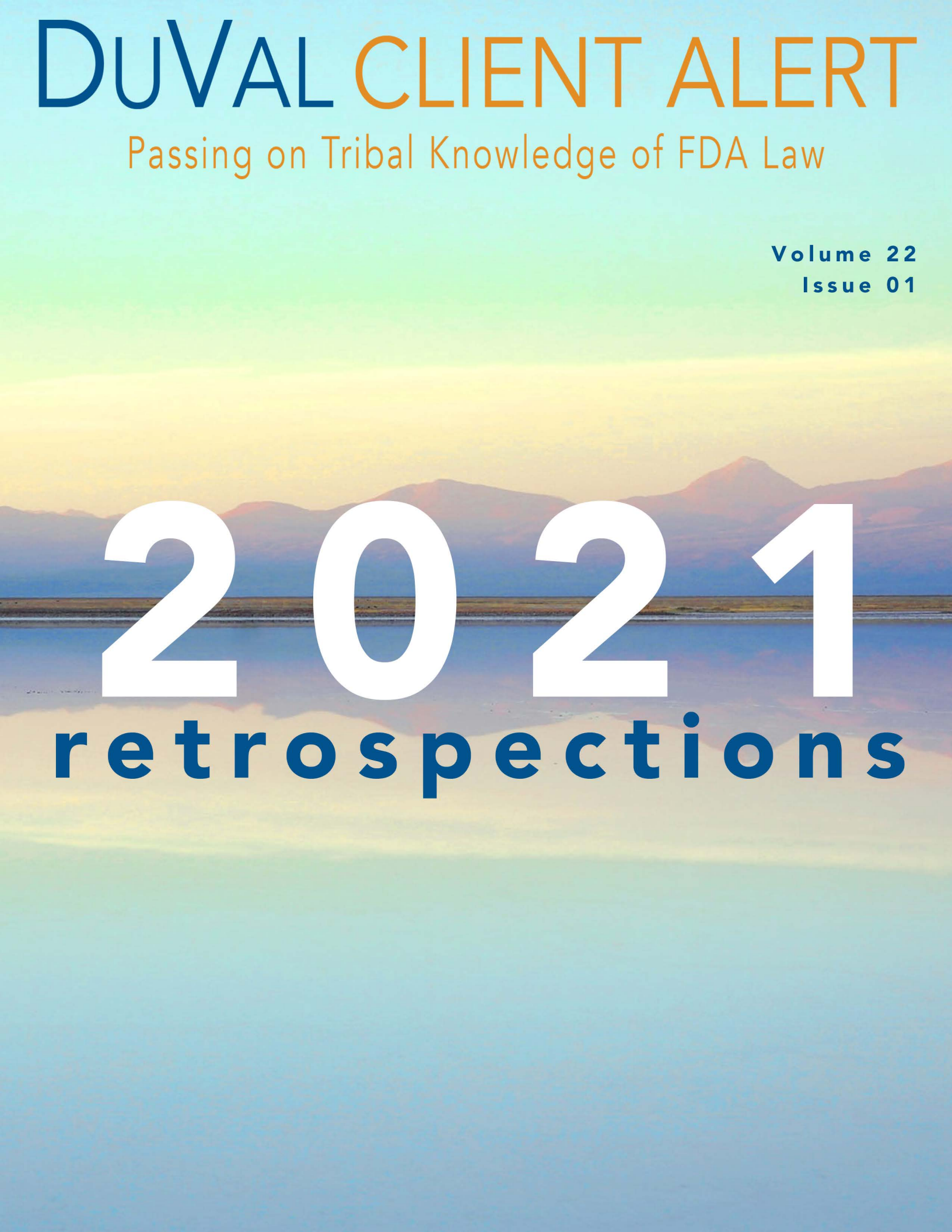
DuVal Client Alert

Passing on Tribal Knowledge of FDA Law

Volume 22
Issue 01



2021 retrospections

EXECUTIVE SUMMARY

In this Client Alert, DuVal & Associates, P.A. provides industry retrospections from 2021 and an outlook of our expectations for 2022. The retrospections are based on our collective experiences from 2021. From the frontlines at FDA to client strategy meetings, we share the industry and business insights we gained while advocating for device clearances and approvals, negotiating Pre-Submission meetings, responding to warning letters, and interacting with FDA and other regulatory bodies.

We also share our outlook for 2022, and identify how the developments from the past year may influence ongoing changes in the Q-Sub and De Novo Programs, FDA's new intended use regulations, and the regulation of digital health, among others. Finally, the new year will likely be shaped by the expected confirmation of Dr. Robert Califf, MD, as the new FDA commissioner, as well as the negotiation and authorization of the Medical Device (MDUFA V) and Prescription Drug (PUDFA VII) user fee programs. We hope our insights will be helpful to you and your organization as we (hopefully) transition to a more traditional regulatory landscape beyond the pale of COVID-19.

In concluding 2021, we also want to express our gratitude. We first thank FDA for their tireless work in protecting the public health and working with industry to speed innovative, life-changing pharmaceuticals and medical technologies, particularly in the current environment. While we regularly challenge FDA's decisions on behalf of our clients, we also understand the pressures FDA has been under during the recent past and appreciate their ongoing commitment to public service.

Finally, we thank our clients for the opportunity to work together in 2021. As you know, DuVal & Associates is deeply committed to working with you to manage your legal, regulatory and compliance needs as you work to achieve your device, pharmaceutical and nutritional supplement organizational objectives. It is a privilege to call you our clients, and we are grateful for the opportunity to serve you and your stakeholders.

