View API's Draft – Public Comment for Jan 15 FDA's FR Notice for Permanent Regulatory Flexibilities Exempting Certain Medical Devices

NOTE: API members - Please reply to the API listserv thread with your comments by end of business on Thursday, March 11

Re: 86 FR 4088 - Making Permanent Regulatory Flexibilities Provided During the COVID-19 Public Health Emergency by Exempting Certain Medical Devices From Premarket Notification Requirements

To Whom It May Concern:

The Food and Drug Administration's Federal Register (FR) Notice of January 15, 2021, proposes, in part, to exempt 83 class II devices from premarket review as required under section 510(k) of the Food, Drug, and Cosmetic Act. Amongst the product codes listed in Table 6 ("Class II Devices and Unclassified Devices Proposed Exempt from 510(k) Requirement") of the Notice are several that comprise core components of digital pathology systems. As referenced in the Notice, the Association for Pathology (API) Informatics provides its insights, recommendations, and requests for comment on this proposal.

API is the only national organization dedicated exclusively to pathology informatics and enables the critical role of informatics to provide safe, effective, and efficient patient care. The API supports practice and innovation in pathology informatics through research, education, and advocacy. Moreover, the API plays an active role in legal, ethical, social, and regulatory issues related to pathology informatics. It also seeks to develop relationships with other professional societies and industry partners with similar interests and goals.

The Association of Pathology Informatics aligns with the FDA's priorities in risk management, interoperability, and standardization. We fully support the direction behind this FR Notice as it relates to digital pathology devices. More broadly, API supports the FDA's recent efforts to establish a more agile and adaptive regulatory framework that can keep pace with the accelerating innovation pace in medicine. Within that framework, we seek to provide the FDA with continuous feedback as part of the larger community of early users of digital and computational pathology technologies.

Before the COVID-19 Public Health Emergency (PHE), digital pathology device regulation contributed to the lower adoption rate in the United States than in other countries. Likewise, until recently, this regulation required end-to-end evaluation of Whole Slide Imaging (WSI) systems. One result of the pandemic was a pivot toward telemedicine, and this pivot occurred in pathology as

well. Many labs began to use digital pathology devices for remote sign-out to facilitate continuity of care while protecting pathologists and laboratory staff (telepathology). In April of 2020, the FDA issued its guidance on remote digital pathology devices during the COVID-19 PHE, which permitted modification to FDA-cleared digital pathology devices and the marketing of non-510(k)-cleared digital pathology devices intended for telepathology. This relaxation of oversight, along with the Centers for Medicare & Medicaid Services (CMS) Memorandum of March 26, 2020, gave laboratories the flexibility to respond to the crisis by assembling digital pathology systems using consumer off-the-shelf (COTS) computer monitors, research use only (RUO) slide scanners, and other interoperable components. A useful byproduct of this forced experiment was a large body of real-world experiential feedback regarding the safe application of digital pathology for patient care. The attached document is our best attempt to summarize the findings and opinions of our members.

To briefly summarize API's feedback: We support continuing FDA oversight to varying degrees for the digital pathology product codes QKQ, PSY, and OEO. By contrast, based on our members' vital feedback, we believe that FDA oversight of the digital pathology product code PZZ (digital pathology display) is no longer required. Detailed comments and recommendations for each of these digital pathology product codes are attached below.

API is thankful for the opportunity to comment on these specific product code decisions, which are critical to our field's future. More broadly, we are grateful to work with the Department of Health and Human Services to pursue our shared interest and provide the country's citizens with the highest possible healthcare standard.

Sincerely,

Association for Pathology Informatics Governing Council

GENERAL COMMENTS

Ramifications of regulation in digital pathology

The COVID-19 pandemic has introduced pathologists to digital pathology for remote signout, who may not have otherwise engaged with digital pathology. Simultaneously, the rapid shift to remote work environments has also exposed limitations in the current regulatory framework. Questions remain regarding the future of digital pathology device regulation and whether current regulatory exemptions will revert or expand. Because of the antiquated pre-COVID-19 regulation of digital pathology devices, there is considerable clinical inertia to revert to traditional practice patterns. The challenge is improving the current regulatory framework.

