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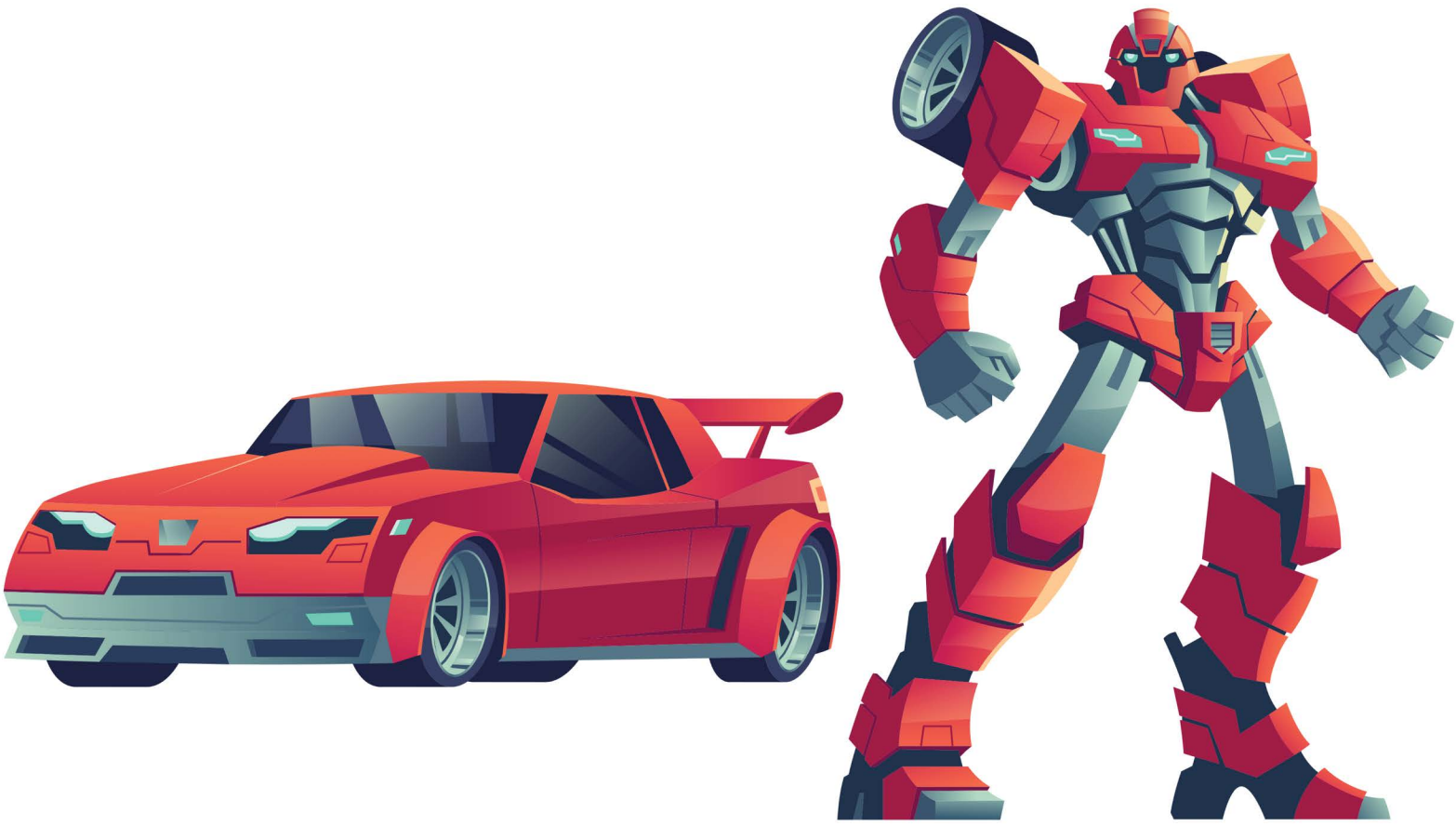
When Do 510(k) Modifications Transform a Device?



When Do 510(k) Modifications Transform a Device?

