DuVal Client Alert

Passing on Tribal Knowledge of FDA Law

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FDA's Three New 510(k) Guidance Documents—Context and Comment

"FDA Continues to Take Steps to Strengthen the Premarket Notification [510(k)] Program - Program Updates."

In this self-declaration on its website, FDA announced the release in September 2023, of three newly proposed guidance documents ostensibly aimed at "strengthening" the 510(k) program. The three guidance documents cover:

- Best Practices for Selecting a Predicate Device to Support a Premarket Notification [510(k)] Submission;
- Recommendations for the Use of Clinical Data in Premarket Notification [510(k)] Submissions; and
- Evidentiary Expectations for 510(k) Implant Devices.

Our concern is that the word "strengthening" is a euphemism for taking the 510(k) program further from its statutorily-grounded mandate and transforming it into a PMA-like program where the Agency operates with virtually unfettered and unbounded discretion to request the quantity and quality of data it wishes for a 510(k) submission. This is despite the fact the 510(k) program was specifically designed to find ways to avoid reproving science and expedite product clearances consistent with FDA's mission to speed medical product innovation and apply statutory Least Burdensome requirements. But contrary to its regulatory mandates, FDA review staff seemingly find it hard to hide their disdain for the 510(k) program as evidenced by how often FDA reviewers operate outside the 510(k) program's statutorily-defined boundaries and request information that FDA **wants**, not what FDA **needs**, to make a substantial equivalence decision. In this respect, the 510(k) review process has

increasingly become a scientific exploration for FDA subject to the scientific whims and curiosities of young reviewers and middle management. Simple 510(k) submissions are unnecessarily converted into mini-PMAs, and we fear FDA's "strengthening" of the 510(k) program is merely a continuation of that trend.

FDA's three proposed guidance documents cannot be viewed in isolation and they require historical context—bear with us. If you know CDRH well, as we do, there has been an incremental effort over the last 14 years to emasculate the 510(k) program. Dr. Shuren's inaugural attempt, upon coming into the Office of the Center Director, was a big and bold one. Whether it was a trial balloon or as a serious bull rush to make wholesale change, we do not know. But it evoked a serious response from industry and, as a result, the Congress. Dr. Shuren commenced his tenure by empaneling the Institute of Medicine (IOM, now called the National Academy of Medicine) to rewrite the 510(k) program without legislative authority or industry acquiescence. That ill-fated attempt was thwarted by a groundswell of serious opposition—industry, Congressional and White House letters, lobbying and meetings, trade association responses, docket submissions and Citizen's Petitions. Our firm represented the Minnesota Medical Device Alliance (MMDA—not MDMA the actual trade association), a temporary and voluntary association of 105 medical device companies, venture capitalists, and inventing physicians. On behalf of MMDA, we submitted a 52-page Citizen Petition challenging the FDA's administration of the 510(k) program in 2013. Following MMDA's Citizen Petition, the Washington Legal Foundation filed a 10-page Citizen Petition and held a national webinar supporting our Citizen Petition.

After that pushback, then FDA Commissioner Dr. Margaret Hamburg and Dr. Shuren, realized they had created a tsunami of opposition and commenced an apology tour which is well-documented. Since that time, Dr. Shuren has made some important improvements to the process of accessing Agency input.

One almost must be an insider to understand how FDA has continued to reshape the 510(k) program and continues to do so. This is the lens through which we view the erosion of the 510(k) program and comment on the newly proposed 510(k) program guidance below. Before commenting on that erosive dynamic, however, it is also important to provide FDA credit. After all, in the COVID-19 and post-COVID-19 environments, the Agency undertook herculean efforts to modernize the device submission and review process in several respects including, without limitation, the establishment of the Breakthrough Devices Program, the implementation of the CDRH Portal and the eSTAR program. These efforts by the Agency have introduced greater efficiency in 510(k) submissions and review processes. Additionally, the Agency has

continued to provide innovative and strategic management, such as through its evolution of the Digital Health Center of Excellence and the recent elevation of the Office of Strategic Partnerships and Technology Innovation (OST) to a CDRH Super Office, which is intended to provide "leadership and strategic direction on medical device cybersecurity, digital health, standards and patient science, while providing oversight and coordination for CDRH in matters relating to public health emergency preparedness and responsive activities." *See* FDA Press Release, Jan. 24, 2024. We are hopeful these efforts will help improve the 510(k) process, and not leave it in the dust, especially as it relates to digital health products, cybersecurity, and the like. However, as the fruits of FDA's innovation with respect to the 510(k) program will take time to materialize, we presently offer the following observations regarding the Agency's current management of the 510(k) program and the newly proposed 510(k) program guidance.

First, the Agency is slowly, but surely, morphing the 510(k) into a mini-PMA program. In the intervening years, FDA's attempts to change the 510(k) program have varied but one common dynamic has persisted: FDA has continued to take bite-sized nibbles around the edges of the 510(k) program to alter the program slowly and fundamentally from its original, statutory intent. We have observed this dynamic, which is colloquially referred to as "administrative creep," through our professional experiences and interactions with FDA. In our work we live in the trenches with Agency reviewers, lower and middle management, program operations staff, the ombudsman, and upper management, negotiating submissions and pushing back. The CEOs and regulatory professionals we represent in Pre-Submission meetings, Submission Issues Requests (SIRs), LB Flag meetings, 517A appeals, and appeals under 21 CFR 10.75, know the Agency is slowly, but surely, transforming the 510(k) into a mini-PMA program.

Second, we frequently inherit files where the Agency has given the company an NSE or an AINE letter, or it has become obvious in pre-sub discussions, that the Agency is asking for data that is beyond the realm of a low to moderate risk 510(k). It is often well beyond what was asked of a recent predicate device. Sometimes the Agency has reneged on its own previous pre-sub commitments. Whatever the starting point, the ending is the same—more data and unnecessary complexity. In fact, we increasingly find ourselves making PMA-level data argumentation (biostatistics and deep clinical analyses and ridiculous levels of biocompatibility, overbroad cybersecurity requests, and unnecessary human factors and patient experience information) in a world where it has been and should be much simpler for low to moderate risk devices. In so proceeding, FDA review staff often overlook Least

Burdensome requirements based on the sheer might of their administrative position in contrast to their actual grant of regulatory authority.

Third, FDA seemingly takes every opportunity to state in a pre-submission meeting what their "ideal" would be and later treats their advice as if it was mandated direction not followed. FDA's pre-sub input is rightfully understood as the ideal only and meant to guide, not to dictate or demand. They raise issues such as choice of control, randomization, length of follow-up, and primary endpoint selection. They share the additional sentiment that these "are recommendations only and the sponsor can use whatever approach they deem fit if they believe it meets the 510(k) standard." Sponsors take these recommendations under advisement, but if they choose to go an alternate, but justifiable route, or come up a bit short, FDA is quick to start their NSE decision with "as we told you in the pre-submission meeting…". And that is the point where we lose fidelity to the standard. Scientific arguments for why sponsors deviated from FDA's wish list fall on increasingly deaf ears. Sponsors become mired in granular data arguments and an appeal to upper management is often the only mechanism to get out of the trees, survey the forest, and focus on whether the standard has been met - a standard that inherits the presumption of safety and effectiveness of the predicate.

