American Society of Anesthesiologists™

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February 26, 2021

Janet Woodcock, Acting Commissioner
Food and Drug Administration
Department of Health and Human Services
Attention: 0991-ZA52
200 Independence Avenue SW
Washington, DC 20201

Submitted electronically via www.regulations.gov

RE: 0991-ZA52; Making Permanent Regulatory Flexibilities Provided During the COVID-19 Public Health Emergency by Exempting Certain Medical Devices From Premarket Notification Requirements; Request for Information, Research, Analysis, and Public Comment on Opportunities for Further Science and Evidence-Based Reform of Section 510(k) Program

Dear Acting Commissioner Woodcock:

On behalf of the 53,000 members of the American Society of Anesthesiologists® (ASA), I appreciate the opportunity to respond to the Federal Food and Drug Administration (FDA) Request for Information (RFI) on "Making Permanent Regulatory Flexibilities Provided During the COVID-19 Public Health Emergency by Exempting Certain Medical Devices From Premarket Notification Requirements."

Anesthesiology has always been an innovative specialty, using technology and other resources to meet the needs of patients. ASA recognizes the increased use of medical devices in health care for diagnosing and treating patients and appreciates the opportunity to share our professional expertise and comments on the subject. The ASA understands that it has been necessary for the agency to exercise regulatory flexibilities to meet the emergent demand for personal protective equipment, disinfectant products, and other devices during COVID-19 pandemic, however, we assert that regulatory flexibilities should not extend beyond the public health emergency or become part of the FDA's permanent regulatory framework.

Specifically, we oppose the agency proposal to permanently remove the premarket notification 510(k) process for Artificial Intelligence (AI) and Machine Learning (ML) class II devices from current regulation and request that the agency continue to require new device products to demonstrate "substantial equivalence" to those already FDA approved.

Arguably, any rule proposal put forth to permanently remove the 510(k) process would be in direct conflict with the agency's recently released Action Plan which includes FDA's vision for a

"total product lifecycle-based regulatory oversight" of AI/ML-based device products.[1] Should the agency move toward deregulation, we believe it would be adopting a risk assessment and management approach far too reliant on post-market data collection and adverse event reporting. Unquestionably, any removal of AI/ML-based device products from 510(k) premarket notification will jeopardize public safety in ways that are both unpredictable and unforeseeable. Therefore, we advise the FDA to take a precautionary approach in regulating the risks associated with the increased use of AI technologies in medicine.

Machine learning (ML) has been increasingly applied to artificial intelligence research in medicine to aid in clinical decision support. However, ML algorithms are themselves subject to biases that are difficult to recognize.[2] [3] An ML algorithm trained on a data set that is missing an important subset of the patient population to which it is applied may produce misleading or inaccurate results when applied to that larger population. ML algorithms trained on data sets heavily weighted toward one gender perform worse when applied to a population heavily weighted toward the opposite gender. For example, an ML algorithm to detect atelectasis and pneumothorax will not detect these conditions as well in women if it is trained on a mostly male population.[4] Similarly, an ML algorithm trained on a mostly white population may not produce accurate results when applied to a more heterogenous population. Images from fair-skinned individuals are overrepresented in one of the most-often used public databases of pigmented lesions.[5] ML algorithms trained on this large data set may therefore be less likely to detect malignant melanoma in darker-skinned individuals.[6]

In addition, an ML algorithm trained on one optical coherence tomography (OCT) machine used for retinal imaging performs poorly if adjustments are not made when images from a different OCT machine are used.[7] These examples of distributional shift, which occur as a result of differences between training and operational data, can be difficult to detect if appropriate validation steps are not taken. Alarmingly, there is evidence that many ML algorithms used in medicine may be susceptible to this type of error. Kaushal et al. recently reported that ML algorithms powering many clinical applications were trained on cohorts from California, Massachusetts, and New York, with little or no representation from other states.[8] This is of particular concern because compared to more transparent rules-based algorithms that traditionally guide clinical decision making, recommendations made by ML algorithms are more of a "black box." This can make it difficult for a clinician to understand the rationale behind an ML recommendation or an ML-directed input into a treatment device (such as an infusion pump)

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[1] U.S. Food and Drug Administration, Center for Devices and Radiological Health. (2021). *Artificial Intelligence/ Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan.* https://www.fda.gov/media/145022/download

[2] Gianfrancesco MA, Tamang S, Yazdany J, Schmajuk G. Potential Biases in Machine Learning Algorithms Using Electronic Health Record Data. JAMA Intern Med. 2018;178:1544–1547.

[3] Challen R, Denny J, Pitt M, Gompels L, Edwards T, Tsaneva-Atanasova K. Artificial intelligence, bias and clinical safety. BMJ Qual Saf. 2019;28: 231–237.

[4] Larrazabal AJ, Nieto N, Peterson V, Milone DH, Ferrante E. Gender imbalance in medical imaging datasets produces biased classifiers for computer-aided diagnosis. Proc Natl Acad Sci U S A. 2020;117:12592–12594.

[5] Adamson AS, Smith A. Machine Learning and Health Care Disparities in Dermatology. JAMA Dermatol. 2018;154: 1247–1248.

[6] Ibid.

[7] De Fauw J, Ledsam JR, Romera-Paredes B, Nikolov S, Tomasev N, Blackwell S, et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. Nat Med. 2018;24:1342–1350.

