reactive when tested with assays for Human Immunodeficiency Virus. During the inspections, FDA found that unsuitable blood and blood components had been released and distributed as a result of improperly designed software.

From 1996 to 2014, FDA received 201 MDRs for BECS and BECS accessories. The majority (86 percent) of the MDRs were for device malfunctions. In addition, one death and nine injuries were reported. The reported patient death was not attributed to the BECS. The information provided in the reports of the nine injuries was insufficient to accurately identify the nature of the injuries or the attribution to BECS. The remaining reports included events classified in various categories such as user error, operational problems, and labeling.

Similarly, from 2006 to 2013, BECS manufacturers initiated 56 voluntary device recalls. The deviations included programming errors, inadequate design requirements, and incorrect implementation of the design. The potential consequences of the BECS deviations included presenting donors with incorrect donor history questionnaires, failing to save certain test results in donor records, and failing to identify donors as deferred. The recalls were classified as class II and class III. A class II recall is a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. A class III recall is a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences. No recalls were classified as class I, a situation in which there is reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death.

FDA presented the following risks to health associated with BECS and BECS accessories: (1) Transfusion reaction or death from the inadvertent release and transfusion of incompatible blood or blood components; (2) transfusion injury from the transfusion of inaccurately labeled and/or stored blood components; (3) transfusion injury or death from the release of blood components from otherwise ineligible donors (for example, the transmission of infectious diseases from the inadvertent release of blood components that have tested positive for transfusion-transmitted disease agents); and (4) donor injury from inappropriate or excessive donation of blood or blood components.

FDA also proposed the measures described in table 1 to mitigate the risks to health associated with BECS and BECS accessories. The Panel agreed that the risks to health and

mitigation measures identified by FDA and summarized in table 1 are applicable to BECS and BECS accessories.

FDA next presented the following special controls for the Panel's considerations: (1) Software performance and functional requirements are provided in the premarket submission including detailed design specifications (e.g., algorithms or control characteristics, alarms, device limitations, and safety requirements); (2) verification and validation testing and hazard analysis are to be performed and provided in the premarket submission; (3) labeling includes software limitations, unresolved anomalies, annotated with an explanation of the impact on safety or effectiveness, revision history, and hardware and peripheral specifications; (4) traceability matrix performed and provided in the premarket submission; and (5) performance testing is performed and provided in the premarket submission, as necessary to ensure the safety and effectiveness of the system, and when adding new functional requirements, (e.g., electrical safety, electromagnetic compatibility, or wireless coexistence).

The Panel members generally agreed with the special controls proposed by FDA. One Panel member commented that requiring the performance of verification and validation and hazard analysis is not sufficient without defining what type of testing is necessary, and expressed particular concern regarding the acceptable level of verification for BECS. Another member asked whether many of the proposed special controls should be considered general controls for the purposes of software manufacturing considering the evolution of technology.

Table 1--Health Risks and Mitigation Measures for BECS and BECS Accessories

Identified Risks to Health	Mitigation Measures
Transfusion reaction or death	Performance and functional requirements
Transmission of infectious disease	Performance and testing
Donor health risk from too frequent or inappropriate donation	Labeling

III. Proposed Classification and FDA's Findings

After considering the recommendations of the Panel and the valid scientific evidence, including the published literature, MDRs, recall information, and FDA's extensive inspection and regulatory experiences with these device types (Ref. 3), FDA proposes to classify BECS and BECS accessories into class II (special controls) with premarket review. FDA believes general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness for these devices and that there is sufficient information to establish special controls to provide such assurance. FDA believes that special controls, in addition to general controls, would provide a reasonable assurance of the safety and effectiveness of BECS and BECS accessories and would, therefore, mitigate the risk to patients of transfusion reaction or death and transmission of infectious disease and risks to donors because of inappropriate donations.

The special controls proposed for BECS and BECS accessories, specifically performance and functional requirements, device verification and validation, hazards analysis, traceability, and performance testing, collectively ensure that the manufacturer performs and documents the activities necessary to decrease the risk of malfunction that could result in the adverse events noted above. Further, appropriate labeling ensures that the user of the device is provided clear instructions for use, including the limitations of the device, to reduce the risk of user error that could result in the risks to health associated with these devices.

FDA has amended the proposed definition of BECS accessories consistent with the recommendation of the Panel and made other minor edits to the definition of BECS and the special controls presented to the Panel in the proposed regulation.