While every guidance document and company correspondence FDA has with a sponsor expresses generic openness to allowing the sponsor to justify a different study design and/or methodological approach, our view is that the pre-submission process is increasingly used by review teams to carve off technologies from the protection and intent of the standard before the journey even begins. In so proceeding, FDA review staff often overlook Least Burdensome requirements based on the sheer might of their administrative position as compared to actual, regulatory authority.

Finally, FDA review staff today seem inexperienced and can make any Class II moderate risk device appear novel, groundbreaking, untested, surprisingly complicated, and necessitating the very best of the Agency's resources to examine it. These requests appear to be political cover for the reviewers. Because when you wave the banner of patient safety, you create a higher moral and ethical plane for yourself. Then FDA alone becomes the champion of patient safety. Never mind that the benefits of the device to patients and physicians have been completely ignored. By doing so, reviewers create a smoke screen, a pretext, for asking for the quantum and quality of data they want. And, frankly, asking for more than is necessary to make the regulatory decision, makes the job of the review staff easier.

When we take some of the world's best physicians and test house scientists into an FDA meeting on simple devices that are from tried and true, well-known, product categories, they uniformly express how unnecessarily complex FDA reviewers can make a clearance. Any former FDA reviewer will tell you the same thing after they leave the Agency and represent industry. And the escalation of data requirements at times is not thoughtful. Often little thought is put into the impracticality, true relevance, and necessity of their data requests.

The foregoing commentary forms the backdrop for our review of FDA's latest attempt to morph the 510(k) program

FDA's most recently proposed guidance documents are nuanced but play themselves out in the context of a submission when Agency questions and expectations are subtly manipulated to request information that may seem to be superficially satisfactory and within the statutory framework of the 510(k) program, but really fall into an academic realm where scientific curiosity is king and practical regulatory application is abandoned. FDA is increasingly bent on being more prescriptive in FDA submissions, i.e., **telling** a sponsor what to submit, as if they are on the development team of the manufacturer.

While their guidance documents and speeches declare they are open to alternative data to make the substantial equivalence determination, we know better, based upon our experience. The Agency itself reminds industry of its openness to alternative approaches using this language at the front of every proposed or final guidance (emphasis added):

> This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. ***You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.*** To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

There are now over 133 guidance documents interpreting some facet of the 510(k) program. These three new guidance documents fall into that realm. The new proposed guidance, in shorthand, proposes the following:

- Best Practices for Selecting a Predicate Device to Support a Premarket Notification [510(k)] Submission;

- Recommendations for the Use of Clinical Data in Premarket Notification [510(k)] Submissions; and
- Evidentiary Expectations for 510(k) Implant Devices.

We tackle each of these, briefly, below.

Guidance 1--Best Practices for Selecting a Predicate Device to Support a 510(k) Submission

FDA's first draft guidance recommends best practices for selecting a predicate device to support a 510(k) submission. In 2018, CDRH Center Director Dr. Shuren and FDA Commissioner Scott Gottlieb, M.D., proposed that predicates 10 years old or older should not serve as proper predicates for a 510(k) submission. This was despite the fact that older predicates legally remain, and often are, viable predicates under the statute. It was yet another attempt by CDRH to legislate as an administrative body and showed a stunning indifference to the statutorily mandated construct for the 510(k) program. There was huge industry pushback on that initiative and it was pulled back. Undaunted, CDRH is at it again with this new guidance.

The proposed guidance is a mix of practical things the industry already does when searching for a predicate. Industry knows FDA will ask a lot of tough questions and draw comparisons to any predicate chosen. FDA's goals for this guidance are laudable, but may not be balanced well enough to allow for new ideas:

> ***FDA considers it a best practice to select a predicate that was cleared using well-established methods***, as this will continue to advance the 510(k) Program, by encouraging the evolution of safer and more effective medical devices in the 510(k) program over time, and ensure that the subject device is evaluated using updated scientific methods whenever possible.

"Best Practices for Selecting a Predicate Device to Support a Premarket Notification [510(k)] Submission," (September 7, 2023), page 8 (emphasis added).

Our first concern is that FDA may attempt to go from this guidance to a number of mandatory checklist items in the eStar program. Data are negotiable and anything that becomes formulaic and prescriptive precludes the kind of creativity both FDA and industry need to develop and review devices. For example, we have encountered situations where current standards or FDA guidance documents that FDA wants a

sponsor to apply to their device may not necessarily apply to some technological differences.

Our second concern is there might be a better, albeit newer, way to test those differences. It is good to have predictability and consistency, but flexibility may be needed for a new device. The Agency can become trapped by well-worn paths of its own making and become rote and formulaic. As FDA itself has stated:

> ***Given the diversity of technologies*** evaluated under this review standard, this guidance adopts a flexible approach to determining "substantial equivalence" ***to accommodate evolving technology while maintaining predictability and consistency to promote confidence among device developers***, practitioners, and patients.

See "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]," July 28, 2014, page 6 (emphasis added).

FDA has stated this in the past as well:

> …the Center focuses on the technological differences that are medically and scientifically significant ***and avoids the difficulties that would arise from a mechanistic application of rigid formal criteria to the wide variety of substantial equivalence questions posed by new devices*** proposed for marketing under a 510(k). Substantial equivalence determinations of necessity require the Center to exercise reasonable scientific judgment.

See 510(k) Blue Book Memo, page 7 (emphasis added).

The new proposed guidance, in shorthand, proposes the following:

1) Predicate Devices Cleared Using Well-Established Methods;
2) Predicate Devices That Meet or Exceed Expected Safety and Performance;
3) Predicate Devices Without Unmitigated Use-Related or Design-Related Safety Issues; and
4) Predicate Devices Without an Associated Design-Related Recall.

The entire proposal appears to add yet another layer of analysis to an increasingly over-burdened 510(k) review process. It is helpful that FDA outlines its thinking here if it does not trap FDA into losing receptivity to other, newer, approaches. The draft

guidance recommends that a 510(k) submission explain how any known concerns with the chosen predicate have been mitigated with the subject device. Our concern is that these "best practices" would be grafted into the 510(k) submission process and essentially (indirectly) add new statutory criterion to be formally considered before clearance.

Industry understands that when they choose a predicate, there may be limitations raised by how old the chosen predicate is and the type and amount of data that was submitted to clear it. But to summarily pronounce older predicates that may have medical device reports (MDRs) or recalls is not the end of the story. Many times, MDRs or recalls involve older versions of products since safely modified. Moreover, MDRs reported in clinical trials have typically already been considered by FDA in the clearance of the product. In addition, to add a new formal requirement to engage in lengthy analysis of this information takes it out of the realm of a 510(k) and into the realm of a PMA. Moreover, to require an extensive examination into design changes for a predicate could be quite burdensome. Suffice it to say, if this guidance provides prompts or insights to what review staffs look at, it is helpful. If these prompts become added formal written expectations for a submission, we would object. We will have to see how this guidance, if finalized, plays out long-term in application.