Federal Notice 86 FR 4088 includes components of a digital pathology workflow (product codes PZZ, QKQ, PSY, and OEO). API supports and encourages the easing of regulation for digital pathology devices. However, our understanding that this FR notice goes further in proposing permanent removal of FDA oversight from the class II devices named. While API endorses the PZZ digital pathology product code's permanent removal, it may be premature to permanently deregulate the other digital pathology product codes (QKQ, PSY, and OEO). To this end, the API requests comment on instituting an "accommodative" approach that preserves critical oversight while significantly reducing the overall regulatory burden.

With permanent deregulation of the QKQ, PSY, and OEO digital pathology product codes, come possible computational pathology burdens. Given the dependencies of image analysis and artificial intelligence (AI) applications on these products, foreseeable after permanent oversight removal for these three digital pathology product codes is the potential for undesirable and unintended consequences.

Permanent oversight removal for these three digital pathology product codes will reduce interoperability and standardization. Less interoperability and standardization then impede longer-term digital pathology development and application and inconsistent and non-efficacious deployment downstream of image analysis and AI applications reliant on these digital pathology components. The overall result is the disempowerment of pathologists, who might better leverage digital and computational pathology to benefit our patients and professional colleagues.

How device regulation in digital pathology is different from other medical devices and <u>recommendation for API engagement</u>

Regulation in digital pathology is different from other disciplines because of its regulation on two fronts by CMS and the FDA. CMS regulates digital pathology practice through CLIA'88 (42 CFR 493), and the FDA regulates the digital pathology devices themselves. Other fields concern themselves only with the FDA.

For digital pathology, the FDA need not broadly regulate all aspects of a given device, especially given the FDA's limited resource bandwidth. Though well-intentioned, broader FDA regulation has the potential to create an overburden without the intended outcome of device safety. Moreover, because digital pathology regulation with CMS and FDA is intertwined but uncoordinated, total FDA permanent regulatory flexibility has unforeseen consequences with CMS regulations, which are difficult to disentangle for the practicing pathologist.

In contrast, the FDA need not retract entirely from regulating digital pathology. Instead, FDA can take a coordinated approach to device regulation that complements CMS's additional layer of oversight regulation, providing a "middle ground" for moving forward. We propose that the FDA focus on individual devices in a controlled, systematic approach within a tighter scope (i.e., manufacturing). CMS then focuses on integrating and using digital pathology devices in laboratory testing (i.e., clinical practice).

API strives to establish best practices and works with other pathology organizations to navigate the regulatory interplay with the CMS and the FDA required for the pathology practice's digital pathology transformation. CMS and the FDA should lean on API members' collective wisdom, based on our real-world experience in safely translating digital pathology technologies into clinical practice.

Flaws in our risk surveillance with recommendation and request for comment

Risk surveillance data gets collected from the Manufacturer and User Facility Device Experience (MAUDE) database. MAUDE revealed a lack of non-death-related adverse events the last ten years (including the pandemic) for specific Class II devices, specifically the four digital pathology product codes (PZZ, QKQ, PSY, and OEO) identified in the FR Notice. API understands that the absence of events contributed to the conclusion that 510(k) premarket notification is no longer necessary to ensure devices' safety and effectiveness under these product codes. However, API is concerned that this absence of reported risk events does not reflect the risk reality to warrant permanent oversight removal for three (QKQ, PSY, and OEO) digital pathology product codes.

While MAUDE is a vital source of information, being a "passive surveillance system," MAUDE has limitations and potential for incomplete, inaccurate, or biased reporting. MAUDE gears towards capturing risk, but less so with the FDA's efforts about interoperability (ref 1) and standardization (ref 2) , which is vital for our comments and recommendations specific to three (QKQ, PSY, and OEO) digital pathology products codes.

MAUDE is not widely known publicly. Moreover, searching, categorizing, and aggregating risk surveillance data is highly manual and lacking specificity. Capturing risk events is somewhat challenging in digital pathology - especially within short time frames. For example, take the event of a malignant tumor missed or incorrectly classified by a pathologist using a particular combination of devices resulting in sub-optimal treatment or patient harm. How would this adverse event be recorded in MAUDE for reporting to the FDA? How one would trace back a diagnosis and the resulting clinical decision(s) to an individual device is unclear.

