



Digital Pathology Association
370 Medical Drive, Suite A
Carmel, Indiana 46032

March 12, 2021

Re: RIN 0991-ZA52, 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:

Reference is made to the Federal Register (FR) Notice on January 15, 2021, requesting information, research, analysis, and public comment on opportunities for further scientific and evidence-based reform of the program implementing section 510(k) of the Federal Food, Drug, and Cosmetic Act. As requested in the FR Notice, the Digital Pathology Association (DPA), is providing information, comments, and recommendations on such opportunities.

The DPA is a non-profit organization comprised of pathologists, scientists, technologists, and industry representatives who are dedicated to advancing the field of digital pathology. The organization's mission is to facilitate education and awareness of digital pathology applications in healthcare and life sciences, and to facilitate access to these technologies. The DPA applauds the Department of Health and Human Services' (the Department's) efforts to evaluate if current information on the safety and efficacy of certain Class I and Class II devices, which include those in digital pathology, are sufficient to warrant a reduction in certain regulatory requirements.

We would like to thank the Department for the opportunity to comment on this important topic. Should the Department and/or their Agencies or Centers have any questions on any of these points, we welcome the opportunity to provide clarification.

Sincerely,

Esther Abels
On behalf of
Digital Pathology Association
Regulatory & Standards Task Force



General Comments

Overall, the DPA agrees with the Department’s effort to reduce the regulatory burden on medical devices in order to balance benefit and cost when safety and scientific evidence suggests it is appropriate to do so. The current practice of pathology is increasingly adopting and incorporating digital pathology into clinical workflows. Numerous published studies have shown high accuracy for providing primary diagnoses using whole slide images (WSIs) of glass slides.¹⁻¹⁰

Additionally, the Coronavirus Disease 2019 (COVID-19) national public health emergency (PHE) has presented a unique opportunity to observe the use of certain digital pathology systems in a real-world setting. A Food and Drug Administration (FDA) guidance has enabled the remote use of digital pathology systems that have not undergone clearance through the 510(k) pathway (either as a new device or modification to an existing device) for this intended use.¹¹ For example, this policy enables the use of various hardware and software devices that are not currently cleared for remote sign out of cases. An additional guidance published by the Centers for Medicare & Medicaid Services (CMS) has also allowed for viewing of digital pathology images and sign out cases in different settings outside of a medical facility under certain conditions.¹²

The Department’s analysis of data collected from the Manufacturer and User Facility Device Experience (MAUDE) database revealed a lack of non-death-related adverse events for certain Class II devices within the last 10 years (including reporting during the PHE), which includes product codes for digital pathology devices. These findings led the Department to conclude that 510(k) premarket notification is no longer necessary to assure the safety and effectiveness of devices under these product codes. However, the Department also recognized that while MAUDE is an important source of information, it also has limitations due to it being a “passive surveillance system”. In recognition of this limitation, the DPA is providing additional information relevant to the determination of permanent 510(k) exemption for certain Class II medical devices.

Given the DPA’s specific expertise in digital pathology devices, comments are limited to certain digital pathology product types identified in the FR Notice.

Digital Pathology Displays

Display hardware (i.e., monitors) are used to review WSIs of histopathology slides when performing a pathology diagnosis (as opposed to glass slides under a light microscope). Pathologists must determine if the monitor being used has sufficient resolution to enable an accurate diagnosis, regardless of whether the monitor is an FDA-cleared device. Additionally, clinical laboratories are required by US regulations (i.e., 42 CFR 493.1253) and/or their respective accreditation bodies (e.g., College of American Pathologists [CAP])¹³, to verify or



validate the performance of digital pathology systems within their laboratory that are used for clinical diagnosis, but it is not required that the devices used within these systems are FDA-cleared devices.

A recently published review examined the available literature on the impact of different display types on pathologists' diagnostic performance.¹⁴ While the authors note that there is a need for more primary literature that directly examines or compares performance characteristics of different grades of displays and their specifications, they recommend “pathologists take the lead to establish baseline minimum display specifications for [their] future ‘microscope’”.¹⁴

As noted above, the COVID-19 PHE has presented a unique opportunity to examine the use of a variety of monitors to perform diagnoses, including in a remote setting (e.g., in-home use). A recently published study examined the performance of remote review and reporting of pathology specimens within an institution that implemented remote review and sign out of cases during the PHE.¹⁵ The study reported successful validation of remote use of digital pathology systems, including the use of a variety of displays ranging from consumer grade laptop computers to higher specification desktop computers with high definition dual monitors. These results are similar to numerous other peer-reviewed studies that demonstrated high accuracy between diagnoses performed using WSIs as compared to glass slides, regardless of whether the monitor used was FDA-cleared.^{1-5,7,10}

Overall, it has been demonstrated that it is not necessary for digital pathology displays to be FDA-cleared products in order to produce an accurate pathology diagnosis. High-quality products that meet certain specifications and that pathologists have found to be suitable in exercising their professional judgment have been shown to be sufficient. This recommendation is justified by clinical laboratories and individual pathologists having the expertise to determine if a monitor is safe for use in diagnosis, as well as high-quality products being used in medical practice for displays both prior to and during the PHE.¹⁴ This is additionally strengthened by the guidance on remote use of digital pathology devices during the COVID-19 PHE, in which it is stated that pathologists “use their clinical judgement to determine whether the quality of the images from remote digital pathology devices are sufficient for interpretation of the pathological images.”¹¹ A manufacturer could consider including recommendations for predetermined specifications, for example reference to color standards and/or minimum resolution, as a guide to users.

