or lacking a principal inspector, the manager of the responsible Flight Standards Office.

(3) An AMOC that provides an acceptable level of safety may be used for any repair, modification, or alteration required by this AD if it is approved by The Boeing Company Organization Designation Authorization (ODA) that has been authorized by the Manager, Los Angeles ACO Branch, FAA, to make those findings. To be approved, the repair method, modification deviation, or alteration deviation must meet the certification basis of the airplane, and the approval must specifically refer to this AD.

(4) AMOCs approved previously for AD 2017–24–10 are not approved as AMOCs with this AD.

(5) Except as specified by paragraph (i) of this AD: For service information that contains steps that are labeled as Required for Compliance (RC), the provisions of paragraphs (m)(5)(i) and (ii) of this AD apply.

(i) The steps labeled as RC, including substeps under an RC step and any figures identified in an RC step, must be done to comply with the AD. If a step or substep is labeled ''RC Exempt,'' then the RC requirement is removed from that step or substep. An AMOC is required for any deviations to RC steps, including substeps and identified figures.

(ii) Steps not labeled as RC may be deviated from using accepted methods in accordance with the operator's maintenance or inspection program without obtaining approval of an AMOC, provided the RC steps, including substeps and identified figures, can still be done as specified, and the airplane can be put back in an airworthy condition.

(n) Related Information

(1) For more information about this AD, contact Peter Jarzomb, Aerospace Engineer, Airframe Section, FAA, Los Angeles ACO Branch, 3960 Paramount Boulevard, Lakewood, CA 90712–4137; phone: 562–627–5234; email: *peter.jarzomb@faa.gov.*

(2) For service information identified in this AD, contact Boeing Commercial Airplanes, Attention: Contractual & Data Services (C&DS), 2600 Westminster Blvd., MC 110–SK57, Seal Beach, CA 90740–5600; telephone 562–797–1717; internet *https://www.myboeingfleet.com.* You may view this referenced service information at the FAA, Airworthiness Products Section, Operational Safety Branch, 2200 South 216th St., Des Moines, WA. For information on the availability of this material at the FAA, call 206–231–3195.

Issued on December 10, 2021.

Lance T. Gant,

Director, Compliance & Airworthiness Division, Aircraft Certification Service.

[FR Doc. 2022–01014 Filed 1–20–22; 8:45 am]

BILLING CODE 4910–13–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA–2021–N–0851]

Medical Devices; Immunology and Microbiology Devices; Classification of Human Leukocyte, Neutrophil and Platelet Antigen and Antibody Tests

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is proposing to classify Human Leukocyte Antigen (HLA), Human Platelet Antigen (HPA), and Human Neutrophil Antigen (HNA) devices, a generic type of device, into class II (special controls). FDA is identifying proposed special controls for HLA, HPA, and HNA devices that are necessary to provide a reasonable assurance of safety and effectiveness. FDA is also giving notice that we do not intend to exempt these device types from premarket notification requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act). FDA is publishing in this document the recommendations of the Blood Products Advisory Committee, serving as a device classification panel, 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 on the proposed rule by April 21, 2022.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before April 21, 2022. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of April 21, 2022. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://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 *https://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):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, 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–2021–N–0851 for ''Medical Devices; Immunology and Microbiology Classification of Human Leukocyte, Neutrophil and Platelet Antigen and Antibody Tests.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- 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 *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. 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 dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/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 *https://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 Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

FOR FURTHER INFORMATION CONTACT: Myrna Hanna, 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:

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I. Executive Summary

A. Purpose of the Proposed Rule

FDA is proposing to classify HLA, HPA, and HNA devices, a generic type of device, into class II (special controls). The Agency believes that the special controls established by this proposed rule, together with general controls, would provide reasonable assurance of the safety and effectiveness of these devices. FDA is also giving notice that we do not intend to exempt HLA, HPA, and HNA devices from premarket notification requirements of the FD&C Act.

B. Summary of the Major Provisions of the Proposed Rule

FDA is proposing to classify HLA, HPA, and HNA devices, a generic type of device, into class II with special controls. This proposed rule provides device descriptions that include indications for use of the devices and the special controls that will provide reasonable assurance of the safety and effectiveness of these devices.

C. Legal Authority

FDA is proposing this action under the device provisions of the FD&C Act including section 513 of the FD&C Act (21 U.S.C. 360c).