Guidance 2--Recommendations for the Use of Clinical Data in 510(k)s

Our thinking about this proposed guidance is, in part, a continuation of the discussion above but it also focuses on how review staff determine the need for new clinical data. Note that as we discuss this guidance be aware that requests for clinical data for low to moderate 510(k) devices are dramatically on the rise. This guidance looks at four different and expected times when new clinical data might be necessary for a submission:

> V. Scenarios When Clinical Data May be Necessary to Determine Substantial Equivalence
>
> 1) There are ***differences between the indications for use*** of the new device and the predicate device, and clinical data may be needed to determine SE.
> 2) There are **differences between technological characteristics** of the new device and the predicate device, and clinical data may be needed to determine SE.
> 3) ***SE*** between the new device and the predicate device ***cannot be determined by non-clinical testing*** (analytical, bench, and/or animal).

4) ***A newly identified or increased risk*** for the predicate device suggests clinical data may be needed for the new device to determine SE.

"*Recommendations for the Use of Clinical Data in Premarket Notification [510(k)] Submissions*," September 7, 2023, page 6 (Emphasis added).

These criteria are self-explanatory and self-evident and we will not elaborate on them in this DuVal Client Alert.

Guidance 3-- Evidentiary Expectations for 510(k) Implant Devices

FDA sets forth it purpose for the last proposed guidance as follows:

> This document is intended to clarify our evidentiary expectations for 510(k) Implants. By "evidentiary expectations," we mean that this document is intended ***to assist industry in design and execution of appropriate performance testing*** that may be necessary to support 510(k) submissions for implants. It ***also provides general recommendations for other content, including proposed labeling***, to include in these submissions.

"*Evidentiary Expectations for 510(k) Implant Devices*," September 7, 2023.

Once again, our thinking about this proposed guidance is, in part, a continuation of the discussion above in Guidance 1, but it also focuses on how review staff determine the need for new clinical data. In Guidance 3, FDA reduces to writing its expectations for non-clinical data and clinical for implantable devices. We find it largely unremarkable, in that these are the things we hear from FDA on implantable submissions all the time. It is helpful that FDA lays them out in writing. Here the general considerations FDA memorializes:

IV. Recommendations for 510(k) Implants

General Considerations

1) What are the indications for use of the device?
2) What is the intended duration of implantation?
3) What is the anticipated patient and physician experience with the implant?

The Agency then lays out non-clinical sections on Biocompatibility, Sterility and Shelf Life Reprocessing and Cleaning, Software and Cybersecurity, Electrical Safety and Electromagnetic Compatibility, Magnetic Resonance (MR) Compatibility, Other Non-Clinical Performance Testing, Animal Testing, and Implant Device Design Considerations. Finally, there are sections on Human Factors/Usability, Clinical Performance Testing, Patient Experience Information, and Labeling and Other Recommendations. It is helpful general guidance. ***Where the rubber meets the road is in individual discussions/negotiations with the Agency on all of these.***

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Current Status of the FDA Q-Submission Program

The FDA Q-Submission program provides opportunities for many interactions with FDA including Pre-Submissions (Pre-Subs), Submission Issue Requests (SIRs), Breakthrough Device Designation (BDD) Requests, and Safer Technology Program (STeP) requests. In 2023, FDA made two updates to its Q-Submission Program. Based on our experience with the Q-Submission program, we discuss these updates and how we expect these to impact the program in 2024. For a detailed overview of using the FDA Pre-Submission program, see our three-part Client Alert series available in the Resources tab of www.duvalfdalaw.com.

In June 2023, FDA updated its Q-Submission guidance document (the previous version was released in 2021). The changes from the previous version can generally be categorized as clarifications rather than significant changes to the program. The most significant updates include:

- ***Communications Excluded from the Q-Submission Process:*** Discussion has been added to clarify that 513(g) classification requests, general clarification questions about guidance documents that are not in the context of a specific device, and Emergency Use Authorization (EUA) communications, are all outside the scope of this program.
- ***Predetermined Change Control Plans (PCCPs):*** Discussion added to indicate that obtaining feedback on PCCPs prior to their submission in a pre-market submission (e.g., 510(k), De Novo, PMA) is appropriately completed through a Pre-Sub. As PCCPs gain in popularity (and the necessity for reasonable post-market maintenance of main products), this is expected to become an increasingly popular topic for Pre-Subs.
- ***Time to Pre-Sub Meeting:*** The previous guidance indicated that a Pre-Sub meeting would typically be held within 60 – 75 days. This has been changed to 70 – 75 days. This may seem small but appears indicative of an increasing timeframe for the scheduling of these meetings which is important to note for managing product development schedules. Prior to 2020, we often would be able to have Pre-Sub meetings scheduled within about 45 days; our experience over the past couple of years indicates that 70 – 75 days is the new normal.
- ***CDRH Portal Submission:*** Now that the CDRH Portal is available for use in completing submissions to CDRH, utilizing this valuable tool for all CDRH submissions (including Q-Submissions) makes great sense. We love this tool and strongly recommend using it whenever possible.
- ***Meeting Minutes Format:*** The evolution of the Q-Submission guidance continues to provide additional recommendations for the format and content of meeting minutes. The updates in the current guidance indicate that minutes should provide summary-level detail, not be a transcript of the meeting, and not ascribe statements to specific personnel. Remember it is guidance, not law. While we agree that the minutes should not be a transcript, we disagree with FDA on this issue. We recommend that the minutes contain enough detail so that the communication is clearly memorialized. We have pushed back on FDA (but do not fall on our sword over it) that names be associated with statements made as an Office Director's commitment is more important than a lead reviewer. Meeting minutes are critical. They memorialize commitments and conversations for context. It is often several years between when the meeting occurs, and the results need to be referenced in a commercialization submission. Particularly when there may have been personnel changes (either at FDA or the sponsor), the minutes need to be written clearly enough to ensure that someone who did not participate in the meeting will still be able to

understand what was discussed, what decisions were made, and by whom. We do defer to the Agency on this but continue to push for more flexibility.

The second change that impacted the Q-Submission program in 2023 was the release of a beta version of the Early Submission Requests eSTAR (PreSTAR) within the FDA eSTAR program. Like the eSTAR templates (see our Client Alert Series on the FDA eSTAR program), the PreSTAR is an interactive PDF template that is designed to guide the user through the preparation of a Pre-Sub that will meet the expectations from the current guidance document. The current version only includes functionality for Pre-Subs (either written feedback only or meeting with written feedback). A few considerations if using the PreSTAR template:

- ***Limited Topic Areas:*** the guidance suggests that no more than 4 significant topics should be included in an individual Pre-Sub (e.g., animal study, biocompatibility, benchtop performance testing, clinical study, etc.). The PreSTAR template turns this recommendation into a requirement by precluding the inclusion of more than 4 significant topics. We think this is practical and acceptable.
- ***General Product Characteristics:*** In addition to a written description of the product that is the subject of the Pre-Sub, the Pre-STAR also includes a series of "General Product Characteristics" questions that should be answered. In the current version, these questions are optional, so not required for acceptance of the PreSTAR. However, to improve the quality of the feedback provided, wherever the information is known, it is recommended that it be included.
- ***Supporting Information for Questions:*** Notably, the PreSTAR does not include a section to provide supporting information that leads up to an individual question (e.g., a summary of the proposed clinical study design and how it was selected, to support specific questions about the proposed design). As a workaround to this, the information can be included as an attachment to the individual question(s). Where there are multiple questions about a single topic area, the detailed background information could be provided as an attachment for the first question and referenced for subsequent questions.