In recognizing MAUDE's obscurity and limitations in capturing specificity, API recommends publicizing MAUDE more widely with a re-design to enhance MAUDE for continually monitoring, particularly for product codes relating now and for the future in digital pathology and computational pathology. A re-designed MAUDE provides comprehensive and accurate data of risk, interoperability, and standardization issues required for specific Class II medical devices considering 510(k) exemption.

Digital and computational pathology-enabled organizations like API, DPA, and the Alliance for Digital Pathology (ref 3) can further promote MAUDE's visibility and recruit the expertise to enhance MAUDE's functionality. A re-designed MAUDE becomes the mainstay surveillance tool to capture risk, interoperability, and standardization for a dynamic digital and computational pathology ecosystem. API requests for comment on this recommendation.

Request for comment about an "accommodative" regulatory framework versus permanent regulatory flexibility

API would like to reinforce opening regulatory flexibility and further advocate for an "accommodative" regulatory framework for the QKQ, PSY, and OEO digital pathology product codes. API recognizes that permanent removal demands a high bar to sustain continual pathology/medical community and public trust. Likewise, API believes permanent regulatory flexibility yields a rigidity that does not offer "continuous learning" and iteration. To protect the community and public trust, API further endorses stepwise regulatory openings with mechanisms to ensure continual monitoring and "smart" oversight with more waived devices.

API proposes this “accommodative” regulatory framework as a thoughtful and adaptive approach to regulatory flexibility because it enables "continuous learning" and iteration. A re-designed enhanced MAUDE provides continual technical and manufacturing oversight central to our framework, capturing at higher specificity the issues of risk, interoperability, and standardization. It makes feasible stepwise regulatory openings and close monitoring during periods of regulatory leniency (ref 4). Clinical evaluation is then up to the pathologists and laboratories who use the systems.

Our proposed “accommodative” regulatory framework thus aligns closely with the way CMS regulates pathology practice and with the “FDASIA Health IT Report.” The latter report recommends “local” accountability (rather than “national regulation”) through a local control system or accreditation to address local configuration, implementation, and training of end-users. We believe that our "accommodative" regulatory framework overcomes the overburdening pre-COVID-19 regulatory hurdles by opening stepwise with close monitoring while providing incentives to attract community use, industry innovation to gain widespread acceptance of digital pathology. API requests for comment on an "accommodative" regulatory framework versus permanent regulatory flexibility for devices now and in the future that do not meet the threshold for permanent regulatory flexibility.

Comments and Recommendations Specific to These Four Digital Pathology Product Codes identified in the FR Notice.

1. **PZZ – Digital Pathology Display (21 CFR 864.3700)**

   API recommends that digital pathology displays are not FDA-regulated as medical devices and endorses the permanent regulatory flexibility on devices under this product code.

   FDA regulates digital pathology devices. However, this is not necessary for digital pathology displays. Required instead are high-quality digital pathology display products that meet minimum specifications to produce an accurate pathology diagnosis. There is enough evidence that digital pathology displays, with enough resolution, will provide accurate diagnoses.

   Evidence shows having a display used in an FDA-cleared system is not necessary. Non-medical-grade (i.e., non-FDA-cleared), high-quality monitors (including COTS monitors) that a clinical laboratory deems safe can be used to perform pathologic diagnoses (ref 5,6,7). During the peak of the COVID-19 surge, Memorial Sloan Kettering Cancer Center (MSKCC) in New York City performed digital pathology signout safely and efficaciously in a remote setting at

scale using a wide variety of displays. Digital pathology displays ranged from consumer-grade laptop computers to higher specification desktop computers with high definition dual monitors, none of which were medical grade [ref 8].