[8] Kaushal A, Altman R, Langlotz C. Geographic Distribution of US Cohorts Used to Train Deep Learning Algorithms. JAMA. 2020;324: 1212–1213.

and its methods of failure. Moreover, because these ML algorithms are used in many types of clinical decision making, with outcomes becoming apparent on different time scales, it may take several years for errors to become apparent. Therefore, the lack of reported safety events in the MAUDE database for these particular devices should not be reassuring.It should also be noted that these changes run counter to the regulatory stance that the FDA has taken with respect to mobile medication applications. Software that is intended to analyze patient-specific medical device data, alter the function or settings of an infusion-pump, or control existing medical devices (e.g. valves in extracorporeal membrane oxygenator devices) are explicitly listed amongst the types of software that are the focus of FDA's regulatory oversight.[9] We agree that these categories of software, whether implemented on a mobile platform or not, carry substantial potential risks to patient safety and have been correctly identified as requiring oversight, regulation, and ongoing monitoring for postmarketing safety. Specific items including in Table 6 of the proposed rule should be closely assessed, clarified, or removed entirely from the proposed rule, including those items related to ventilation, drug infusion, cardiopulmonary bypass, CPB check valve, oxygenators, and extracorporeal systems. A recently published editorial in the *British Journal of Anaesthesia* summarizes these and other considerations.[10]

Given the complexities involved in assuring the proper training and validation of ML algorithms on target populations, the lack of easily identifiable failure modes, and the possibility that recommendations and inputs made by these algorithms will be given more weight than they deserve, the ASA cannot support permanent removal of the 510(k) premarket notification requirements for AI-driven products.

While ML algorithms have contributed to the acceleration of clinical decision making, we fear that physicians and clinicians may be prone to trust the recommendations of an intelligent machine over their own judgement and may be less likely to catch its errors or malfunctions if they believe ML algorithms to be reliable and devices to be safe. We ask the FDA to take into serious consideration the fact that ML algorithms have been proven to vary greatly from one another due to differences in the machine training and operationalized data sets – and these variances leave room for device performance issues to go undetected without proper regulatory review. The FDA's long-standing regulatory oversight of new market entrants should be maintained in order to ensure that devices entering the market do not impose increased risk to human health and safety. In fact, one of our anesthesiologist members recently reported experiencing multiple issues at a medical institution with infusion pumps that were not thoroughly vetted by the FDA. Should the agency decide to permanently waive the 510(k) process, device malfunctions would go undetected prior to market entry.

In addition to concerns about permanent removal of the 510(k) premarket notification requirements for AI-driven products, the ASA also expresses concerns about waiver of premarket notification for other non-AI driven products listed, specifically: Airway Monitoring System; Oximeter, Tissue Saturation, Reprocessed; Neuraxial Administration

[9] Food and Drug Administration. Policy for Device Software Functions and Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff. Appendix C. 2019.
[10] O'Reilly-Shah VN, Gentry KR, Walters AM, Zivot J, Anderson CT, Tighe PJ. Bias and ethical considerations in machine learning and the automation of perioperative risk assessment. Br J Anaesth. 2020 Dec;125(6):843–6.

Set — Intrathecal Delivery; Oximeter, Reprocessed; Cerebral Oximeter; C-Arm Fluoroscopic X-Ray System; Infusion Safety Management Software; Oxygenator, Long Term Support Greater Than 6 Hours; Extracorporeal System For Long-Term Respiratory/Cardiopulmonary Failure.

Waiving premarket notification requirements for these products would potentially allow commercialization without any means to credibly verify performance claims. Unforeseeable clinical failure of the enumerated products would have a direct impact on patient safety, including risk of death for some of these devices that play a critical role in life support. The ASA supports the current process for these products, which is an important step in the chain of harm prevention by ensuring thorough vetting prior to reaching the bedside.

The ASA would support the development of alternative regulatory approval pathways for proven, useful medical technologies that have encountered regulatory challenges to adoption in the United States.

While ASA believes the potential risk to patients from emerging AI/ML based technologies requires ongoing regulatory oversight, we acknowledge that the current approval and clearance pathways impose a barrier to the introduction of useful medical devices into the U.S. market. The impact of this barrier is visible to the anesthesiology community in the adoption of highly effective and safe patient care technologies outside of the U.S. through the CE mark regulatory process. Examples for both intravenous and inhaled anesthetic delivery that have been in use internationally for many years include target-controlled infusion pumps and devices for more effective inhaled anesthetic delivery. Without an appropriate alternative for regulatory approval, AI/ML based technologies of value to patient care will likely have the same future. Lessons from the CE mark regulatory process for medical devices could be used to inform regulatory reform in the U.S. The ASA believes that an alternate or revised pathway for regulatory approval of medical devices may help reduce current barriers to market entry and better ensure that patients in the U.S. will benefit from existing and emerging technologies. We welcome the opportunity to work with the agency on the development of any alternative regulatory pathways in the future.

In sum, we oppose the agency proposal to permanently waive the 510(k) process and base its risk assessment on a post-market adverse event reporting process — one which the FDA itself describes as imperfect and problematic.[11] As device technology continues to evolve and the types of medical devices expand exponentially, the FDA must remain vigilant in upholding its mission to protect and promote the public health by minimizing unnecessary risks and ensuring that devices provide clinical benefit. ***In order to assure that health care professionals have access to well-designed and safe technologies to provide high quality care, ASA holds that the 510(k) premarket notification process should be maintained.***

[11]MAUDE - Manufacturer and User Facility Device Experience.
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM

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Thank you for your consideration of our comments. We welcome the opportunity to speak with you further. Please contact Heather Kazmark, M.A., ASA Consultant (h.kazmark@asahq.org) or Matthew Popovich, Ph.D., ASA Director of Quality and Regulatory Affairs (m.popovich@asahq.org) for questions or further information. They may also be contacted at 202-289-2222.

Sincerely,

Beverly Philip, MD, FACA, FASA
President
American Society of Anesthesiologists