In 2022, we remain committed to continue providing the broad services, practical advice, and innovative advocacy that has set DuVal & Associates apart over the past twenty years (first 2.5 years as Klepinski & DuVal), and we intend to do so through our most recently completed industry survey of FDA, DuVal Client Alerts, and other industry-leading efforts to pass on our tribal knowledge of FDA law.

Our best wishes and sincere thanks,

Mark

Topic Quick Links

Digital Health and Multiple Function Device

Aaron Hage, J.D.
Senior Director of Legal-Regulatory & Compliance

The digital health space continued to grow in 2021, and is becoming an integral part of healthcare during the COVID-19 pandemic. Over the past two years people have become more accustomed to telehealth and taking an active role in their health, including using wearable technology to monitor health and wellbeing.

Although polls show that most individuals prefer in-person healthcare visits,[1] there is no doubt that individuals also prefer to take a more active role in their own healthcare. This includes making use of their own wearable sensor data for diagnostic purposes, the use of mobile medical applications to allow individuals to make their own healthcare decisions, and participation in clinical trials using an individual's real-world data collected from digital health technologies.

The pace of digital health technological innovation continues to outpace the regulatory capabilities of FDA and its authority granted by Congress. The 21st Century Cures Act, passed into law over five years ago does not adequately address the current technology space and the regulatory issues presented. As a result, FDA has been left to regulate on the fly through guidance documents and enforcement discretion during the recent past. For example, because the 21st Century Cures Act was too prescriptive with respect to the ever-evolving and ever-growing medical device landscape, for which FDA could not reasonably keep up, FDA was required to take a risk-based approach to reasonably regulate the digital health landscape. Following the enactment of the 21st Century Cures Act, FDA released a number of guidance documents to help interpret its stance on the law and enforcement priorities, including the following: *General Wellness: Policy for Low Risk Devices*, *Policy for Device Software Functions and Mobile Medical Applications*; *Clinical Decision Support Software*; and *Multiple Function Device Products: Policy and Considerations*.

These guidance documents have broadened industry's ability to bring low-risk devices to the market and remain outside FDA's enforcement. In contrast, the guidance on *Multiple Function Device Products: Policy and Considerations* have allowed for broader

[1] 53% of individuals polled prefer in-person visits to video visits. Predmore ZS, Roth E, Breslau J, Fischer SH, Uscher-Pines L., *Assessment of Patient Preferences for Telehealth in Post–COVID-19 Pandemic Health Care*, JAMA Netw Open. 2021;4(12):e2136405. doi:10.1001/jamanetworkopen.2021.36405

applications within FDA review of medical devices. Under this policy, during a pre-market or postmarket review (e.g. PMA, 510(k) review, establishment inspection) FDA will only review the aspects of the device that are subject to FDA's enforcement. Those aspects that are deemed "other functions," whether those functions are outside the definition of a device, exempt from review, or subject to FDA's enforcement discretion, will only be reviewed to the extent they impact the device functions that are subject to FDA enforcement. This policy has a large effect on digital health products that incorporate both device functions, such as hearing aids and EKG monitors, with functions that are outside the scope of a medical device, such as sensors used to detect exertion during exercise.

Of course, FDA retains broad latitude to review these functions as part of an FDA review when the "other function" may be an impact on the device function. Therefore, companies need to think about how they design hardware and software to isolate the different functions and have a robust risk-management process that will allow the company to demonstrate why the "other function" would not impact the device function. Without such evidence FDA may dig into this "other function" and slow down the review of the device, delaying clearance or approval.

Beyond these guidance documents, FDA also implemented a Software Precertification Pilot Program in 2017 that would introduce a new regulatory pathway that focuses on assessing the safety and effectiveness of software and subsequent integrations based on a company's "culture of quality" rather than an evaluation of the software product. In general industry, specifically larger established firms, has applauded this pathway because it removes regulatory barriers to market. ***However, less established firms that have not proven the same "culture of quality" with FDA may remain stuck in an overly burdensome pathway that will place these companies, and ultimately the consumer, at a disadvantage.*** Yet, pathways to market for medical devices are statutorily defined within the Food, Drug, and Cosmetic Act (FD&C Act), and without amendment this pre-certification pathway is not likely to come to fruition. As of the end of 2021, the competitive and legal concerns regarding this pathway remain.

In 2022, FDA will continue to grapple with how to best regulate the digital health space. The Cures 2.0 Act was introduced into Congress in 2021, and will continue to move through Congress in 2022. However, the bill, in its current form, is not likely to trigger any short-term changes to the FD&C Act as it relates to digital health, including any implementation of FDA's pre-certification program. The current draft of the bill only requires that FDA provide a report that outlines how FDA ensures collaboration and alignment. In addition, the bill requires FDA to outline approaches and establish a task force to recommend ways for patients to engage in real-word data generation. ***Therefore, in 2022 we can expect the same level of uncertainty as we have seen in the past few years, as FDA continues to update its enforcement policy through a***

risk-based approach. This approach this cuts both ways. On the one hand companies can take advantage of FDA's enforcement discretion and find creative ways to remain outside FDA's regulatory scheme. On the other hand, these same companies will be subject to FDA's evolving positions and always be waiting for the other shoe to drop, which may create uncertainty for companies, especially smaller ones, looking to enter the digital health space.

FDA's evolving thinking will be once again in the forefront in 2022 as it once again expected to release updated and new guidance documents, including final guidance on *Clinical Decision Support Software*, and draft guidance on *Marketing Submission Recommendations for A Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions* and *Risk Categorization for Software as a Medical Device: FDA Interpretation, Policy, and Considerations*. Like the related suite of already released digital health guidance documents, these publications will provide digital health companies with leeway to navigate the FD&C Act, particularly for low-risk devices. ***However, companies will need to have the end in mind and plan for the regulatory position within FDA to shift at any time.*** In summary, we can expect more of the same in 2022.