D. Costs and Benefits

The benefits of this proposed rule consist of the cost savings resulting from the reduction in regulatory and economic burden that accompanies the decrease in the number of information requests and incomplete submissions submitted by manufacturers and handled by FDA; however, we lack the information needed that would allow us to quantify these benefits. The number of requests for additional information following manufacturers' 510(k) submissions is small and widely dispersed over the duration of time these devices have been marketed. The classification procedure and outlined special controls will be helpful for HLA, HPA, and HNA manufacturers in preparing their submissions. Further benefits may be derived from the decreased time a notification submission will need to be reviewed and the subsequent potential benefits realized by consumers and manufacturers.

The costs of this proposed rule include one-time upfront labeling redesigns, in addition to initial learning and reading costs. The total estimated one-time costs of this proposed rule are $434,885 (in 2020 dollars). The present value of these costs is $434,885 because they are one-time costs that are expected to occur in the first year. The annualized cost of this proposed rule over 10 years is $54,201 at a seven percent discount rate and $45,632 at a three percent discount rate.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/acronym	What it means
510(k)	Premarket Notification.
BPAC	Blood Products Advisory Committee.
CFR	Code of Federal Regulations.
FDA	Food and Drug Administration.
FD&C Act	Federal Food, Drug, and Cosmetic Act.
HLA	Human Leukocyte Antigen.
HPA	Human Platelet Antigen.
HNA	Human Neutrophil Antigen.
MAUDE	Manufacturer and User Facility Device Experience.
MDR	Medical Device Report.
Ref	Reference.
TRALI	Transfusion-Related Acute Lung Injury.
U.S.C	United States Code.

III. 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 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 (21 U.S.C. 351, 352, 360, 360f, 360h, 360i, or 360j) or any combination of such sections) are sufficient to provide reasonable assurance of safety and effectiveness of the device; 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 promulgation 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) on 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, along with a proposed regulation classifying the device, and provides an opportunity for interested persons to submit comments; 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 and part 807 of the regulations (21 CFR part 807). The 510(k) premarket notification is a submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective as (*i.e.,* substantially equivalent to) a legally U.S. marketed class I or II device of that same generic type. A generic type of device is a grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness (21 CFR 860.3(i)). When determined to be substantially equivalent, the subject device may be legally marketed in the United States. The legally marketed device to which substantial equivalence is determined is known as the predicate device. A predicate device can be a preamendments device or a postamendments device.

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 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

The first product license for Leukocyte Typing Serum was issued in December 1974, by the Bureau of Biologics, FDA. An FDA guideline for the production, testing, and lot release of Leukocyte Typing Serum was issued in 1977 and subsequently codified as Additional Standards in the biologics regulations under 21 CFR 660.10 through 660.15.

In the **Federal Register** of August 1, 1980 (45 FR 51226), FDA published a proposed rule recommending that the Additional Standards for Leukocyte Typing Serum be removed with the subsequent revocation of the existing product licenses. The proposed rule was prompted by the realization of the growing complexities of the HLA system and the difficulty in achieving standardization. The proposed rule was supported by the argument that the products, while biologics, were also medical devices that could be appropriately and efficiently regulated under the FD&C Act as amended by the Medical Device Amendments of 1976 (21 U.S.C 301 et seq). The Agency's intent to classify HLA reagents and kits was described in the preamble to the 1980 proposed rule.

In the **Federal Register** of August 10, 1982 (47 FR 34532), FDA issued a final rule revoking the additional standards for Leukocyte Typing Serum. The final regulation instructed all manufacturers of Leukocyte Typing Serum to register and list under part 807. For those products not currently licensed, manufacturers would be required to submit premarket notifications (510(k) submissions). The first 510(k) cleared HLA device used a preamendment HLA device as predicate.

Since 1982, FDA has cleared approximately 100 HLA device premarket notifications (510(k)) submissions. Since 1993, FDA has cleared seven HPA assays through the 510(k) premarket notifications pathway. Five devices were cleared for the detection of antibodies against HPA and two were cleared for HPA typing. Since 2006, FDA has cleared four HNA devices through the 510(k) premarket

notifications pathway. Two devices were cleared for the detection of antibodies against HNA and two were cleared for HNA typing.