The FDA Q-Submission program continues to be a valuable tool for de-risking certain Investigational Device Exemption (IDE) or premarket (e.g., 510(k), De Novo, PMA) submissions. Trends that we have seen in 2023 that are expected to impact the use of the program in 2024 include:

- ***Increased Reliance on Supplemental Communications:*** FDA increasingly will not engage in discussion of any information that is considered to have not been included in the original Q-Submission communication. Gone are the days of a Pre-Sub meeting being a forum for the continuation of the communication and scientific exchange of information. This trend decreases the value of the meeting, relegating it to obtaining clarification of written feedback that was provided (Pre-Sub) or blinded provision of FDA feedback with limited opportunity for sponsor reaction (SIR). For a Pre-Sub, it is generally advisable to request a meeting, then decide based on the pre-meeting feedback whether to rely on that written feedback or proceed with the meeting to obtain any clarification. For a SIR, it is often preferred to request written feedback so that the final feedback is available in a shorter timeframe without having to wait for final meeting minutes.
- ***Increased Return to In-Person Meetings:*** FDA has increasingly been willing to engage in in-person meetings following the move to exclusively virtual meetings during the COVID-19 pandemic. Interestingly, the language in the updated Q-Submission guidance provides expanded clarification that virtual meetings are often more efficient than in-person meetings. However, if an in-person meeting is desired, it can be requested again. Even if an in-person meeting is requested, some FDA staff may still participate virtually. We recommend determining who will be onsite and who will be virtual (to ensure that key FDA participants will be onsite) before deciding if it is worth the extra expense that may be needed to support an in-person meeting (e.g., travel expenses and additional out-of-office time).

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Laboratory Developed Tests

This upcoming year could lead to much upheaval in the Laboratory Developed Tests (LDTs) space as FDA looks to finalize its proposed rule on LDT enforcement under the Food, Drug, & Cosmetic (FD&C) Act in April 2024, which will ultimately require pre-market submissions on LDTs as early as 2027.

LDTs are medical diagnostic tests created and performed within a single laboratory, tailored to a specific lab's needs and capabilities. The FDA has spent the past thirteen years asserting its regulatory authority over LDTs by claiming that LDTs are in vitro diagnostic devices (IVDs) and regulated under the FD&C Act. However, understanding they were on shaky legal ground, the Agency exercised a risk-based approach to regulating LDTs and put the burden on Congress to provide the FDA with the proper authority to regulate LDTs.

This Verifying Accurate Leading-edge IVCT Development (VALID) Act attempted to provide a new statutory and regulatory scheme for LDTs by redefining the definition of a device to include LDTs and to broaden the interstate commerce trigger that is required for the Agency to regulate LDTs. In this way, FDA would have the authority to regulate LDTs that remain wholly within the laboratory when the test service is offered for sale in interstate commerce. However, the VALID Act was generally considered to be the lesser of two regulatory evils as it included provisions for grandfathering in many existing LDTs. Without the VALID Act, the FDA had threatened to try to force LDTs under its current regulatory scheme which could kill off many safe and commonly used LDTs.

However, the VALID Act never became law and FDA started to make good on its threat of enforcing LDTs under the current regulatory scheme through its proposed rule on

LDTs. Yet, once again FDA treads on perilous legal ground. The FDA appears to understand that it is Congress that has the authority to regulate interstate commerce, by stating in the proposed rule:

> "Modern Commerce Clause jurisprudence holds that Congress has 'authority to regulate even purely local activities that are part of an economic 'class of activities' that have a substantial effect on interstate commerce.'"

However, the Agency fails to understand its authority as it states in the proposed rule:

> "There is no overarching requirement in the FD&C Act that FDA-regulated articles have a particular nexus with interstate commerce. Interstate commerce is not a prerequisite to FDA jurisdiction (beyond the constitutional minimum). Rather, under the FD&C Act, a limited number of provisions include specific interstate commerce ''elements,'' and thus require a particular connection with interstate commerce in order for those provisions to apply."

As Judge Royce Lambert famously stated in the 1999 Washington Legal Foundation case against the FDA, the Agency "exaggerates its overall place in the universe." Contrary to FDA's beliefs, it is Congress that has the constitutional authority to broadly regulate interstate commerce, and Congress is not obligated to pass on its full authority to FDA. In the case of the FD&C Act, the "limited number of provisions" that include a specific interstate commerce element are the basic acts that FD&C Act prohibits and regulates (21 U.S.C. § 331). Other subsidiary provisions that do not speak to interstate commerce are in place to ensure compliance with the provisions that speak to the interstate commerce requirements. Nothing in the statutory language provides the Agency with general authority to regulate anything that merely affects interstate commerce. That authority remains with Congress. Therefore, it remains problematic that FDA intends to circumvent the interstate commerce requirements and regulate LDTs that are created within a laboratory and remain within that laboratory.

The upcoming year will bring a lot of uncertainty to the LDT space, and if the final rule is finalized it will have a significant impact on industry, innovation, and the practice of medicine. It will be interesting to see if FDA softens its stance on LDTs or if Congress will step in and provide a legal pathway for FDA to regulate LDTs. If Congress fails to step in, it may invite a lawsuit to challenge FDA's expansionist view of its authority.

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Cybersecurity and Evolving Expectations for Medical Devices

INTRODUCTION

A cardiologist recently recommended a remote cardiac monitor for my grandfather due to his heart condition. The device was ordered, and I happened to be at my grandfather's house the day it arrived. After receiving the package, my father and I, despite our collective professional experience (*I'm a regulatory lawyer who counsels medical device clients on cybersecurity concerns, and my father is a cardiovascular surgeon who uses medical devices in his practice*), simply took the device out of the box, plugged it into an electrical outlet, and connected it to the landline. We did so without looking at the device's labeling or reading the entirety of the device's instructions. Although this approach was likely not the most prudent, we proceeded as we did because we expected the device was safe and would work as intended. ***Stated simply, our expectation of safety and effectiveness shaped our use of the device.***

In considering the cybersecurity of medical devices, my experience in installing my grandfather's remote cardiac monitor, and my expectation of its safe and effective use is telling. After all, most of the cybersecurity challenges faced by medical device manufacturers, whether on a premarket or post-market basis, are predicated on similar expectations. ***In short, most medical device users expect their devices to be safe and effective***. And, consistent with this user expectation is FDA's expectation that cyber devices should provide a reasonable assurance of safety and effectiveness. In fact, in evaluating recent healthcare cybersecurity concerns, legislative activities, and FDA guidance documents, ***three primary cybersecurity expectations have evolved for medical device manufacturers and govern their design, manufacture, and sales***

of medical devices: (1) the expectation a device is designed with appropriate risk mitigation, validation and cyber protections to establish a safe and effective use; (2) the expectation a device can be updated to mitigate new risks and vulnerabilities; and (3) the expectation that the use, risks and vulnerabilities of a device can be adequately communicated to patients and clinicians.

This DuVal Client Alert evaluates these expectations in light of the evolving and rapidly changing cybersecurity requirements for medical devices and provides an update regarding recent, legislative activities and FDA guidance documents concerning device cybersecurity.