Off-Label Communications and The New Intended Use Regulations

Bryan Feldhaus, J.D., LL.M
Vice President of Legal-Regulatory and Compliance

After a nearly five-year delay, FDA's new "intended use" rule, 21 CFR § 801.4, finally became effective on September 1, 2021. Under the new rule, FDA clarifies the types of evidence relevant to determining the intended use of a medical device under the Food, Drug & Cosmetic Act. Although some commentators have opined the new rule will increase exposure for drug and device manufacturers regarding off-label communications, we do not believe the amendment represents a material change drug and device manufacturers in 2022 for at least three reasons.

First, the new intended use rule does not stake out any new enforcement authority for FDA. Contrary to most new regulations, the new intended use rule does not represent an expansion of FDA's authority. Instead, FDA has explained that it simply codified its prior approach regarding the evidence relevant to determining a product's intended use. ***Specifically, the new intended use regulation provides examples of the***

types of evidence that FDA may use to determine the intended use of a manufacturer's products for the purposes of regulatory or civil action and/or criminal enforcement. Importantly, and notwithstanding the new rule, FDA continues to assert it is not limited to statements made by the manufacturer in determining intended use. FDA reaffirms it can establish a product's intended use based on knowledge of the following: actual use by customers, consumer conduct, the environment in which the product is sold, the absence of labeling, witness testimony, training programs, internal documents and financial arrangements, to name a few evidentiary sources.

Second, the new intended use rule limits enforcement based upon mere knowledge of off-label use. The concern with prior iterations of 21 CFR § 801.4 was that a manufacturer's mere knowledge of an off-label use by a health care provider (and that knowledge alone) could either (1) create an affirmative obligation for the manufacturer to provide information (called "adequate labeling") about those uses; or (2) subject the manufacturer to enforcement for off-label uses. This was a difficult burden for manufacturer's to accept given that the mere awareness of an off-label use could have been used by FDA to enforce off-label promotion. However, the recent amendments to Section 801.4 amend the regulation to confirm that ***a manufacturer's "mere knowledge" of an unapproved use cannot, in and of itself, establish a new intended use for prosecution purposes.*** Instead, FDA may consider such knowledge — along with other factors — as evidence of intended use, but cannot rely on mere knowledge alone. Although this change may ease some concern, manufacturers must remain mindful that FDA continues to possess substantial discretion in enforcing the off-label use or promotion of a medical device or drug. Moreover, if a manufacturer has knowledge of an off-label use then it is likely FDA also has that knowledge and can identify other factors to support an off-label use prosecution.

Finally, FDA's enforcement authority remains restricted by the First Amendment protections. For years, FDA has asserted that even if off-label promotional speech is truthful speech otherwise protected by the First Amendment, FDA can independently prosecute it as adulterated and misbranded the use was not approved. And just as frequently as FDA has made that argument, the courts have rejected it finding that truthful speech cannot be the basis for a civil violation or criminal prosecution. As a result, FDA has increasingly accepted off-label communications and begrudgingly accepted off-label promotion with appropriate disclosures/disclaimers to make it truthful and non-misleading. In fact, dissemination of literature about off-label uses is permitted under two current FDA guidance documents: "Responding to Unsolicited Requests for Off-Label Information about Prescription Drugs and Medical Devices" (December 2011), and "Distributing Scientific and Medical Publications on *Unapproved New Uses – Recommended Practices – Revised Guidance*," (February 2014).

FDA's more recent guidance entitled "*Medical Products Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers,*" (June 2018), states that "[i]f a firm communicates information that is not contained in its product's FDA-required labeling but that is determined to be consistent with the FDA-required labeling, FDA does not intend to rely on that communication to establish a new intended use." ***Thus, while the new "intended use" regulation permits FDA to rely upon a single piece of evidence to demonstrate a new, off-label intended use and prosecute a manufacturer, we do not believe the regulation materially affects FDA's enforcement of off-label promotion.*** After all, the First Amendment remains the polestar when evaluating the lawfulness of off-label communications, and operates as a restriction with respect to FDA's enforcement authority.

After considering the new intended use regulation and the landscape of off-label promotion, we do not believe much has changed with the amendment to Section 801.4. While there may be some initial growing pains associated with the amended Section 801.4, and even some expansion of FDA's authority under the new provision, the amendments were intended to clarify, and not change, the definition of intended use. Indeed, FDA's own comments affirm this conclusion. (See 86 FR 41383) ("FDA is finalizing amendments to its intended use regulations for medical products . . . to better reflect the Agency's current practices in evaluating whether a product is intended for use as a drug or device, including whether a medical product that is approved, cleared, granted marketing authorization or exempted from premarket notification is intended for a new use.") ***Therefore, although there was a five-year delay in implementing the amended regulation, we do not believe the amendments to Section 801.4 will materially change off-label communications in 2022 or beyond.***

Combination Products-Genus Medical Technologies v. FDA

Patrick Johnson, B.S.
Regulatory, Quality & Compliance Consultant

FDA's regulation of drug, device and combination products has an extensive legislative, judicial and experiential history that would lead one to expect that the regulatory pathway for a given product type, especially one that has been in the U.S. market for decades, should be well-established. ***In Genus Medical Technologies v. FDA[2], the decision of the United States Court***

[2] Genus Medical Technologies, LLC v. United States Food and Drug Administration, _____ F.3d_____, 2021 WL 1437211 (D.C. Cir. 2021)

of Appeals for the District of Columbia serves to reinforce that this has not been the case and illustrates the need for greater clarity in this regard.