WSI Systems

WSI systems include both hardware and software components (e.g., digital scanners, monitors, image viewing, and image management). The first WSI system was cleared in 2017 under the product code PSY as a DeNovo Request for a Class II determination (Philips IntelliSite



Pathology Solution: DEN160056), an outcome the DPA strongly advocated for. Since this first clearance, only one other complete WSI system has been cleared under this product code, which occurred in 2019 (Aperio AT2 DX System: K190332). Both device clearances were supported by large clinical studies, which showed that the devices presented low risks. Additionally, while these devices may have a somewhat limited market history in the United States (US), they have been widely used both in the US and abroad¹⁶⁻²⁰, and the risk for adverse events has remained low according to reported information. Given the experience now available for these devices, the DPA advocates that the special controls and FDA's guidance on technical performance assessment (TPA) of digital pathology WSI devices²¹ that define the evidence and studies necessary for clearance for these devices, particularly the scope of clinical studies, should be reexamined. This reexamination should also include improved allowances for interoperability between components of WSI systems (i.e., modularization), including a lessening of the requirements around end-to-end testing.

The DPA has long advocated for a more modularized approach to digital pathology system components and allowing for interoperability within these components in order to promote innovation and access. For example, clinical care teams want to include pathology workflows in an institution's enterprise informatics initiative, and interoperability of standalone WSI product combinations with other clinical products, such as picture archiving and communication systems (PACS) and analysis algorithms, allows for exchange of information to improve care for patients. Therefore, customers can use various hardware and software device combinations that are compatible; this would include exchange of information between non-medical devices, with 510(k) exempt and/or Class II devices. Conversely, barriers to interoperability represent barriers to adoption and utilization.

The DPA appreciates that certain components within WSI systems, such as the viewing software (product code QKQ) and digital pathology displays (product code PZZ), have recently been cleared as individual devices, and the performance characteristic data used to support clearance for these devices represented a reasonable subset of studies compared with the special controls listed under the regulation number for this product code (21 CFR 864.3700) and within FDA's TPA guidance. While the first 510(k) clearance for a digital pathology display under product code PZZ was not tied to any particular WSI system (MMPC-4127F1 [PP27QHD]: K172922), both clearances for the viewing software (Sectra Digital Pathology Module: K193054 and FullFocus: K201005) specified platforms upon which the software must operate in the product labeling, which limits access to the technology to only those users who have both platforms. This limits distribution of products that are subsystems of WSI systems and impairs commercial adoption. Instead, all of the individual subsystems should be able to operate as independent,



platform-agnostic components that interoperate within a WSI system (i.e., modularized components).

To facilitate a modularized approach, each hardware and software component should have an individual product code. Product codes exist for the digital pathology display hardware and image viewing/management software (PZZ and QKQ) as noted above, but a product code for the digital image acquisition hardware does not currently exist and should be created. Special controls for each component, as well as interoperability testing between components, can then be defined, and the regulatory requirements for each examined individually. The DPA recommends approaching modularization of the WSI system components systematically and in partnership with digital and computational pathology-enabled organizations like the Association for Pathology Informatics (API), the Alliance for Digital Pathology, and CAP.

The DPA welcomes the opportunity to collaborate with FDA on refining the TPA guidance to better define interoperability for these types of devices to ensure consistent outputs are achieved. Our expert members -- pathologists, scientists, and technologists – can provide specific recommendations based on their experience and use in medical practice. Additionally, the DPA is in the process of conducting an observational clinical trial in which real world data (RWD) is being collected on the safety and quality of remote sign out of pathology cases during the COVID-19 PHE according to FDA’s guidance, which enables the remote use of digital pathology systems that have not undergone 510(k) clearance.¹¹ The DPA intends to share the Real World Evidence (RWE)/results of this clinical trial with industry members and regulators in an effort to support discussions that drive appropriate changes to current guidance and requirements, including 510(k) exemption.

Digital Analysis Applications for Pathology

The OEO product code describes devices that aid in the interpretation of immunohistochemistry (IHC) staining for human epidermal growth factor receptor 2 (HER2), a well-established biomarker for breast cancer. This aid to pathologists includes computer-assisted assessment of the IHC staining by image analysis. Numerous devices have been cleared under this product code, and these devices have been used on the market for over a decade. Therefore, the reporting in the MAUDE database provides robust evidence of the safety for these devices. Therefore, the DPA agrees with the Department’s assessment that this type of device should be exempted from 510(k) premarket notification, including for other well-established biomarkers of this type that have received multiple 510(k) clearances (e.g., ER, PR, Ki67, etc). These devices can all be grouped under similar technology characteristics, such as IHC nuclear, cytoplasmic, and membranous staining. The DPA recommends that these devices remain subject to Good Manufacturing Practices (GMP) requirements, as well as postmarketing controls.



These previously cleared devices represent “locked” applications (i.e., do not change over time), which differ from artificial intelligence (AI)/machine learning (ML)-based software that has the potential to continuously learn, particularly from real-world experience. The development of AI/ML-based software as a medical device (SaMDs) is rapidly expanding, including in the field of pathology, and the technical understanding around these types of algorithms is becoming well understood. However, AI/ML algorithms remain an emerging technology that should undergo careful evaluation when applied in a clinical setting. In a recently published discussion paper, FDA recognized that these devices should have appropriately tailored regulatory oversight to prevent unnecessary barriers to access to innovation,²² and FDA’s action plan for AI/ML-based SaMDs outlines actions the Agency will take to develop a framework²³. The DPA appreciates these approaches and is interested in continuing to collaborate with FDA to develop special controls and mitigations to ensure a balance between innovation and the safety and efficacy of AI/ML in digital pathology. Creating or providing well-curated benchmark and external datasets by multiple sites, guided by medical experts, will be essential to ascertain the safety and reliability of AI/ML methods.



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