Section 510(m) of the FD&C Act provides that a class II device may be exempted from the premarket notification requirements under section 510(k) of the FD&C Act, if the Agency determines that premarket notification is not necessary to assure the safety and effectiveness of the device. The Agency does not intend to exempt BECS and BECS accessories from 510(k) premarket notification as allowed under section 510(m) of the FD&C Act. FDA believes premarket notification is necessary for these devices to assure their safety and effectiveness.

IV. Proposed Effective Date

FDA proposes that any final regulation based on this proposal become effective 30 days after its date of publication in the Federal Register.

V. Environmental Impact

We have determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed regulation is consistent with historical regulatory oversight given to this type of device, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$144 million, using the most current (2014) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

This rule proposes to classify BECS and BECS accessories into Class II devices with special controls and subject to premarket review. The proposed special controls for these devices are necessary to provide a reasonable assurance of safety and effectiveness. FDA has cleared 220 BECS and BECS accessories under the 510(k) program consistent with the recommendations in the FDA guidance, “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices,” dated May 2005 (Ref. 4). As current practice, manufacturers already conform to the risk mitigations that are being proposed as special controls for BECS and BECS accessories, so this rule would essentially formalize current practice and will not result in any additional associated costs. Likewise, this classification will not result in any significant changes in how 510(k) premarket notifications for the affected devices are

submitted or prepared by manufacturers or in how they are reviewed by FDA. Therefore, compliance with the special controls proposed for this device would not yield significant new costs for affected manufacturers. Because the classification of these devices to Class II (special controls) would not impose significant new obligations on manufacturers, the Agency concludes that the proposed rule, if finalized, will impose no additional regulatory burdens.

VII. Paperwork Reduction Act

This proposed rule refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3520). The collections of information in 21 CFR part 807 subpart E have been approved under OMB control number 0910-0120, and the collections of information in 21 CFR subpart 801 have been approved under OMB control number 0910-0485. Therefore, FDA tentatively concludes that the proposed requirements in this document are not subject to review by OMB because they do not constitute a “new collection of information” under the PRA.

VIII. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <http://www.regulations.gov>. FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. Blood Product Advisory Committee Meeting transcript--March 20, 1998 (<http://www.fda.gov/ohrms/dockets/ac/98/transcpt/3391t2.pdf>).

2. Blood Product Advisory Committee Meeting transcript--December 3, 2014
(<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm386681.htm>).

3. FDA Executive Summary. Blood Products Advisory Committee Meeting--
December 3, 2014
(<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm427392.htm>).

4. Guidance for Industry and FDA Staff: Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, May 2005,
<http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm089543.htm>.

List of Subjects in 21 CFR Part 864

Blood, Medical devices, Packaging and containers.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, FDA proposes to amend part 864 as follows:

PART 864--HEMATOLOGY AND PATHOLOGY DEVICES

1. The authority citation for 21 CFR part 864 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. In subpart J, add § 864.9165 to read as follows:

§ 864.9165 Blood establishment computer software and accessories.

(a) Identification. Blood establishment computer software (BECS) and BECS accessories are devices used in the manufacture of blood and blood components to assist in the prevention of disease in humans by identifying ineligible donors, by preventing the release of

unsuitable blood and blood components for transfusion or for further manufacturing into products for human treatment or diagnosis, by performing compatibility testing between donor and recipient, or by performing positive identification of patients and blood components at the point of transfusion to prevent transfusion reactions. A BECS accessory is intended for use with BECS to augment its performance or to expand or modify its indications for use.

(b) Classification. Class II (special controls). The special controls for these devices are:

(1) Software performance and functional requirements including detailed design specifications (e.g., algorithms or control characteristics, alarms, device limitations, and safety requirements).

(2) Verification and validation testing and hazard analysis must be performed.

(3) Labeling must include:

(i) Software limitations;

(ii) Unresolved anomalies, annotated with an explanation of the impact on safety or effectiveness;

(iii) Revision history; and

(iv) Hardware and peripheral specifications.

(4) Traceability matrix must be performed.

(5) Performance testing to ensure the safety and effectiveness of the system must be performed, including when adding new functional requirements (e.g., electrical safety, electromagnetic compatibility, or wireless coexistence).

Dated: February 24, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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