CYBERSECURITY DEVELOPMENTS FOR MEDICAL DEVICES

As stated above, medical device security is an essential element in providing safe and effective patient therapies. However, the security of devices is increasingly under attack due to evolving cybersecurity threats and vulnerabilities. In fact, the cybersecurity threats afflicting the healthcare sector and, medical devices specifically, far outpace cybersecurity risks in other non-healthcare sectors.

For example, the Department of Health and Human Services 405(d) program, which is a federal program within HSS dedicated to providing the healthcare sector with information to strengthen cybersecurity protections, estimates a 16% increase in the number of vulnerabilities related to Internet-of-Things (IoT) devices compared to a 0.4% growth rate for vulnerabilities overall. Most of the vulnerabilities afflicting medical devices arise from five different threats: social engineering; ransomware; loss or theft of equipment or data; insider, accidental, or malicious data loss; and attacks against connected medical devices.

To mitigate cybersecurity risks for medical devices referenced above, there have been several, recent developments relevant to medical device manufacturers, which are the focus of this Client Alert.

First, Section 524B was enacted, which incorporated cybersecurity requirements into the Food, Drug & Cosmetic Act. On December 29, 2022, Section 3305 of the Consolidated Appropriations Act was enacted, which added Section 524B to the Food, Drug & Cosmetic Act. Section 524B, which is entitled "Ensuring Cybersecurity of Medical Devices," became effective on March 29, 2023, and authorized FDA to establish cybersecurity requirements for manufacturers of digital health devices.

Therefore, under Section 524B(a), any person who submits a 510(k), PMA, PDP, De Novo, or HDE for a cyber device (as defined in Section 524B(c)), is required to submit information to FDA to ensure the cyber device meets the requirements of Section 524B including, without limitation, risk mitigation and validation requirements, design considerations, etc.

Second, FDA issued its final guidance relating to cybersecurity requirements for premarket submissions for medical devices. On September 26, 2023, FDA issued its final guidance entitled "Cybersecurity in Medical Devices: Quality Systems Considerations and Content of Premarket Submissions." This Guidance provides recommendations on medical device cybersecurity requirements and the information that must be included in premarket submissions. Importantly, this Final Guidance supersedes FDA's prior premarket cybersecurity guidance from 2014, and supplements FDA's post-market cybersecurity guidance, guidance for medical devices containing off-the-shelf software, and premarket submissions guidance for device software functions.

Finally, several other resources and best practices have been recently issued for medical device manufacturers. These resources, such as the Medical Device Cybersecurity Response Playbook and the Playbook for Threat Modeling for Medical Devices, were published through the joint collaboration between FDA and The MITRE Corporation. Additionally, other, relevant resources have been provided to educate the medical device industry regarding expectations and requirements for cyber devices.

1. Legislative Changes under Section 524B

In 2022, the "Protecting and Transforming Cyber Healthcare Act" ("the Patch Act"), was proposed as legislation in the United States House of Representatives and Senate. The Patch Act intended to ensure the cybersecurity of devices by requiring any premarket submission for cyber devices to contain information necessary to demonstrate a reasonable assurance of safety and effectiveness as well as compliance with specific, cyber requirements. The Patch Act, however, was ultimately not enacted as separate legislation. Instead, several, related provisions from the Patch Act were incorporated into and enacted with the 2023 Consolidated Appropriations Act, including Section 3305, which added Section 524B to the Food, Drug & Cosmetic Act.

Section 524B, which is entitled "Ensuring Cybersecurity of Medical Devices," and is referred to in the Section 524B legislation, is intended to promote the reasonable assurance of the safety and effectiveness of cyber devices. To this end, Section 542B has three primary effects. First, it amended the FD&C Act by adding Section 524B provisions relating to cyber devices for premarket device submissions. Second, it empowered the FDA to adopt regulatory standards for cyber devices and premarket review. Finally, it authorized FDA to regulate and issue guidance regarding device cybersecurity.

The newly-enacted Section 524B(a) states its overarching intent:

> "For purposes of ensuring cybersecurity throughout the lifecycle of a cyber device, any person who submits a premarket submission for the cyber device shall include such information as the Secretary may require ***to ensure that the cyber device meets such cybersecurity requirements as the Secretary determines to be appropriate to demonstrate a reasonable assurance of safety and effectiveness***, including at a minimum the cybersecurity requirements under subsection (b)."

In furtherance of this intent, Section 524B established a new definition of a cyber device, which includes any device that: (1) includes software validated, installed, or authorized by the sponsor as a device or in a device; (2) has the ability to connect to the internet; and (3) contains any such technological characteristics validated, installed, or authorized by the sponsor that could be vulnerable to cybersecurity threats. Additionally, the Section 524B Legislation requires that anyone who submits an application or submission under the 510(k), De Novo, or PMA pathways that meet the definition of a cyber device must provide such information as required by FDA to ensure the device meets stated cybersecurity requirements. Additionally, Section 524B Legislation authorizes FDA to evaluate cybersecurity as part of a substantial equivalence determination.

There are four specific obligations imposed by Section 524B. ***First,*** a manufacturer must submit to FDA as part of its premarket notification a plan to monitor, identify, and address cybersecurity vulnerabilities and exploits. ***Second,*** a manufacturer must design, develop, and maintain processes and procedures to provide a reasonable assurance that the device and related systems are cybersecure and make available post-market patches and updates to address vulnerabilities. Additionally, updates necessary to address vulnerabilities must be made on a reasonably justified regular cycle for known, unacceptable vulnerabilities, and as soon as possible out of the

regular cycle for critical vulnerabilities that could cause uncontrolled risks. ***Third***, a manufacturer must provide a Software Bill of Materials identifying software components with the premarket application or submission (Information regarding SBOMs is included in the October 2021 National Telecommunications and Information Administration (NTIA) Multistakeholder Process on Software Component Transparency document "Framing Software Component Transparency: Establishing a Common Software Bill of Materials (SBOM)."); and ***Finally***, a manufacturer must comply with such other requirements as the Secretary may require through regulation to demonstrate a reasonable assurance of cybersecurity.

2. FDA Guidance, "Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions" dated September 27, 2023

To help companies satisfy the cybersecurity requirements of Section 524B, FDA has issued recent guidance relating to cybersecurity. The most important is FDA's final guidance entitled, "Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions," ("Final Guidance") which was initially issued as draft guidance by FDA in April 2022 (prior to the enactment of Section 524B) and was issued as final guidance on September 27, 2023. *See https://www.fda.gov/media/119933/download.* This Final Guidance supersedes FDA's earlier guidance entitled "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices," dated October 2, 2014.[1]

In issuing the Final Guidance, FDA recognizes recent events across healthcare have "stressed the importance of cybersecurity to patient safety," including the WannaCry ransomware that affected hospital systems and medical devices across the globe, vulnerabilities in commonly used third-party components, like URGENT/11 and SweynTooth, which led to safety concerns across a broad range of devices used in various clinical specialties, and a 2020 ransomware attack on a German hospital that

[1] In addition to superseding the 2014 Premarket Cybersecurity Guidance, the 2023 Final Guidance is intended to supplement the 2016 Postmarket Cybersecurity Guidance, "Postmarket Management of Cybersecurity in Medical Devices," December 2016, the 2005 OTS Software Guidance, "Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software," January 2005, and the 2023 Premarket Submissions for Device Software Guidance, "Content of Premarket Submissions for Device Software Functions," June 2023.

forced patients to be diverted to another hospital. Final Guidance p.3. It also explains its expectation that "***cybersecurity is a shared responsibility among stakeholders throughout the use environment of the medical device system, including healthcare facilities, patients, healthcare providers, and manufacturers of medical devices***." *Id*. pp.3-4.