On September 15, 2000, the Blood Products Advisory Committee (BPAC) (2000 BPAC), serving as a device classification panel, provided recommendations to FDA regarding the classification of in vitro diagnostic reagents and kits for use in determining the HLA phenotype or genotype of an individual, or for detecting antibodies to HLA antigens (Ref. 1). The scope of the discussion included devices that are used to support platelet and leukocyte transfusions, or organ and stem cell transplantation. The classification of HLA kits used to predict disease was not discussed at the meeting. The 2000 BPAC agreed unanimously that HLA devices should be classified as class II medical devices. The panel did not agree that the devices should be exempt from the requirement to submit a 510(k). Although the 2000 BPAC recommended classification of the HLA devices as class II, the classification was not finalized by FDA because of competing priorities.

On November 30, 2017, FDA sought recommendations from the BPAC, serving as a device classification panel (the Panel) (Refs. 2 and 3), to discuss the classification of HLA, HPA, and HNA devices. FDA proposed to the Panel that HLA, HPA, and HNA devices be classified as a generic device type. The rationale to classify these devices together was based on the similarities in the biological properties of the three antigen systems, the use of similar technologies for the detection of antigens and antibodies, the clinical use of the test results, and the special controls required to mitigate risks. FDA proposed that these are devices that do not differ significantly in purpose, design, materials, energy source, function, or other features related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness. 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 the Panel meeting that would provide a basis for different recommendations or finding. The recommendations of the Panel are summarized in Section V.

IV. Legal Authority

We are issuing this proposed rule under section 513(a) of the FD&C Act. FDA has authority under this provision of the FD&C Act to issue a regulation to establish special controls for class II devices for which general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance. Under this authority, FDA is establishing special controls for HLA, HPA, and HNA devices.

V. Description of the Proposed Rule and Panel Recommendations

This section summarizes the Panel's deliberations on November 30, 2017.

A. Identification

FDA described HLA, HNA, and HPA devices for the Panel's consideration:

Human Leukocyte, Neutrophil and Platelet antigen and antibody devices consist of HLA, HNA, and HPA typing and antibody detection devices.

- HLA typing devices are used to determine HLA types, to aid in transfusion or transplantation donor and recipient matching, or to aid in the diagnosis of diseases.
- HLA antibody detection devices are used to detect antibodies to HLA antigens to aid in donor and recipient matching in transfusion or transplantation.
- HPA typing devices are used for the detection of human platelet antigens to aid in donor and recipient matching in blood transfusion or to aid in the diagnosis of diseases.
- HPA antibody detection devices are used to detect autoantibodies and alloantibodies against platelet glycoproteins to aid in donor and recipient matching in blood transfusion or to aid in the diagnosis of diseases.
- HNA typing devices are used for the detection of human neutrophil antigens to aid in donor and recipient matching in blood transfusion or to aid in the diagnosis of diseases.
- HNA antibody detection devices are used to detect autoantibodies and alloantibodies against neutrophil antigens to aid in donor and recipient matching in blood transfusion or to aid in the diagnosis of diseases.

FDA clarified the following devices are not included in the proposed classification:

- HLA, HPA, or HNA devices used as a companion diagnostic device, a device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.
- HLA, HPA, or HNA assays that are intended for clinical use and designed, manufactured, and used within a single laboratory.

B. Recommended Classification of the Panel

The Panel recommended that HLA, HNA, and HPA devices be classified into class II with special controls with premarket review. The Panel agreed that general controls were not sufficient to provide reasonable assurance of safety and effectiveness of HLA, HPA, and HNA devices. The Panel believed that HLA, HPA, and HNA devices present a potentially unreasonable risk of illness, injury, or death. Considering these risks, the Panel agreed that sufficient information exists to establish special controls for these devices. Consequently, 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.

The Panel considered the following valid scientific evidence to make their recommendation regarding the safety and effectiveness of these devices under its conditions of use. Specifically, the Panel considered the history of safety and effectiveness of HLA, HPA, and HNA devices over many years of use; the results of an FDA review of the scientific literature; medical device reports (MDRs) of adverse events or malfunctions; device recalls, and FDA's regulatory experiences with the devices.

