DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

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

Docket No. FDA-2021-N-0851

## Preliminary Regulatory Impact Analysis
## Initial Regulatory Flexibility Analysis
## Unfunded Mandates Reform Act Analysis

Economics Staff
Office of Economics and Analysis
Office of Policy, Legislation, and International Affairs
Office of the Commissioner

**Table of Contents**

# I. Introduction and Summary

## A. Introduction

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 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.

B. Summary of Costs and Benefits

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

The proposed rule's costs are summarized in Table 1; we are unable to quantify benefits for this rule. Costs are calculated as the one-time costs of relabeling affected devices to comply with the rule and costs associated with reading and understanding the rule. The total estimated one-time costs of this 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 rule over ten years is $54,201 at a seven percent discount rate and $45,632 at a three percent discount rate.

The benefits of this 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 the 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 rule include one-time upfront labeling redesigns, in addition to initial learning and reading costs.

Consistent with Executive Order 12866, Table 1 provides the costs and a description of benefits for this proposed rule.

**Table 1: 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 | | | | | 7% | | |
| | | | | | | 3% | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Monetized $/year | | | | | | | |
| | From/To | From: | | | To: | | | |
| Effects | State, Local or Tribal Government: | | | | | | | |
| | Small Business: | | | | | | | |
| | Wages: | | | | | | | |
| | Growth: | | | | | | | |

## II. Preliminary Regulatory Impact Analysis

A. Background

The FDA proposes to classify HLA, HPA, and HNA devices as a generic device type 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. This classification applies to devices with the following product codes: MZI, MZH, and MYP. In addition, one device subject to the classification has been assigned product codes MAO.

These devices are used in the setting of transplantation and transfusion, and for 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.

B. Need for Federal Regulatory Action

HLA, HPA, and HNA devices have not been classified under the FD&C Act, section 513 (21 U.S.C. 360c), which established the risk-based device classification system for medical devices. Currently these devices are regulated as unclassified devices, subject to 510(k) premarket notification requirements. This proposed rule, if finalized, will classify HLA, HPA, and HNA devices into class II (special controls), specify the indications for their use, and establish special controls, consistent with the recommendations in the FDA guidance document "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" (Ref. 1). The proposed rule aligns with the FDA's efforts to classify all preamendments devices. Regulatory action is necessary to classify HLA, HPA, and HNA devices as class II devices.

This proposed rule will help ensure that these HLA, HPA, and HNA devices are used safely because they have the potential for malfunctions that may cause adverse health consequences. All the devices cleared by the FDA are already following most of the proposed special controls because the device manufacturers recognized the potential risks of their devices. Without this rule, industry may be uncertain about requirements for 510(k) submissions and subsequently submit information requests to the FDA that could otherwise be avoided. This rule provides important clarification on the four product codes (MZI, MZH, MYP, MAO) covered by this rule,

making it easier to understand the various types of devices and, therefore, reducing the number of information inquiries submitted to the FDA.

C. Baseline Conditions

The rule's impact is estimated relative to the baseline, which is the industry landscape in absence of the proposed regulatory action. To establish the baseline market, we determine the number of listed HLA, HPA, and HNA devices and the number of manufacturers. We have identified 49 HLA, HPA, and HNA devices currently marketed and 11 manufacturers of these devices. The above numbers reflect devices and manufacturers actively registered with the FDA's Establishment Registration and Device Listing database as of May 2019. The proposed rule details a greater number of cleared devices and manufacturers, but many of these manufacturers are either no longer active or have been consolidated with other firms. The above numbers reflect devices and manufacturers actively registered with FDA's Establishment Registration and Device Listing database as of May 2019.

The only change current manufacturers may need to make are minor updates to the device labeling. Therefore, this proposed rule will have little impact on current manufacturers, and it helps ensure that all future 510(k) submissions will comply with these requirements.

D. Benefits of the Rule

We do not quantify the public health benefits of the proposed rule because the rule would require the adoption of practices that manufacturers of currently marketed devices already generally follow and would not change the use of the devices. The current and updated requirements for premarket notification (510(k)) review of HLA, HPA, and HNA devices have been recognized by the Blood Product Advisory Committee (serving as a Device Classification

Panel) as an effective means of minimizing adverse health consequences that may result from device malfunctions (Ref. 2). We acknowledge the possibility that malfunctions could occur in the future and it is possible that clear, consistent instructions may avoid some potential future adverse events, but we cannot quantify these benefits.

This proposed rule provides reasonable assurance of safety and effectiveness of these devices and helps ensure that all new 510(k) submissions meet the same standards as the currently marketed devices. HLA, HPA, and HNA devices provide important public health benefits through informed decisions regarding whether to accept and transplant an organ for a specific recipient, facilitating transfusion, reducing rejection, and assisting in prompt disease diagnosis. The proposed rule will provide additional assurance that the current level of public health protection is maintained.

While there are no quantifiable public health benefits, this regulation, including special controls, provides benefits to potential manufacturers of new devices by clarifying important information about the devices. These clarifications may generate cost savings by reducing the time and effort firms take to prepare their submissions. Likewise, it will decrease the time needed by the FDA in handling potential information requests and incomplete submissions.