To this end, the 2023 Final Guidance applies to all devices "with cybersecurity considerations, including but not limited to devices that have a device software function or that contain software or programmable logic." It specifically applies to all premarket submissions including 510(k)s, De Novos, and PMAs, as well as 510(k) exempt devices and cyber devices as defined in Section 524B of the FD&C Act. Finally, the 2023 Final Guidance "describes recommendations regarding the cybersecurity security information to be submitted for devices" for premarket submissions, including the submission of Software Bills of Materials as part of a premarket submission, as well as other information relating to device cybersecurity. These recommendations are built into four key principles identified by FDA relating to cybersecurity management for cyber devices.

The first principle relates to Quality System Regulation for digital devices. Under this principle, FDA recommends that manufacturers establish cybersecurity risk management and validation processes, such as those that may be incorporated in a Secure Product Development Framework (SPDF), to demonstrate a reasonable assurance of safety and effectiveness for certain devices with cybersecurity risks. FDA states:

> "***Software validation and risk management are key elements of cybersecurity analyses and demonstrating whether a device has a reasonable assurance of safety and effectiveness.*** FDA requires manufacturers to implement development processes that account for and address software risks throughout the design and development process as part of design controls, as discussed in FDA's regulations regarding design control, which may include cybersecurity considerations. For example, these processes should address the identification of security risks, the design requirements for how the risks will be controlled, and the evidence that the controls function as designed and are effective in their environment of use for ensuring adequate security."

2023 Final Guidance, p.10.

The second principle relates to designing devices for security. FDA's Guidance states devices should be designed to achieve security objectives, and that FDA will assess a device's ability to achieve such objectives, including authenticity, authorization, availability, confidentiality, and updatability and patchability:

> When reviewing premarket submissions, ***FDA intends to assess device cybersecurity based on several factors, including, but not limited to, the device's ability to provide and implement the security objectives below throughout the device architecture.*** The security objectives below generally may apply broadly to devices within the scope of this guidance, including, but not limited to, devices containing artificial intelligence and machine learning (AI/ML) and cloud-based services.

2023 Final Guidance, p.11. Per this principle, the Guidance also states premarket submissions should include information that specifically identifies how security objectives are integrated into the device design. One way to do this is by adhering to consensus standards that FDA has recognized for cybersecurity support concerning device submissions, such as AAMI/UL 2900-1:2017 and IEC 810001-5-1: 2021.

The third principle concerns transparency. This principle addresses user expectations as foreshadowed at the beginning of Client Alert. The Guidance explains it is important for device users to have access to information pertaining to the device's cybersecurity controls, potential risks, and other relevant information. This is because "[a] lack of cybersecurity information, such as information necessary to integrate the device into the use environment, as well as information needed by users to maintain the medical device system's cybersecurity over the device lifecycle, ***has the potential to affect the safety and effectiveness of a device***." *Id.* p.12. Accordingly, the Guidance encourages that cybersecurity information, including risks and vulnerabilities be included in labeling to adequately inform users. For example, a failure to disclose all of the communication interfaces or third-party software could fail to convey potential sources of risks. Similarly, labeling that does not include sufficient information to explain how to securely configure or update the device may limit the ability of end users to appropriately manage and protect the medical device system. *See Id.*

The final principle concerns submission documentation. The Guidance states submissions should contain information about cybersecurity design and documentation, as well as a broader security architecture. It also confirms FDA will

evaluate the cybersecurity information and protections for the purpose of evaluating substantial equivalence. FDA explains:

> "Device cybersecurity design and documentation are expected to scale with the cybersecurity risk of that device. Manufacturers should take into account the larger system in which the device may be used. For example, a cybersecurity risk assessment performed on a simple, non-connected thermometer may conclude that the risks are limited, and therefore such a device needs only a limited security architecture (i.e., addressing only device hardware and software) and few security controls based on the technical characteristics and design of the device. However, if a thermometer is used in a safety-critical control loop, or is connected to networks or other devices, then the cybersecurity risks for the device are considered to be greater and more substantial design controls should result."

Id. p.12.) Therefore, it's critical for manufacturers to accurately evaluate and understand the risk profile, intended use, and actual use environment of a device and include that information in a device submission so that FDA can effectively evaluate related cybersecurity risks.

Compliance with these principles in a premarket submission is critical for medical device manufacturers. This is because under Section 513(i) of the FD&C Act, and 21 CFR 807.100(b)(2)(ii)(B), FDA will evaluate the cybersecurity information and the protections the cybersecurity controls provide to demonstrate substantial equivalence. *See* FDA Guidance, p.13 ("In the 510(k) context, FDA evaluates the cybersecurity information submitted and the protections the cybersecurity controls provide in demonstrating substantial equivalence.") Additionally, FDA's Guidance clarifies ***that inadequate cybersecurity information in device labeling may result in misbranding or adulteration***:

> "In addition, inadequate cybersecurity information in the device labeling may cause a device to be misbranded under section 502(f) of the FD&C Act if its labeling does not bear adequate directions for use or under section 502(j) of the FD&C Act because it is dangerous to health when used in the manner recommended or suggested in the labeling, among other possible violations. For cyber devices, failure to comply with any requirement under section 524B(b)(2) (relating to ensuring device cybersecurity) is considered a prohibited act under section 301(q) of the FD&C Act."

Final Guidance, p. 13.

3. Cybersecurity Best Practices for Medical Devices

In addition to the Section 524B Legislation and 2023 FDA Final Guidance, there are ***several other resources for medical device manufacturers.*** For example, FDA's development of its Digital Health Center of Excellence within CDRH, its FDA Fact Sheet "FDA's Role in Medical Device Cybersecurity," and its Cybersecurity FAQs provide information regarding the implementation and requirements under Section 524B, the definition of cyber devices, the application of Section 524B requirements and post-market obligations under FDA's 2014 and 2016 Guidance Documents.

The Medical Device Cybersecurity Regional Incident Preparedness and Response Playbook ("Playbook"), which is a collaborative effort between FDA and MITRE, recommends best practices for cybersecurity protection and outlines a framework for responding to cybersecurity incidents involving medical devices. This Playbook is a particularly helpful document because it is addressed to clinicians, device manufacturers, and healthcare delivery obligations and represents the most recent recommendations on cybersecurity incident responsiveness.

Finally, the Playbook for Threat Modeling for Medical Devices," which is another collaborative playbook from FDA, MITRE and the Medical Device Innovation Consortium (MDIC), identifies best practices for understanding cyber device threat modeling, and how organizations can develop an effective approach to threat modeling for medical devices. This includes, without limitation, incorporating effective threat modeling in medical device design choices and requirements, device testing strategies, existing device manufacturing policies and processes, and device development with contract manufacturers or other third parties.