C. Risks to Health and Special Controls

As required by section 513(d)(1) of the FD&C Act, FDA provided to the Panel the following summary of valid scientific evidence regarding the benefits and risks of HLA, HPA, and HNA devices. A systemic literature review indicates that the use of these devices has improved patient care in transfusion and transplantation, and in disease diagnosis. HLA matching between the donor and recipient is a key strategy to reduce rejection. The presence of anti-HLA antibodies, especially donor-specific antibodies, has been associated with worse outcomes after transplantation or transfusion. Identification of HLA antibodies allows for informed decisions regarding whether to accept and transplant an organ for a specific recipient. In similar fashion, HPA and HLA devices provide a means to detect and identify related antigens and antibodies facilitating transfusion with compatible blood (platelet) products. In addition, HNA and HLA devices provide laboratorians and clinicians tools to investigate transfusion-related acute lung injury (TRALI) reactions and/or mitigate the risk of future TRALI reactions associated with implicated blood donors.

However, available literature, MDRs, and medical device recall data indicate that HLA, HPA, and HNA devices can malfunction. These devices may generate false positive, false negative, or inconsistent results and have the potential to cause adverse health consequences. Suspected device-associated deaths, serious injuries, and malfunctions are reported to FDA through the Manufacturer and User Facility Device Experience (MAUDE) database. Prior to the Panel meeting, FDA conducted queries of the MAUDE database to identify MDRs related to the use of HLA, HPA, and HNA devices. The search was restricted to reports that FDA received and entered into the database before May 1, 2017. There were 477 MDRs for HLA devices. Most MDRs (464) were reported for HLA genotyping devices, while 13 MDRs were reported for HLA antibody detection devices. All MDRs with reportable category information are malfunctions. The most frequent malfunctions are incorrect reactivity assignments that lead to mistype or no type HLA results. There have been no reported deaths or serious injuries related to these malfunctions. These medical device reports suggest that 510(k) premarket notification of HLA devices is a necessary means to minimize adverse health consequences that may result from HLA device malfunctions. Compared to HLA devices, there are few HPA and HNA devices in the U.S. market and few reported MDRs. The queries of the MAUDE database prior to the Panel meeting identified only two MDRs for HPA devices and no MDRs for HNA devices. However, these devices share similar technologies and clinical applications to HLA devices and have the potential for malfunctions that may cause adverse health consequences. Therefore, 510(k) premarket notification of HPA and HNA devices is needed to minimize adverse health consequences that may result from HPA or HNA device malfunction.

Similarly, prior to the Panel meeting, FDA searched the Medical Device Recalls database for all recalls received before May 1, 2017, for these devices. Of the total 37 HLA device recalls, none were classified as class I recalls, in which the violative product could cause serious adverse health consequences or death. A total of 19 recalls were classified as class II, and 18 were classified as class III. Most of the recalls (32 of 37) were for products that failed to provide correct testing results (false negative, false positive, mistype, or no type). The root causes leading to incorrect HLA typing results include incorrect reactivity assignments, lack of testing sample(s) with specific allele before releasing, and manufacturing errors. The HLA antibody device recalls were due to manufacturing errors during the production of recombinant HLA proteins, such as unstable transfectant. No recalls were reported for HPA and HNA devices. However, these devices share similarities with the HLA devices and are likely prone to similar malfunctions.

FDA presented the following risks to health associated with HLA, HPA, and HNA devices: Patient injury or death due to: (1) Poor graft survival or function due to transplantation of incompatible hematopoietic cells, tissue, or organ; (2) graft rejection because of the transplantation of incompatible hematopoietic cells, tissue, or organ; (3) graft-versus-host disease because of the transplantation of incompatible immune system cells; (4) incorrect or delayed diagnosis of medically related conditions or assessment of future risk of adverse outcomes because of incorrect HLA, HPA, or HNA test results; (5) transfusion reaction (*e.g.,* transfusion associated lung injury, post transfusion purpura) due to incorrect HLA, HPA, or HNA test results; and, (6) platelet refractoriness because of incorrect HLA or HPA typing or antibody detection results.

FDA next proposed to the Panel measures to mitigate the risks to health associated with HLA, HNA, and HPA devices. The identified risks to health and the special controls to mitigate these risks (explained in the paragraph immediately after the table) are summarized in the following table:

TABLE 1—SUMMARY OF RISKS TO HEALTH AND PROPOSED SPECIAL CONTROLS

Risk to health	Method of mitigation (*i.e.,* special control)
Inaccurate test results (*i.e.,* false positive or false negative results) can result in adverse health consequences.	Special controls (1) and (2).
Failure of software to correctly interpret test results can result in adverse health consequences	Special controls (1)(e) and (1)(f).