CMS and their respective accreditation bodies (e.g., College of American Pathologists [CAP] and The Joint Commission) regulate clinical laboratories and handle digital pathology displays as an integrated digital pathology practice component through 42 CFR 493. These accreditation bodies can verify or validate the digital pathology systems used for clinical diagnosis. Not required are devices used within these systems that are FDA-cleared. Clinical laboratories and individual pathologists have the expertise to determine if a monitor has sufficient resolution and is safe to make accurate diagnoses and determine which commercial grade products to use in medical practice, regardless of whether the monitor is an FDA-cleared device.

Opening up the FDA's deregulation on digital pathology displays creates innovative opportunities to investigate mobile devices' feasibility and enable remote site digital signout, where the necessity to obtain medical grade devices is unwarranted. CMS then addresses digital pathology display insufficiencies occurring for digital pathology signout rather than FDA.

Furthermore, digital pathology displays engage human vision, which is more resilient to image artifacts and noise, over computer vision. Therefore, there are NO foreseeable dependencies for image analysis and artificial intelligence (AI) applications on digital pathology displays. With permanent oversight removal for digital pathology devices, API predicts no undesirable and unintended consequences for computational pathology.

2. **QKQ – Digital Pathology Image Viewing and Management Software (21 CFR 864.3700)**

   API recommends that Digital Pathology Image Viewing and Management Software are not FDA-regulated as medical devices evaluated for risk, BUT rather as medical devices evaluated to ensure interoperability and standardization through an "accommodative" regulatory framework. API also requests comment.

   Digital pathology image viewing and management software are components in the "pixel pipeline" of digital pathology systems. In radiology and other imaging disciplines outside of pathology, similar image viewing and management software get referred to as “medical device data systems [ref 9].” These systems exist as class I, so long as they do not modify the pixels [ref 10,11]. There is enough evidence to show a low risk of using digital pathology image viewing and management software components under this product code, justifying the argument for not regulating these components for risk. Moreover, for digital pathology, the accountability for risk is on clinical laboratories. Individual pathologists have the expertise to verify and validate such components are safe to make accurate diagnoses and determine which commercial-grade products to use in medical practice. Therefore, such components and their risk performance align more under CMS, regulating pathology practice, versus the FDA.

   Excluding risk evaluation, continual evaluation for interoperability and standardization is our proposed approach to FDA regulatory oversight, which is not currently present for components defined as “medical device data systems[9].” Other pathology organizations (i.e., Digital Pathology Association [DPA]), API, advocate a modularized approach to digital pathology system components that enable interoperability and standardization. Continual

oversight for interoperability and standardization for components under QKQ will enable the standardized, safe, and efficacious deployment of image analysis and AI applications dependent on QKQ components. Having interoperability and standardization structured within these components through an "accommodative" regulatory framework will promote innovation and access for new platforms and applications to ensure a robust market for an enabled digital and computational ecosystem.

3. **PSY – Whole Slide Imaging System (21 CFR 864.3700)**

   API does NOT endorse the permanent regulatory flexibility, particularly for specific components under the PSY (Whole Slide Imaging System) product code that does not fall under the PZZ and QKQ product codes. Instead, API recommends that for these non-PZZ and QKQ components, create a new product code. For components under that new product code, API recommends approaching opening systematically and in partnership with digital and computational pathology-enabled organizations like API, DPA, and the Alliance for Digital Pathology [(ref 3)]. Such components need evaluation for risk and to ensure interoperability and standardization. Likewise, such evaluations get best aligned through an "accommodative" regulatory framework. API also requests comment.

   The WSI system includes hardware and software components encompassing digital scanners, digital pathology displays, digital pathology image viewing, and management software. Except for digital scanners, the latter three components fall under PZZ (digital pathology display) and QKQ (digital pathology image viewing and management software) product codes, with regulation targeted according to those product codes. PZZ and QKQ components' broad inclusion under PSY creates confusion, warranting a new, independent product code for the remaining PSY component -- digital slide scanners.