CONCLUSION

Medical device users expect devices to be safe and effective. This is also an expectation of FDA. Through the legislative activity and guidance documents implemented in 2023, FDA is more robustly evaluating medical device premarket submissions to ensure safe and effective use relating to cybersecurity concerns. However, as with anything cyber-related, the expectations, regulatory obligations, and best practices relating to cyber devices will continue to rapidly evolve. In fact, FDA has already identified prioritized guidance that CDRH intends to issue in 2024 relating to digital health devices and cybersecurity. Therefore, it will be critical for medical device

manufacturers to remain current with FDA's expectations and guidance documents relating to digital health and cyber devices, especially as those guidance documents relate to premarket submissions.

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Digital Health Medical Devices

Digital Health is a broad term that describes non-medical and medical devices that include digital health technologies (DHTs) such as computing platforms, software, connectivity, and sensors for health-related applications. These technologies may be used as a medical product, in a medical product, as companion diagnostics, or as an adjunct to other medical products (devices, drugs, biologics). Topics under the term "Digital Health" include:

- Artificial Intelligence (AI) and Machine Learning (ML)
- Clinician Decision Software
- Cybersecurity
- Digital therapeutics (DTx)
- General wellness products
- Health Information Technology (IT)
- Medical Device Data Systems (MDDS)
- Medical Device Interoperability
- Medical Extended Reality (XR) (includes Augmented Reality/Virtual Reality (AR/VR))
- Mobile Health (mHealth) and Mobile Medical Applications
- Multiple function devices
- Personalized medicine

- Remote patient monitoring (RPM)
- Software as a Medical Device (SaMD)
- Telehealth and telemedicine
- Wearable devices, Patient-Generated Health Data (PGHD)
- Wireless Connectivity

The FDA launched the Digital Health Center of Excellence (DHCoE) within CDRH in September 2020 and established the Digital Health Advisory Committee in October 2023 to advise the FDA on issues related to DHTs. The objectives of this Center are to build partnerships, share knowledge, and innovate regulatory approaches for digital health products. DHCoE maintains a list of AI and ML-enabled devices which currently includes 691 devices, consisting of 668 510(k)s, 20 De Novos, and 3 PMAs. The vast majority of devices are for radiology (531), followed by cardiovascular (71), neurology (20), and hematology (15) use. DHCoE also maintains a list of AR/VR Devices, which currently includes 38 devices, consisting of 36 510(k)s and 2 De Novos, of which most are used in orthopedics (15) and radiology (14), and Companion Diagnostic Devices.

The DHCoE website has a list of 23 FDA guidance documents (21 final and 2 draft guidance documents) that include Digital Health content, totaling more than 600 pages. It is time-consuming to read and integrate information across all these guidance documents to determine if your product is a device that requires FDA's oversight. To help with this assessment, consider using FDA's interactive Digital Health Policy Navigator which provides a guided decision tree with links to key guidance documents and other resources that include supporting information. The decision tree has three possible outcomes: your product is likely not a device, it is likely a device but one that FDA intends to exercise enforcement discretion (meaning no submission required), or it is likely a device that requires FDA's oversight (likely will need a premarket submission). Another useful tool is the Mobile Health App Interactive Tool which helps mobile health app manufacturers determine the US federal laws that apply to their products, including the FD&C Act, HIPAA rules, and the FTC Act.

In 2023, the FDA completed the following digital-health-related guidance activities:

- Updated two guidance documents:
    - *Content of Premarket Submissions for Device Software Functions* (June 14, 2023)
    - *Off-the-Shelf Software Use in Medical Devices* (August 11, 2023)

- Issued new draft guidance documents:
    - *Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML-Enabled Medical Device Software Functions* (April 3, 2023)
    - Also released the *Predetermined Change Control Plan for Machine-Learning-Enabled Devices: Guiding Principles* (October 2023) with Health Canada and UK's Medicines and Healthcare products Regulatory Agency (MHRA)

- Issued a final guidance:
    - Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions (Sep 27, 2023).

The Food and Drug Omnibus Reform Act of 2022 (FDORA) added section 515C "Predetermined Change Control Plans for Devices" to the FD&C Act. Section 515C provides FDA with express authority to approve or clear PCCPs for devices requiring premarket approval or premarket notification. The Predetermined Change Control Plan (PCCP) is based on years of FDA discussion papers/action plans, public workshops, and the Software Precertification (PreCert) pilot program, to manage iterative improvements of AI/ML devices efficiently. A PCCP is for ML-DSF (machine-learning-enabled device software function) devices. These devices improve their algorithm(s) performance through interactive modifications, including learning from real-world data. To decrease regulatory burden after approval/clearance, a PCCP describes anticipated modifications that may be made and managed by the manufacturer (e.g., through their Quality System and Good Machine Learning Practices (GMLP)) to provide a means to implement modifications that generally would otherwise require an additional marketing submission. A PCCP includes a description of modifications, modification protocol (to develop, validate, and implement a modification), and impact assessment (benefits, risks, and risk mitigations) and is submitted with the original device submission.

DHTs and products will continue to advance and enhance medical devices. DHT trends include continued and increased use of telemedicine and RPM tools, wearables, mobile health applications, FemTech, computer-aided detection (CADe) and diagnostic devices (CADx), and the use of generative AI. Leverage the FDA's DHCoE for resources and updates on Digital Health products and associated policies, regulations, and guidance documents.

Austin Wetmore
Legal Assistant

FDA Guidance in Transition:

Top Guidance Documents of 2023 and Implementation Considerations on the Path Ahead

FDA has issued 237 guidance documents in 2023, including 63 guidance documents issued by or in collaboration with CDRH. For context, this is an increase from the 206 guidance documents issued by FDA in 2022, with 53 of those guidance documents related to CDRH.

There are a few trends we have noticed with respect to FDA's issuance of guidance documents. **First**, as DuVal & Associates meticulously digested in the four "acts" of our "The eSTAR and I," Client Alert series, FDA has taken several steps through its guidance documents to modernize the 510(k) and De Novo premarket submission processes. Another trend we have observed is FDA's evaluation and modernization of software, Artificial Intelligence (AI) and cybersecurity requirements for medical devices, which has also resulted in several new guidance documents. Furthermore, FDA's attention toward trial monitoring formats and risks has also regained traction due to the impact of recent innovations that allow different interaction options with patients.

In the following list, we have identified those guidance documents issued by FDA in 2023 that we believe are particularly impactful for the medical device industry. The titles below include hyperlinks to the FDA website's document copies:

1. **Electronic Submission Template for Medical Device 510(k) Submissions (Final Guidance):** Originally introduced in September 2022, with the final guidance copy being issued on October 2, 2023, this guidance provides background on the structure of electronic submissions and outlines the required

information to be addressed within each portion of an eSTAR submission. FDA also asserts the currently allowed exemptions for interactive review responses, amendments, and withdrawal requests for 510(k) submissions under this format.

2. **Communications From Firms to Health Care Providers Regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products Questions and Answers (Draft Guidance):** This guidance offers insight into the FDA's current definitional interpretations of scientific information on unapproved uses (SIUU) including recommendations regarding what is relevant or scientifically sound to communicate. This includes guidance on proper disclosure statements to be included within a communication. FDA also addresses the proper relationship between SIUU and marketing or promotion regarding product use.

3. **Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions (Final Guidance):** Due to the rapidly evolving cybersecurity landscape, this guidance addresses FDA's updated recommendations for risk management in accordance with Quality System (QS) regulations as well as mitigation throughout a total product life cycle. FDA provides a detailed breakdown with applicable regulations, particularly CFR 820, regarding how a Secure Product Development Framework (SPDF) addresses security risk management, security architecture, and cybersecurity testing.