FDA proposed the following special controls (cross-referenced in the table above) to the Panel for HLA, HPA, and HNA devices: (1) Premarket submissions must include detailed documentation of the following information: (a) Device accuracy study using well-characterized samples representing as many targets as possible; (b) precision studies to evaluate possible sources of variation that may affect test results; (c) comparison studies to evaluate the device's performance compared to a predicate; (d) specific information that addresses or mitigates risks associated with false positive antibody reactivity *e.g.,* reactivity with denatured/cryptic epitopes, if applicable; (e) description of how the assay cutoff was established and validated as well as supporting data; (f) documentation for device software, including, but not limited to, software requirement specifications, software design specification, *e.g.,* algorithms, alarms and device limitations; hazard analysis, traceability matrix, verification and validation testing, unresolved anomalies, hardware and software specifications; electromagnetic compatibility and wireless testing; (g) for multiplex assays in which large numbers of probes and/or primers are handled during manufacturing process, premarket submissions should provide the design specifications that are in place to prevent incorrect reactivity assignment; (h) description of a plan on how to ensure the performance characteristics of the device remain unchanged over time when new HLA alleles are identified, and/or reactivity assignments are changed from the assignments at the time the device was evaluated; and (2) device labeling must include: (a) A limitation statement that reads, ''The results should not be used as the sole basis for making a clinical decision;'' and (b) a warning that reads ''The device has not been cleared or approved for use as a companion diagnostic.''

The Panel members agreed with the special controls proposed by FDA.

VI. 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 regulatory experience with these device types, FDA proposes to classify HLA, HPA, and HNA devices as class II devices (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 there is sufficient information to establish special controls to provide such assurance. FDA believes that special controls, in addition to general controls, would provide reasonable assurance of the safety and effectiveness of HLA, HPA, and HNA devices and would, therefore, mitigate the risks to health associated with their use.

We are proposing to classify the devices as a generic type of device because of the similarities in the biological properties of the three antigen systems, the use of similar technologies for the detection of antigens and antibodies, the clinical use of the test results, and the special controls required to mitigate risks. The proposed device identification includes the indications for use of HLA, HPA, and HNA devices subject to the classification. The following devices are not included in the proposed classification: HLA, HPA, or HNA devices used as a companion diagnostic device, a device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.

The proposed regulation also includes special controls that are necessary to provide a reasonable assurance of the safety and efficacy of the devices. When developing the special controls, we considered the recommendations provided in the FDA guidance document entitled ''Recommendations for Premarket Notification (510(k)) Submissions for Nucleic Acid-Based Human Leukocyte Antigen (HLA) Test Kits Used for Matching of Donors and Recipients in Transfusion and Transplantation'' (Ref. 4).

Section 510(m) of the FD&C Act provides that a class II device may be exempted from 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 HNA, HPA, and HNA devices 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.

VII. 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**.

VIII. Preliminary Economic 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 us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because of the limited impact of this proposed rule, 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 $158 million, using the most current (2020) 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.

If finalized, the proposed rule would classify HLA, Human HPA, and HNA devices as a generic group of devices into class II (special controls). The Agency believes that the special controls included in this proposed rule, together with general controls, are necessary to provide reasonable assurance of the safety and effectiveness of these devices. The special controls in the proposed rule are already generally practiced by manufacturers of currently cleared devices; the primary change consists of a labeling update. FDA is also giving notice that we do not intend to exempt HLA, HPA, and HNA devices from premarket notification requirements of the FD&C Act.

The proposed rule's costs are summarized in table 2; we are unable to quantify benefits for this proposed rule. Costs are calculated as the one-time costs of relabeling affected devices to comply with the proposed rule and costs associated with reading and understanding the proposed rule. The total estimated one-time costs of this rule are $434,885 (in 2020 dollars). The present value of these costs is $443,885 because they are one-time costs that are expected to occur in the first year. The annualized cost of this proposed rule over 10 years is $54,201 at a seven percent discount rate and $45,632 at a three percent discount rate.