E. Costs of the Rule

The FDA's Medical Device Registration and Device Listing database identifies 11 manufacturers of approximately 49 HLA, HPA, and HNA devices, actively registered as of May 2019. We anticipate that these medical device firms will incur costs to read and understand the requirements of the rule. The length of the rule is approximately 7,500 words; assuming a

reading speed of 200 words per minute along with time to access and review the rule, we estimate a burden of one hour to read and understand the rule. The average hourly wage rate for a lawyer in the medical equipment and supplies manufacturing industry is $86.53 (Ref. 3). We double this rate to account for overhead costs. This results in an hourly labor cost of $173.06. The estimated labor costs from reading and understanding this rule are about $1,904 (=$173.06 hourly labor cost * 11 manufacturers * 1 hour each).

Manufacturers of these devices also will revise current labeling due to the special controls required by the proposed rule. This revision is a minor change to include a one-sentence warning. The required labeling is very similar to the cleared indications for use and warnings labeling of currently cleared devices, so little change from current labeling is expected. Using the FDA's labeling cost model (Ref. 4), we estimate a one-time cost of the labeling change for currently marketed HLA, HPA, and HNA devices to be about $8,576 per product for an estimated total up-front cost of $420,224 (=49 products * $8,576).

The total estimated one-time costs of this rule are $422,128 (=$1,904 + $420,224). The present value of these costs is also $422,128 because they are up-front costs that are expected to occur within the first year of compliance with the rule. The annualized cost of this rule over ten years is $52,622 at a seven percent discount rate and $44,303 at a three percent discount rate (2018 dollars).

This estimate is updated to 2020 dollars to reflect inflation between 2018 and 2020. In 2020 dollars, the total one-time cost of this rule is estimated at $434,885. The annualized cost of this rule over ten years is $54,201 at a seven percent discount rate and $45,632 at a three percent discount rate (2020 dollars).

F. Distributional Effects

We do not expect there to be any distributional effects of this rule. If this rule changes the number of 510(k) submissions for the devices, it would cause an increase or decrease in user fees paid to the FDA by the sponsor of the 510(k) submission. However, we do not expect this rule to have a significant impact on the number of future 510(k) submissions.

G. International Effects

We do not expect there to be any significant international effects of this rule. Both domestic and international manufacturers of these devices are subject to the current and proposed special controls and labeling requirements. There are no expected adverse effects on imports or exports of these devices.

H. Regulatory Alternatives

We identified three alternatives to the rule. First, these devices could be continued to be regulated as unclassified devices. This alternative would not provide an assurance of safety and effectiveness and would continue the current level of inconsistent information for potential new marketers. There would be no costs and benefits associated with this alternative as it would be the same as the baseline.

Second, these devices could be regulated as class I devices. General controls alone are not sufficient for the potential risks and would not provide reasonable assurance of the safety and effectiveness of these devices; therefore, this option was not chosen. Finally, HPA, HLA, and HNA devices could be regulated as class III devices, reserved for the highest risk devices.

However, based on their risk profile, the Blood Product Advisory Committee (serving as a Device Classification Panel) recommended classifying these devices into Class II.

## III. Initial Small Entity Analysis

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this rule affects a limited number of device manufacturers, we propose to certify that the proposed rule will not have a significant economic impact on a substantial number of small entities. This analysis, as well as other sections in this document, serves as the Initial Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

### A. Description and Number of Affected Small Entities

The FDA Establishment Registration & Device Listing database indicates that there are 11 entities that manufacture these devices. The Small Business Administration (SBA) defines entities classified in North American Industry Classification System (NAICS) code 339112 "Surgical and Medical Instrument Manufacturing" to be small if they employ fewer than 1,000 workers. Using internal information and information from Dun & Bradstreet, we identified three manufacturers that could be considered small firms, each producing one type of HLA device.

### B. Description of the Potential Impacts of the Rule on Small Entities

Current manufacturers of HLA, HPA, and HNA devices will each have an upfront cost of about $8,749 (=$173 + $8,576) to read the rule and update their labeling. This is not expected to have a significant impact on a significant number of small businesses. Small firms that submit

information inquiries or premarket notification requests for HLA, HPA, and HNA devices may find a more streamlined process due to this proposed rule.

C. Alternatives to Minimize the Burden on Small Entities

Regulating these devices as class I may slightly decrease the cost while not providing reasonable assurance of the safety and effectiveness of these devices. Regulating these devices as class III would have no improvement in risk reduction but would significantly increase the cost to small businesses.

## IV. References


1) US Food and Drug Administration. Center for Biologics Evaluation and Research. (2015). *Guidance for Industry: 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*. Silver Spring, MD: US Department of Health and Human Services. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-premarket-notification-510k-submissions-nucleic-acid-based-human-leukocyte-antigen

2) US Food and Drug Administration. Blood Products Advisory Committee. (2017). *Device Classification Panel Meeting of the Blood Products Advisory Committee: Classification of Human Leukocyte, Neutrophil and Platelet Antigen or Antibody Tests.* Silver Spring, MD: US Department of Health and Human Services. Available: https://www.fda.gov/media/109187/download

3) Bureau of Labor Statistics, "May 2018 National Industry-Specific Occupational Employment and Wage Estimates NAICS 339100 - Medical Equipment and Supplies Manufacturing," US Department of Labor, May 2019. [Online]. Available: https://www.bls.gov/oes/current/naics4_339100.htm#23-0000.

4) RTI International. Model to Estimate Costs of Using Labeling as a Risk Reduction Strategy for Consumer Products Regulated by the Food and Drug Administration. 2015.