4. **Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring (Final Guidance):** This guidance cites FDA's allowance for particular, designated non-invasive remote monitoring device categories to maintain limited modifications to the indications, functionality, or hardware or software, without prior submission of a premarket notification.

5. **Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions (Final Guidance):** This "CM&S" guidance updates the 2021 draft by the same name and concerns FDA's approach to its assessment of modeling credibility as it relates to the support of premarket submissions (including 510(k) and De Novo classification requests). FDA provides eight categories of credibility evidence as relates to in silico device testing, CM&S used within medical device software, In silico clinical trials, and C&MS-based qualified tools.

6. **Breakthrough Devices Program: Guidance for Industry and Food and Drug Administration Staff (Final Guidance):** Superseding the 2018 "Breakthrough Devices Program" guidance, this final guidance describes FDA's policies regarding the Designation Request mechanism, criteria, and considerations for program entry. Further, FDA outlines the format of Breakthrough Device Sprint Discussions and Data Development Plans, as well as the pursuit of binding Clinical Protocol Agreements.

7. **Off-The-Shelf Software Use in Medical Devices (Final Guidance):** Replacing the 2019 document of the same title, FDA addresses its concerns regarding the use of OTS Software and recommendations regarding premarket submission documentation. OTS Software testing and development methodologies are considered. FDA also speaks to how changes to OTS Software may be evaluated in the case of an IDE submission and possible implications with product labeling.

8. **Content of Premarket Submissions for Device Software Functions (Final Guidance):** This guidance supersedes and replaces the 2005 "Content of Premarket Submissions for Software Contained in Medical Devices" guidance and provides FDA's recommendations for "basic" and "enhanced" levels of documentation, based on risk, regarding software design specifications (SDS); software development, configuration, and maintenance practices; and software testing for verification and validation.

9. **A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers (Final Guidance):** This guidance provides a Q&A-formatted discussion on managing risks to both participant safety and data integrity throughout all stages of clinical investigations. FDA considers the use of a risk-based approach in the development of monitoring plans, addressing identified risks, and communicating the results of monitoring.

10. **Informed Consent: Guidance for IRBs, Clinical Investigators, and Sponsors (Final Guidance):** Superseding and finalizing the 1998 and 2014 informed consent documents, this guidance includes FDA's address of proper informed consent language and clinical investigation descriptions. Further, this guidance notes the individual responsibilities of an IRB, a clinical investigator, and a sponsor.

11. **Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions (Draft Guidance):** This draft takes another step by FDA in considering the management and mitigation of risk, with PCCPs, regarding the implementation of AI/ML in device development and use.

Looking ahead, in 2024 we expect FDA to continue to expand its library of guidance documents regarding the increasingly intricate impacts of Artificial Intelligence (AI), Machine Learning (ML), and cybersecurity given the growing utilization of software within the use, development, and production of devices. Meanwhile, FDA's consistent concerns regarding biocompatibility will likely result in a further expansion of testing, conformity, and assessment recommendations ahead.

Content matters aside, the development and form of FDA guidance is itself under scrutiny as we ring in the new calendar year. Section 2505 of the "H.R.2617 - Consolidated Appropriations Act, 2023" has required, "FDA to publish reports concerning the FDA's communications to relevant stakeholders, including best practices for developing and disseminating guidance documents."

In response to Section 2505, FDA introduced a notice draft on January 3, 2024, with a request for comment by March 4, 2024. The "Draft Report and Plan on Best Practices for Guidance" provides current FDA considerations as to several key procedural elements. This report outlines practices such as the prioritization of guidance documents (as well as the development of strategies to adjust priorities as needed), facilitation of input, and publication standards.

While the "report" portion of the notice heavily rests upon precedent, within Section V. FDA sets forth a new "Section 2505 Guidance Plan." Concerning a transition plan for updating guidance documents that were issued during the COVID-19 public health emergency, FDA does not provide new information but rather makes reference to its March 2023, "Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies," guidance document with a confirmation that should the Administration change its approach, then such will be announced in the Federal Register.

Addressing its plans for efficient prioritization, development, issuance, and use of guidance documents, FDA has provided potential revisions and amendments to the accessibility of Good Guidance Practices regulation. Of potentially significant

consequence is FDA's reiterated claim that the 2011 GGP Report's authorization of initial interpretation "Level 1 guidance 'for immediate implementation'" with a note that it has not "fully implemented this best practice." See Draft Report, p.25. This is in contrast to the Administration's use of "Level 2" guidance documents to provide "minor updates" on previously existing guidance. Id. ***Furthermore, FDA highlights the value that "immediate implementation" of Level 1 guidance "without prior public participation" had as a key factor in its "success" regarding the rollout of guidance documents during COVID-19.*** Id. The maturation of the Administration's approach harkens back to the statutory instruction of 21 USC 371(h). Therein, the FD&C Act outlays requirements for the introduction of guidance documents but notably makes allowance for several implementation loopholes according to type:

> "(C)(i) For guidance documents that set forth initial interpretations of a statute or regulation, changes in interpretation or policy that are of more than a minor nature, complex scientific issues, or highly controversial issues, the Secretary shall ensure public participation prior to implementation of guidance documents"…
>
> "(D) For guidance documents that set forth existing practices or minor changes in policy, the Secretary shall provide for public comment upon implementation."

21 U.S.C. § 371(h).

Development of this conversation regarding the definitional requirements of 21 USC 371(h) merits close monitoring given the potential step toward expanded FDA implementation authority it may afford.

Further addressing Section 2505, FDA has provided remarks as to streamlining regulatory submissions via guidance documents. As touched upon by our top guidance list, one avenue under Administration review is its approval or clearance of PCCPs, such as for AI/ML devices. An emphasis is similarly placed on CDRH's maintained issuance of device-specific guidance to home in on performance criteria.

Lastly, FDA is contemplating the publishing of Guidance Agendas for Offices within the Office of the Commissioner.

If you would like to provide comment on the "Draft Report and Plan on Best Practices for Guidance," electronic submissions may be made at the Federal eRulemaking Portal at https://www.regulations.gov.

DuVal & Associates

Drug, Device and Food Law

DuVal & Associates is a boutique law firm located in Minneapolis, Minnesota that specializes in FDA regulations for products at all stages of the product life cycle. Our clientele includes companies that market and manufacture medical devices, pharmaceuticals, biologics, nutritional supplements, and foods. Our clients range in size from Global Fortune 500 companies to small start-ups. As one of the only dedicated FDA regulatory law firms in the United States, our mission and absolute focus is providing our clients with appropriately aggressive, yet compliant, guidance on any FDA-related matter. We pride ourselves not only on our collective legal and business acumen but also on being responsive to our client's needs and efficient with their resources. DuVal & Associates understands the corporate interaction between departments like regulatory affairs, marketing, sales, legal, quality, and clinical, etc. As former industry managers in the drug and device spaces, we have been in your shoes. Our firm has extensive experience with government bodies. We understand what it takes to develop and commercialize a product and bring it successfully to the market and manage its life cycle. Impractical or bad advice can result in delays or not allow for optimal results; while practical, timely advice can help companies succeed.

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