The benefits of this proposed rule consist of the cost savings resulting from the reduction in regulatory and economic burden that accompanies the decrease in the number of information requests and incomplete submissions submitted by manufacturers and handled by FDA; however, we lack the information needed that would allow us to quantify these benefits. The number of requests for additional information following manufacturers' 510(k) submissions is small and widely dispersed over the duration of time these devices have been marketed. The classification procedure and outlined special controls would be helpful for HLA, HPA, and HNA manufacturers in preparing their submissions. Further benefits may be derived from the decreased time a notification submission would need to be reviewed and the subsequent potential benefits realized by consumers and manufacturers. The costs of this proposed rule include one-time upfront labeling redesigns, in addition to initial learning and reading costs.

Consistent with Executive Order 12866, table 2 provides the costs and a description of benefits for this proposed rule.

TABLE 2—SUMMARY OF BENEFITS AND COSTS IN 2020 DOLLARS OVER A 10-YEAR TIME HORIZON

Category	Primary estimate	Low estimate	High estimate	Units			Notes
				Year dollars	Discount rate (%)	Period covered	
Benefits:							
Annualized Monetized $/year				2020	7	10	
				2020	3	10	
Annualized Quantified					7		
					3		
Qualitative							Improved labeling and enhanced certainty for 510(k) submissions.
Costs:							
Annualized Monetized $/year	$54,201			2020	7	10	
	$45,632			2020	3	10	
Annualized Quantified					7		
					3		
Qualitative							
Transfers:							
Federal Annualized Monetized $/year					7		
					3		
From/To	From:			To:			
Other Annualized Monetized $/year					7		
					3		
From/To	From:			To:			
Effects:							
State, Local or Tribal Government:							
Small Business:							
Wages:							
Growth:							

We have developed a comprehensive Preliminary Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full analysis of economic impacts is available in the docket for this proposed rule (Ref. 5) and at *https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.*

IX. Analysis of 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.

X. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

XI. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that this proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the proposed rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

XII. Consultation and Coordination With Indian Tribal Governments

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13175. We have tentatively determined that the proposed rule does not contain policies that would have a substantial direct effect on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. The Agency solicits comments from tribal officials on any potential impact on Indian Tribes from this proposed action.

XIII. References

The following references are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at *https://www.regulations.gov.* FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

1. Blood Products Advisory Committee Meeting transcript—September 15, 2000 (pp. 209–220), available at: *https://wayback.archive-it.org/7993/20170404105835/https:/www.fda.gov/ohrms/dockets/ac/00/transcripts/3649t2c.pdf.*

2. Blood Products Advisory Committee Meeting transcript—November 30, 2017, available at: *https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/UCM590282.pdf* .

3. FDA Executive Summary. Classification of Human Leukocyte, Neutrophil and Platelet Antigen or Antibody Tests—November 30, 2017, available at: *https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/UCM586203.pdf.*

4. ''Recommendations for Premarket Notification (510(k)) Submissions for Nucleic Acid-Based Human Leukocyte Antigen (HLA) Test Kits Used for Matching of Donors and Recipients in Transfusion and Transplantation: Guidance for Industry,'' July 2015, available at: *https://www.fda.gov/*

regulatory-information/search-fda-guidance-documents/recommendations-premarket-notification-510k-submissions-nucleic-acid-based-human-leukocyte-antigen.

5. FDA, ''Medical Devices; Immunology and Microbiology Devices; Classification of Human Leukocyte, Neutrophil and Platelet Antigen and Antibody Tests,'' Preliminary Regulatory Impact Analysis Initial Regulatory Flexibility Analysis Unfunded Mandates Reform Act Analysis,'' 2019 (available at *https://www.fda.gov/about-fda/reports/economic-impact-analyses-fda-regulations.*

List of Subjects in 21 CFR Part 866

Biologics, Laboratories, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, we propose that 21 CFR part 866 be amended as follows:

PART 866—IMMUNOLOGY AND MICROBIOLOGY DEVICES

■ 1. The authority citation for part 866 continues to read as follows:

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

■ 2. Add § 866.5960 to subpart F to read as follows:

§ 866.5960 Human Leukocyte, Human Neutrophil, and Human Platelet antigen and antibody devices.

(a) *Identification.* Human Leukocyte, Human Neutrophil, and Human Platelet antigen and antibody devices consist of Human Leukocyte Antigen (HLA), Human Platelet Antigen (HPA), and Human Neutrophil Antigen (HNA) typing and antibody detection devices.

(1) HLA typing devices are used to determine HLA types, to aid in transfusion or transplantation donor and recipient matching, or to aid in the diagnosis of diseases.