Although the Food, Drug & Cosmetic Act (FD&C Act) sets forth distinctly different regulatory schemes for drugs and devices based on their respective statutory definitions (21 U.S.C. § 321(g) defining "drug" and (h) defining "device"), these definitions overlap in that both are "intended for use in the diagnosis of disease or other conditions," in the "cure, mitigation, treatment, or prevention of disease," or "to affect the structure or function of the body of man or other animals." The FD&C Act, however, also provides an exclusionary clause distinction based on a product's mode of action clearly differentiating that a device "does not achieve its primary intended purposes through chemical action within or on the body of man or other animals" and "is not dependent upon being metabolized for the achievement of its primary intended purposes."

Despite the exclusionary distinction, FDA has held a long-standing position that the overlap in the definitions of "drug" and "device" in the FD&C Act provides the agency the administrative discretion to determine which regulatory pathway to apply to a product. In the case of the Genus' Vanilla SilQ barium sulfate imaging agent, FDA chose to regulate the product as a drug with the expressed intent to ensure consistent regulation of imaging agents rather than as a device aligned with the product's mode of action. Due to the significant impact to the costs and timelines required to bring a new product to (and maintain it in) the market in the U.S. under the drug regulatory framework, Genus sought a declaration requiring FDA to regulate Genus's Vanilla SilQ product as a device.

Not surprising, in the Genus decision the D.C. Circuit concluded that "Congress established separate regulatory tracks for drugs and devices" that "Drugs and devices are subject to distinct regulatory regimes" and that ***"[i]t would make little sense, then, for the Congress to have constructed such elaborate regulatory regimes—carefully calibrated to products' relative risk levels—only for the FDA to possess the authority to upend the statutory scheme by reclassifying any device as a drug, no matter its relative risk level."*** _____ F.3d_____, 2021 WL 1437211 at 19 (emphasis added). The Court ruled that if a product meets the exclusionary "mode of action" clause criteria it is a device—it cannot and must not be regulated as a drug. ***The Court stated that interpreting the language any differently would read out the exclusionary clauses entirely and nullify Congress' intent to create two separate regulatory tracks for devices and drugs.***

In reaching this decision, the Court specifically excepted combination products. For a combination product the definition determination must consider the FD&C Act, Section 201(h) "device" definition, and how that statutory definition aligns with the definition

of Primary Mode of Action (PMOA) under the combination product statute, regulation and FDA guidance. See 21 U.S.C. § 321(h). Primary Mode of Action is very similar in phraseology and concept to achievement of its primary intended purpose, especially when one considers FDA's regulations further refine that meaning of PMOA, as follows:

> "[T]he single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product." 21 C.F.R. § 3.2(m).
>
> "In determining the primary mode of action of a combination product, the Secretary shall not determine that the primary mode of action is that of a drug or biological product solely because the combination product has any chemical action within or on the human body." 21 U.S.C. §353(g)

The concepts are very similar under both statutes. The lowest common denominator of the combination products regulation is that its focus is on the single mode of action that provides the most important therapeutic action to make the greatest contribution to the overall intended therapeutic effects. This PMOA definition is akin to the "achievement its primary intended purpose" under Section 201(h), albeit using a lot more words. ***This has made the determination of which statute to apply to any given product confusing.***

The current FDA focus from Genus is "to bring previously classified products into line with the Genus decision" focusing on products that meet the device definition but have been historically regulated as drugs (such as barium sulfate imaging agents). It will be of interest to see what impact the Genus decision will have in regard to the regulation of combination products in 2022.

The 510(k) Program

Mark DuVal, J.D., FRAPS
President & CEO

2021 was a mixed bag for the 510(k) program. The vast majority of products that come to the market are through the 510(k) path. As such, it remains critical that we evaluate how the FDA is doing with clearances. There have been both fans and critics of the 510(k) program. Critics say the program is cumbersome and driven by a three-part definition of (1) same intended use, (2) same technological characteristics, and (3) if there are different technological characteristics, do they raise different questions of safety and effectiveness. We understand that critique and we spend a lot of time ensuring FDA review staff interpret those terms with great fidelity so our clients can remain on the 510(k) path.

To understand FDA's view of the 510(k) path, one has to understand the history of Dr. Shuren's tenure with CDRH. Dr. Shuren has done many good things, but every improvement has a corresponding downside. For example, Dr. Shuren has greatly improved communications with industry but when expressed in terms of guidance documents, his leadership has resulted in too much communication. The proliferation of guidance documents has overwhelmed industry and FDA staff alike. He has also improved the expertise and professionalism of the staff, especially review staff, to address the myriad of new technologies coming to market. But that increased expertise often results in a silo-effect within FDA, which, in turn, invites ultra-granular examination of products that do not merit that much attention. Everything becomes a scientific expedition for FDA reviewers who justify their behavior by waving the banner of patient safety in everything they do, as if this should justify bad decision making. This banner-waving has been at the expense of generalists and scientific pragmatists who understand Least Burdensome requirements and the role of administrative agencies.

Dr. Shuren has also improved the meeting system within FDA, i.e., Pre-Submission meetings, 10-day meetings, LB Flag meetings, 21-day Submission Issues Requests (SIRs), and appeals (under 21 CFR § 10.75 and § 517A and advisory panel meetings). As a result, industry is guaranteed an FDA meeting, which has been a positive development. But the flip side is FDA can use those meetings to protract the review time and distract from meaningful or unequivocal direction. For example, one tactic many clients complain about is what we call being in "Pre-Sub purgatory" where the Agency requests multiple Pre-Subs for discrete issues in which little is

definitively resolved, but much time and money is expended. Each meeting simply kicks other issues (the can) down the road.