   Clearance for PSY devices is relatively recent (2017 and 2019), resulting in limited market history. However, due to MAUDE's biases, the absence of adverse risk events potentially reflects recent market entry and possibly a misrepresentation of safety. API acknowledges that despite such devices new to the market, there is ever-expanding widespread use, yet there is still a low, encouraging number of risk events reported. One scenario that requires more scrutiny is tissue detection. Due to the focusing point engineering of digital scanners, there is potential to miss the scanning of highly fragmented tissues and "out of focus plane" cells. Hence, digital scanning on "wet" (cytologic and hematologic) specimens is yet not FDA-cleared or widespread in clinical practice for diagnoses. The sparse use of digital scanning for “wet” specimens leads to scant reporting. Our proposed "accommodative" regulatory framework will capture risk events with growing use and accumulated experience over time.

   Permanent regulatory flexibility leads to reduced interoperability and standardization long-term. Lack of interoperability locks users to end-to-end vendors with high costs to switch and few opportunities to swap less expensive interoperable components. Radiology suffers from a lack of interoperability with “medical device data systems [(ref 9),]“ but this is avertable in digital pathology if FDA oversight factors interoperability and standardization.

   A consideration for digital scanner evaluation is the inclusion of their corresponding digital image outputs. Besides concerns from permanent flexibility of regulatory oversight for risk, API foresees detrimental computational pathology consequences without oversight for interoperability and standardization of digital scanners (and their digital image outputs). In addition to other components under QKQ, digital scanners (and their corresponding digital

image outputs) should allow for the standardized safe and efficacious deployment of image analysis and AI applications, regardless of output specific to the digital scanner. Unlike human vision, computer vision applications are highly susceptible to artifacts and noise, which vary from scanner to scanner, image pixel data, and image reproduction (color, contrast, texture, etc.).

Interoperability of the different digital and computational pathology components is feasible only with interoperable and standardized data exchange interfaces. To enable interoperability and standardization in this context involves reaching a consensus regarding a standard file format and communication protocol for storage and transmission of images and related information, then evaluating how closely devices adhere. Having interoperability and standardization, structured within digital scanners through our "accommodative" regulatory framework, will promote innovation expansion and access for new platforms and applications to ensure a robust market for an enabled digital and computational ecosystem.

4. **OEO – Automated Digital Image Manual Interpretation Microscope (21 CFR 864.1860)**

API does NOT endorse the permanent regulatory flexibility. Instead, API recommends approaching opening systematically and in partnership with digital and computational pathology-enabled organizations like API, DPA, and the Alliance for Digital Pathology [ref 3]. Such software devices need evaluation for risk and to ensure interoperability and standardization. Likewise, such evaluations get best aligned through an "accommodative" regulatory framework. API also requests comment.

The OEO product code describes software devices that aid in the interpretation of immunohistochemistry (IHC). API acknowledges the clearance of several software devices ("good actors") under this product code over a decade of safe market use. API also believes that MAUDE reporting is proprietary to the software device and not extensible to other software devices. Therefore API is uneasy about endorsing permanent regulatory flexibility for all software devices under the OEO product code. Likewise, there are no disincentives for "bad actors" to enter and integrate into the current pool of "good actors."

Furthermore, API believes there is the extensibility of OEO for AI applications as medical devices (SaMDs), which aid in quantitative interpretation of novel biomarkers and qualitative companion diagnostics. AI SaMDs are rapidly expanding, and the technical understanding around these types of algorithms is still a "black box," requiring more scrutiny when applied to the clinical setting.

Like the FDA, API does endorse a tailored regulatory oversight with the minimal threshold for safety and monitoring of risk events not to overburden innovation and market expansion of promising software devices [ref 12]. API also believes that a robust AI SaMDs market relies on interoperability and standardization. Similarly, software devices should continue remaining subject to continual evaluation for interoperability and standardization. Software devices should provide a level of safeguards and standardization to operate safely and efficaciously on any product under QKQ and PSY.

API recommends regulatory evaluation in partnership with digital and computational pathology-enabled organizations like API, DPA, and the Alliance for Digital Pathology [ref 3]. Such a cooperative partnership will expedite adequate controls and mitigations to balance innovation safety for AI applications in pathology. Already the FDA has an action plan for AI SaMDs that outlines actions in developing an oversight framework [ref 13]. Likewise, an

"accommodative" regulatory framework will capture risk events with newly emerging device software while ensuring such devices achieve appropriate interoperability and standardization.

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