(2) HLA antibody detection devices are used to detect antibodies to HLA antigens to aid in donor and recipient matching in transfusion or transplantation.

(3) HPA typing devices are used for the detection of human platelet antigens to aid in donor and recipient matching in blood transfusion or to aid in the diagnosis of diseases.

(4) HPA antibody detection devices are used to detect autoantibodies and alloantibodies against platelet glycoproteins to aid in donor and recipient matching in blood transfusion or to aid in the diagnosis of diseases.

(5) HNA typing devices are used for the detection of human neutrophil antigens to aid in donor and recipient matching in blood transfusion or to aid in the diagnosis of diseases.

(6) HNA antibody detection devices are used to detect autoantibodies and alloantibodies against neutrophil antigens to aid in donor and recipient matching in blood transfusion or to aid in the diagnosis of diseases.

(b) *Classification.* Class II (special controls). HLA, HPA, and HNA typing devices must comply with the following special controls:

(1) Premarket submissions must include detailed documentation of the following:

(i) Device accuracy study using well-characterized samples representing as many targets as possible.

(ii) Precision studies to evaluate possible sources of variation that may affect test results.

(iii) Comparison studies to evaluate the device's performance compared to a predicate.

(iv) Specific information that addresses or mitigates risks associated with false positive antibody reactivity, *e.g.,* reactivity with denatured/cryptic epitopes, if applicable.

(v) Description of how the assay cutoff was established and validated as well as supporting data.

(vi) Documentation for device software, including, but not limited to, software requirement specifications, software design specifications, *e.g.,* algorithms, alarms, and device limitations; hazard analysis, traceability matrix, verification and validation testing, unresolved anomalies, hardware and software specifications; electromagnetic compatibility and wireless testing.

(vii) Design specifications that are in place to prevent incorrect reactivity assignment or multiplex assays in which large numbers of probes and/or primers are handled during manufacturing process.

(viii) Description of a plan on how to ensure the performance characteristics of the device remain unchanged over time when new HLA alleles are identified and/or reactivity assignments are changed from the assignments at the time the device was evaluated.

(2) The device labeling must include:

(i) A limitation statement that reads, ''The results should not be used as the sole basis for making a clinical decision.''

(ii) A warning that reads ''The device has not been cleared or approved for use as a companion diagnostic.''

Dated: January 11, 2022.

Janet Woodcock,

Acting Commissioner of Food and Drugs.

[FR Doc. 2022–01156 Filed 1–20–22; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF DEFENSE

Department of the Army, Corps of Engineers

33 CFR Part 334

[COE–2021–0006]

Eagle River From Bravo Bridge to Eagle Bay in Knik Arm, Richardson Training Area on Joint Base Elmendorf-Richardson, Alaska; Restricted Area

AGENCY: U.S. Army Corps of Engineers, DoD.

ACTION: Notice of proposed rulemaking and request for comments.

SUMMARY: The U.S. Army Corps of Engineers (Corps) is proposing to revise its regulations to establish a restricted area within the Richardson Training Area on Joint Base Elmendorf-Richardson (JBER), at Eagle River. The United States Army, Alaska (USARAK) G3/5/7 Training and Support Activity-Alaska (TSA–AK) requested establishment of a restricted area which would be located in the area of navigable waters extending from the span on Bravo Bridge across Eagle River to the mouth of Eagle River Knik Arm (Eagle River channel). Establishment of the restricted area would prevent all watercraft navigations and individuals from entering an active military range munitions impact area at all times, except for authorized vessels and individuals engaged in support of military training and management activities. This restricted area is necessary to avoid inadvertent entry into the impact area during live-fire weapons training, exposure to hazardous noise, and inadvertent encounters with unexploded ordnance.

DATES: Written comments must be submitted on or before February 22, 2022.

ADDRESSES: You may submit comments, identified by docket number COE–2021–0006, by any of the following methods:

Federal eRulemaking Portal: http://www.regulations.gov. Follow the instructions for submitting comments.

Email: david.b.olson@usace.army.mil. Include the docket number, COE–2021–0006, in the subject line of the message.

Mail: U.S. Army Corps of Engineers, Attn: CECW–CO–R (David B. Olson), 441 G Street NW, Washington, DC 20314–1000.

Hand Delivery/Courier: Due to security requirements, we cannot receive comments by hand delivery or courier.