To return to Dr. Shuren's tenure, he has worked hard for over a decade to either rid CDRH of the 510(k) path, which he attempted to do early in his Administration using the Institute of Medicine (IOM) to examine the program and make serious recommendations and attempt to alter it through administrative fiat. Dr. Shuren forgot, or ignored the fact at that time, that he and CDRH are administrators, not legislators. CDRH has no place thinking it has the power and the authority to change something Congress has created. There have been many other attempts to dismantle the 510(k) program and they have been renewed more recently. There is not enough time to chronicle all those efforts in this year-end piece. Suffice it to say, the tack CDRH has taken over the last decade is to erode the edges of the 510(k) program for years by using guidance documents and undocumented decision-making within review groups to change or restrict the definition of the 510(k) program and a device's eligibility to stay on the 510(k) path. They have also unilaterally made increasingly burdensome data requests. The totality of that erosion has been substantial and the 510(k) program has been effectively reshaped by FDA over the years. As a result, FDA has been permitted to legislate, instead of merely regulate.

Our longstanding position is that the statutory framework of the 510(k) program is the last line of defense for an Agency that naturally gravitates to "more" whether it is needed or not. Without the 510(k) definitional framework and the Least Burdensome requirements, there would be nothing to prevent FDA from transforming the 510(k) program into a mini-PMA. This is, in fact, occurring as reviewers at the Agency often define many devices off the 510(k) path. Those reviewers believe the 510(k) program is archaic and restricts their ability to ask for the quantum and quality of data they want even if it exceeds Least Burdensome requirements. The Agency's reviewers have also gotten savvy by playing with the definitional elements of the 510(k) program. Reviewers are more frequently identifying minor technological differences with a device to suggest there are different questions of safety and effectiveness thus moving the device off the 510(k) path and onto the de novo or PMA path.

Once on the de novo or PMA path, FDA is not restricted in its data requests to 510(k) precedent or the standard of substantial equivalence, a comparative standard of safety and effectiveness. Instead, FDA has a clean slate in terms of the data they feel they can request because the standard for a de novo and PMA is reasonable assurance of safety and effectiveness in an absolute and independent sense, allowing the review staff immense freedom to ask for the type and amount of data they want. Industry needs the framework of the 510(k) program to keep FDA tethered to the comparative standard and must be aware of the FDA dynamics at work. FDA is

constantly requesting endless amounts of information for well-established device categories. Where predicate families came to the market years ago without clinical data, the Agency—almost in an unwritten initiative to "update" predicate families—asks for clinical data, where none was historically considered necessary. It often becomes data, for data's-sake.

Despite our concerns, there are bright spots at the Agency. We have seen glimmers of hope at the Division Director and Office Director levels. Rather than allow review staff to misinterpret the definitional determinations of the 510(k) program to push devices off of the path or requesting data that is not commensurate with or proportionate to the risk represented by these devices, Division Directors and Office Directors are giving meaning to Least Burdensome requirements by reigning in review staff and re-focusing their attention. Nonetheless, our appeal to the Agency is to do a better job training review staff to understand the definitional elements of the 510(k) program and to help review staff understand that the continual escalation of data requirements is concerning. .

In the end, it benefits everyone to work efficiently and effectively with the Agency and help them improve to better realize their twofold mission of speeding innovations beneficial to patients to the market while protecting them from unnecessary risks. It is natural that relatively inexperienced and overburdened staff at FDA tend to focus on finding and dwelling on patient risk rather than finding and embracing patient benefit. And it is through this misaligned focus on risk that the predictability of FDA's review processes has suffered. By redefining the 510(k) program, requesting more data, delaying submission reviews, and engaging in other tactics, FDA has imposed more and more obstacles to device approvals and clearances. And, unfortunately, the victims of FDA's tactics are the small and mid-sized medical device companies that are disproportionately burdened by FDA's obstacles as well as the United States citizens that should be able to benefit from innovative medical technologies.

De Novo Program

***Lisa Pritchard*, BSEE**
Vice President of Regulatory, Quality, Clinical and Engineering

In October, FDA issued a final rule on the De Novo Classification Process. The new regulation is 21 CFR Part 860 and becomes effective on January 3, 2022 (90 days after publication of the rule). In association with this update, FDA released multiple guidance documents to assist with the preparation of these submissions.

The De Novo program may be used for commercialization of a new low or moderate risk device for which no acceptable predicate device exists. The submission includes a request for classification of the device type as either Class I (low risk) or Class II (moderate risk), including justification for the selection, recommended special controls (if Class II is recommended), and evidence to support a reasonable assurance of safety and effectiveness for the device. Once the De Novo request is granted, the product is eligible for commercialization in the United States and may be used by future products as a predicate device for clearance through the 510(k) Premarket Notification program. The final rule permits De Novo submission either after submitting a 510(k) and receiving a not substantially equivalent (NSE) determination, or without submission of a 510(k) but following determination that there is no appropriate predicate device.

An important difference between the 510(k) program and the De Novo program as defined in the new rule is that manufacturing and Quality System Regulation (QSR) activities are outside the scope of a 510(k) review, so 510(k)s are not associated with "pre-clearance" manufacturing site inspections. The new rule provides FDA with the ability to determine that an inspection may be required to determine whether general controls would be sufficient to provide an adequate assurance of safety and effectiveness, or whether special controls will be necessary. Although this inspection is not intended for compliance review with the QSR and FDA states these will not be required for most De Novo submissions, time will tell how these inspections are handled and assigned.

Because the De Novo path does not include evaluation of substantial equivalence compared to a predicate device (which can provide the scope of testing required), submitters should be aware of the range FDA will have in asking for more test data which may include human clinical studies. It is critical for these submissions to ensure the submission advocates for the product and the verification and validation that has been followed. Ensure that risks of the product are well-characterized and provide support for the adequacy and sufficiency of the data provided.

Finally, De Novo submissions are associated with significant User Fees, even for small companies. The standard De Novo fee for FY22 (through September 30, 2022) is $112,457. For a company with a small business determination, the fee is still $28,114. Due to the significant range in expectations and this fee that is significantly higher than for a 510(k) submission***, we strongly recommend requesting a Pre-Sub through the FDA Q-Submission program to obtain feedback on the testing strategy prior to submission.*** See our Client Alert series on the Q-Submission program: *Navigating the Strange Pre-Sub Experience* for tips on success with that program.

Novel Device Programs

***Lisa Pritchard*, BSEE**
Vice President of Regulatory, Quality, Clinical and Engineering

FDA has two programs for novel medical devices: the Breakthrough Device Designation (BDD) and the Safer Technologies Program (STeP).

The 21st Century Cures Act defines breakthrough devices as ***(1) providing more effective treatment or diagnosis of a life-threatening or irreversibly debilitating human disease or condition, and (2) providing "breakthrough technology" or offering a treatment option when no other cleared or approved alternatives exist.*** The Breakthrough Device Designation (BDD) program has been gaining in popularity since its inception. This surge reached a high point with the hope for automated Medicare coverage through the CMS Medicare Coverage of Innovative Technologies (MCIT) program which was repealed before it began in 2021. This arguably would have been the most significant benefit from achieving BDD. Without it, the benefits of prioritization in the review queue, an additional, faster, communication pathway (sprint discussions), and management oversight throughout the review process remain important benefits.

In 2021, a little sister was born to the BDD program – the Safer Technologies Program (STeP). This program is very similar in concept to the BDD program but does not have the backing of regulation. As a result, we do not expect this program to be adopted as readily as the BDD program has been. ***The STeP program provides a pathway for products that are not eligible for the BDD program because they are used for a less serious disease or condition.*** Despite strong similarities between the BDD and STeP program, the advent of the STeP program left an important gap in the programs by not allowing eligibility for products that are not eligible for the BDD program for another reason (e.g., products that are intended for use with life threatening or irreversibly debilitating diseases or conditions) but may be safer but not more effective or fail to meet one of the secondary BDD criteria. We hope that this gap will be rectified, either formally through an update to the STeP program, or at least informally through acceptance of these products in the STeP program.

Unfortunately, FDA does not publish metrics for either of these programs, so it is difficult to know exactly how many have been submitted, accepted, and ultimately cleared or approved for commercialization. From our internal experience and research, we have not seen any STeP authorizations through late 2021. With respect to the BDD program, it appears a vast majority of requests for BDD have required some amount of clinical data. Of the 155 requests that we have been involved in or tracked, 111 (71.6%) are confirmed to have included clinical data, and only 8 (5.2%) are confirmed to have received the designation with no clinical data. Of those

supported by clinical data, the majority included more data than what could be considered feasibility or first in human. ***Unless metrics start to be published on the actual benefits of this program, interest in the program may begin to dwindle. Last year, we hoped for improved transparency. We reaffirm that sentiment this year.***

Q-Sub Program

***Lisa Pritchard*, BSEE**
Vice President of Regulatory, Quality, Clinical and Engineering

In January 2021, FDA updated its Q-Submission Program that provides for many types of interactions with FDA. ***For our clients, Pre-Submissions (Pre-Subs) and Submission Issue Requests (SIRs) have been the most popular and useful type of Q-Submissions.***

Pre-Subs can be very helpful to de-risk an IDE or commercialization (e.g., 510(k), De Novo, or PMA) submission. We have found these to be most valuable for obtaining feedback on proposed testing (bench or animal) or clinical study designs. We have seen an increase in the FDA suggestions for use of the Pre-Sub program. Unfortunately, this has also resulted in an increase in the amount of time that it can take to be granted a meeting (70-75 days for most groups within FDA). This should be planned for within the development timeline and strategic decision of whether to engage in a Pre-Sub or how often. Pre-Subs currently are not associated with any user fee. As a result, if they are well done, and ask provocative questions without giving FDA a blank check upon which to write down their wish list (which invariably is much longer than you would want or should be necessary), these can be very helpful in a US commercialization strategy. ***A key challenge that we have seen with this program over the past year is the increase in time to hold the meeting, and undisclosed prohibitions on accepting them within some divisions (e.g., OHT-7) due to excessive continued workload demands due to COVID-19.*** We are hopeful that 2022 will gradually return to a sense of normalcy with this program. Note that at this time, all meetings continue to be held remotely with no visibility to a return to in person meetings in the FDA White Oak facility. Details of how to be successful with this program are discussed in detail in our three-part Client Alert series *Navigating the Strange Pre-Sub Experience*.

Submission Issue Requests (SIRs) are the other popular Q-Submission type. ***SIRs provide an opportunity for obtaining feedback related to requests for additional information that may be received during a submission review.*** The content of these submissions is very similar to the Pre-Sub but is focused on the additional information requests and the proposed response strategy. Our experience has indicated that if an SIR is submitted within 60 calendar days of receipt of the AI request, FDA has been faithful about scheduling the SIR meeting within 21 days of

receipt of the request. If the SIR is received more than 60 days after the request, then the standard scheduling of about 70 – 75 days applies. This should provide a strong motivation to, whenever possible, get the SIR submitted within the first 60 days.

For 510(k) submissions, the strategy for the timing of an SIR request should also consider whether a Least Burdensome Flag (LB Flag) may need to be submitted. The LB Flag is an opportunity for an informal appeal. The deadline for submission of an LB Flag is 60 calendar days after the additional information letter is issued. The LB Flag also requires that you have tried to resolve the issue with FDA before submission. This is often done through the SIR. If an LB Flag may be needed, the SIR should be submitted no later than about 20 – 30 days after receipt of the additional information request to allow time for the SIR to be held, and if necessary, the LB Flag prepared and submitted within the 60-day window. At the present time, the LB Flag is only available for 510(k) submissions, so this is not a factor for IDEs, De Novos or PMAs. ***We urge FDA to consider expanding the LB Flag program to encompass other submission types, and to allow a larger window within which to submit them (such as any time within the review process).***

Least Burdensome

Kathy Herzog, BSME
Regulatory Consultant

The year 2022 marks the 25th year since Congress first directed FDA to use a "least burdensome" (LB) approach when reviewing device applications with the enactment of FDAMA in 1997[3]. ***The intent of the LB approach is to hold FDA accountable to require only the minimum information needed to establish a new or modified device has reasonable assurance of safety and effectiveness during review of premarket applications.*** Unfortunately, FDA's implementation followed Lou Holtz's quote "When all is said and done, more is said than done."

Within the last decade, Congress reinforced the requirement for a LB approach to premarket application review through additional updates to the LB provisions of the FD&C Act[4] with FDASIA[5] enacted in July 2012, and the 21st Century Cures Act enacted in Dec 2016. On February 5, 2019, FDA issued guidance entitled *The Least Burdensome Provisions: Concept and Principles* to identify approaches to implement

[3] Food and Drug Administration Modernization Act is referred to as "FDAMA".
[4] *See* Sections 513(i)(1)(D)(i), 513(a)(3)(D)(ii), and 515(c)(5)(A) of the Food, Drug, and Cosmetic (FD&C) Act.
[5] Food and Drug Administration Safety and Innovation Act is referred to as "FDASIA".

the LB provisions of the FD&C Act. In this guidance, ***FDA defines least burdensome as "the minimum amount of information necessary to adequately address a relevant regulatory questions or issue through the most efficient manner at the right time."*** The term "necessary" means ***the minimum required information that would support a determination that an application provides reasonable assurance of the effectiveness of the device.***

The LB concept applies across the total product lifecycle (TPLC) of any product that meets the statutory definition of a medical device per Section 201(h) of the Act, applies to all premarket regulation activities (e.g., 510(k)s, PMAs, pre-submission meetings), and is intended to expedite regulatory clearances and approvals but does not change applicable premarket submission requirements or the requirement for valid scientific evidence.

Our experience has shown that FDA's implementation of the LB provisions of the Act has not been consistent and the impact to device sponsors on time and money is as significant as the lost opportunity to serve public health. Key areas where LB issues more frequently arise relate to requirements for biocompatibility testing and clinical performance data. Negotiating LB evidence needs with FDA can be quite challenging and can feel more like "Most Burdensome." This is particularly true when FDA requests more evidence to clear or approve a new device than required of a predicate or similar device without scientific rationale, or does not respond in kind to a reasoned and scientific proposal for performance testing. In those situations, we encourage industry to leverage the "**LB Flag**" to seek upper management input on a LB issue for deficiency requests that do not have NSE (not substantially equivalent) potential but where the requested information is not considered by the sponsor as LB or not required of a predicate device and the issue is not resolvable with the lead reviewer (must request within 60 days of receiving the deficiency).

Key strategies for device sponsors to help facilitate a LB approach with their premarket submissions include:

1) Use of pre-submission process to promote early and collaborative discussions between FDA and a device sponsor;
2) Clear and concise premarket submissions;
3) Completion of thorough benefit-risk analyses, to identify serious risks and to compare with the safety profile of similar devices;
4) Use of FDA-recognized voluntary consensus standards when completing testing;
5) Judicious consideration of LB and alternative approaches to clinical and non-clinical performance data (e.g., use of non-US data, literature

analysis, and/or real-world evidence (RWE) for clinical data; use of prior testing or use of computational modeling to reduce bench or animal performance testing);

6) Clear and sound justification for why the performance data plan (clinical and non-clinical) is sufficient to support a determination of reasonable assurance of safety and effectiveness;
7) Consideration and justification for the use of post-market data collection to reduce the premarket data collection when appropriate and feasible; and
8) Use of available actions to address LB issues, including trying to resolve a LB issue with the lead reviewer, throwing a LB Flag to involve upper management, submitting a Submission Issue Request (SIR) to address one or two critical topics that involve LB, and submitting a formal appeal to address FDA decisions on premarket applications where FDA law was not followed, including LB provisions of the Act.

FDA's implementation of the LB provisions is evolving. Increased FDA staff training and transparency through FDA-self and third party audits[6] and public performance metrics, and industry actions to identify and address LB issues will help to reinforce the importance of the LB principles and hold FDA accountable to effective and consistent implementation of these principles during review of premarket applications.

Important Guidance Documents We Encountered

***Lisa Pritchard*, BSEE**
Vice President of Regulatory, Quality, Clinical and Engineering

The FDA issued 157 guidance documents in 2021 including 42 issued by or in collaboration with CDRH. About one-quarter of those are related to the COVID-19 pandemic. Following is a list, in no particular order, of what we consider the top 12 guidance documents of the year that relate to the Medical Device industry:

1. Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act (Draft Guidance): This draft guidance provides helpful background information about the regulation and authority for postmarket surveillance studies and outlines for completing required reporting. The comment period for this draft guidance is closed and release of the final

[6] *See* FDA's Report to Congress entitled *Least Burdensome Training Audit*, dated June 8, 2018 (required under the Cures Act). See also the United States Government Accountability Office (GAO) FDA Medical Device Review report entitled *Evaluation is Needed to Assure Requests for Additional Information Follow a Least Burdensome Approach,* dated December 2017.

version of this guidance made the CDRH "A-list" for guidance document priorities for FY2022.

2. Content of Premarket Submissions for Device Software Functions (Draft Guidance): Provides a proposed update to the classic 2005 Software guidance. Notably, this proposes a change from content based on three levels of concern to two documentation levels (basic and enhanced). The comment period on this draft guidance is open until February 2, 2022.
3. Testing and Labeling Medical Devices for Safety in the Magnetic Resonance (MR) Environment (Final Guidance): Final version of draft issued in 2019, and replacement for 2014 guidance. This version applies to all medical devices that may be used in an MR environment and provides recommendations for the testing and labeling that should be provided for these devices.
4. Technical Considerations for Non-Clinical Assessment of Medical Devices Containing Nitinol (Final Guidance): Replacement for 2020 version of the same guidance; applies to medical devices with a patient-contacting component containing nitinol. Provides recommendations for testing and submission content based on variability that can be causes by the alloy composition, thermal history, surface processing and preconditioning to which this material is exposed.
5. Electronic Submission Template for Medical Device 510(k) Submissions (Draft Guidance): The comment period for this draft guidance recently closed, and the release of the final guidance is on the "A-list" of CDRH guidance document priorities for FY2022. This provides recommendations for use of the FDA eSTAR electronic submission template for 510(k) submissions. While the ability for an automated system to help ensure all required content is provided, we are concerned about the lack of ability to integrate advocacy, which we find to be essential to successfully navigating through FDA review. FDA clarifies their intentions to move to a requirement for electronic submission of 510(k)s within this draft guidance, indicating that a date will be announced within FY2022.
6. Select Updates for Unique Device Identification: Policy Regarding Global Unique Device Identification Database Requirements for Certain Devices (Draft Guidance): The comment period for this draft guidance closes in early January 2022; release of the final version of this guidance is on the "A-list" of CDRH guidance document priorities for FY2022. This draft guidance lays out the Global Unique Device Identification Database (GUDID) submission requirements for Class I and Unclassified devices. Of note, UDI labeling and standard date formatting for these devices, except for those that are implantable, life-supporting or life sustaining, before September 24, 2022.
7. Requests for Feedback and Meetings for Medical device Submissions: The Q-Submission Program (Final Guidance): The Q-Submission program has become an increasingly important component of many US commercialization

strategies. This guidance provides helpful information about the available types of Q-Submissions and their required content – the art of a Q-submission, though, comes in the gray area of deciding what to ask (and what not to ask), and when it makes sense to do them. One thing to be aware of in this version of the guidance is some conflicting language around pre-meeting feedback for SIR meetings. At least one FDA division has interpreted the language to mean that if you request a meeting, they do not need to provide pre-meeting feedback unless it is specifically requested. Make sure to request both.

8. Safer Technologies Program for Medical Devices (Final Guidance): This guidance introduced a sister to the popular Breakthrough Device Designation program. This program is for products that do not qualify for the BDD program due to use for a less serious disease or condition and are expected to provide a significant improvement in safety.
9. Acceptance Review for De Novo Classification Requests (Final Guidance): This guidance outlines the criteria FDA is using to determine whether a De Novo submission will pass or fail the initial acceptance review and whether a Refuse to Accept letter will be issued. It is important to ensure this is used as a pre-submission checklist to prevent the review from being unnecessarily delayed. It is also important to be well familiar with this checklist to identify when review staff is inappropriately using the RTA as a mechanism to extend their review clock without adversely impacting user fee metrics. The key change from the previous 2019 guidance is the update to require all information from both the required and recommended lists into one required list, and expanded detail of required information to provide for submissions supported by clinical trials.
10. De Novo Classification Process (Evaluation of Automatic Class III Designation) (Final Guidance): This guidance provides very general information about the De Novo program, how to go about the submission, and what to expect during the review process. Of note, this guidance also provides a few recommendations specific to use of a Pre-Sub to inform a De Novo submission. Due to the significant range that FDA can have in data expectations for a De Novo, and the significant associated User Fees, we strongly recommend the Pre-Sub process be used prior to a Direct De Novo submission.
11. Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions (Draft Guidance): As the use of computational modeling continues to increase, this proposed guidance document provides recommendations for a nine step process for assessing credibility of the model selected, and 10 categories of credibility evidence. The comment period for this draft guidance ends on February 22, 2022.

12. Transition Plan for Medical Devices Issued Emergency Use Authorizations (EUAs) During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency (Draft Guidance): During the COVID-19 pandemic, many products have come to market through the Emergency Use Authorization (EUA) process. An EUA provides a temporary path to market while there is a declared public health emergency. This draft guidance outlines a plan for removing products that are marketed through an EUA after the COVID-19 public health emergency is terminated. The draft guidance requests companies with EUAs for reusable life-supporting or life-sustaining devices such as ventilators, to notify FDA of their intent to submit a marketing submission to continue distributing the product after the EUA is terminated. It also outlines recommendations for the inclusion of a transition implementation plan within the full commercialization submission for products that are intended to remain on the market [e.g., through De Novo or 510(k)], a plan for enforcement discretion for continued marketing of products with a full commercialization submission that has been accepted for review but whose review remains ongoing as of the EUA termination date, and expectations for product not intended to continue to be distributed after the EUA termination date. Note that a similar guidance was also issued to define the transition plan for devices that have been under pandemic enforcement policies. The comment period for both of these guidance documents is open until March 23, 2022.

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 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.

CALL ON US FOR ASSISTANCE WITH YOUR REGULATORY NEEDS

For more information, visit our website at www.duvalfdalaw.com or call Mark DuVal today for a consult at 612.338.7170 x102.