INTRODUCTION/EXECUTIVE SUMMARY

Transformers® start out as a car or truck, but with a few gyrations they morph into a fighting machine capable of attacking enemies or defending friends. Surely, they do not look anything like they did before, but has their essential character changed, has their intended use? Do the changes significantly affect their safety or effectiveness? They always had the same purpose, and arguably the same technological characteristics. Is Superman® any different than the seemingly mild-mannered Clark Kent disguised as a reporter? He changes in a phone booth or closet and comes out Superman. He is always the same Superman just packaged differently. He has the same strengths—fast as a powerful locomotive, able to leap tall buildings in a single bound, weakened by Kryptonite. How do we define change?

For medical devices, change is constant, expected and essential to the continuous improvement of medical devices. But wholesale and unnecessary change to the statutory and regulatory scheme governing when that change is immediately reportable to FDA, and requires FDA clearance in the form of a new 510(k), is not. It is even more problematic when that interpretative change is instigated by an Agency that would like to grab more authority and jurisdiction through its self-created guidance documents. In this Client Alert, we explore the pros and cons of FDA's draft guidance on modifications to 510(k)s now that it has been out in draft form for some time.

The draft guidance. Last August, FDA introduced a draft guidance overseeing change or modifications to medical devices entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (hereinafter

Modifications Guidance). This draft guidance, when finalized, will supersede the Agency's 1997 guidance, "K97-1, Deciding When to Submit a 510(k) for a Change in an Existing Device," (hereinafter K97-1). This guidance addresses when a change or modification to an existing change can be documented in an internal letter-to-file (LTF) and when it requires a new 510(k) clearance from FDA before it can come to market. If a change is documented in an LTF, FDA may only review and question that change after-the-fact when it is discovered in routine inspections every two years. In the meantime, the modified device is released to the marketplace. FDA over the years has increasingly challenged modifications that it believes should have been submitted to the Agency in a 510(k) premarket notification.

The old guidance and the 2011 guidance misstep. The draft guidance is set to replace the existing guidance from 1997. You may recall the industry furor FDA sparked when it proposed a predecessor guidance in July 2011 which theoretically required most changes to a medical device to be the subject of a new 510(k). The 2011 proposed guidance called a great many, too many, modifications a "change" requiring the submission of a new 510(k). Industry called upon Congress to actively intervene to stop FDA which Congress did by statute. When Congress passed FDASIA in 2012, it forcibly required FDA to withdraw its proposed 2011 modifications guidance and to revert back to its previous guidance famously known as Blue Book Memorandum K97-1. ***It was an embarrassing setback for FDA to have Congress not only direct it to withdraw this proposed guidance and revert back to its previous guidance, but to also submit any new proposed guidance to Congress before publishing it.***

The balance between the company's quality system and FDA review. ***The problem with FDA's 2011 proposed guidance was that it upset the balance Congress originally tried to strike by having industry take joint responsibility with FDA for determining when changes or modifications to existing cleared devices require a new 510(k).*** That balance was to be

achieved by giving companies the discretion to apply the regulation and eventually FDA guidance to the myriad of situations they confront in the world of device modifications. Companies were expected to have processes in place to effectuate the change and to validate them if necessary all under the umbrella of their quality system under 21 CFR section 820. During inspections, FDA is to review where firms have used LTFs and their corresponding rationale for using a LTF versus filing a new 510(k). The idea and system were built on trust, shared responsibility and administrative practicality.

The foundational intent was that change would be embraced, if not too significant, and only if it truly negatively affected safety and effectiveness would a new 510(k) be required. Changes that were insignificant and/or improved a device would not be the subject of new 510(k). Industry should be incentivized to make incremental improvements (safety or effectiveness) to devices, not penalized. Industry historically has been allowed great latitude in making the initial decision, but FDA in its predictable fashion has attempted to assert itself more forcefully into the process and replace its judgment for that of industry. Indeed, the review of device modifications suddenly became a focal point of many routine FDA inspections with FDA rooting around in design files much more deeply than it had in the past. This resulted in situations where the FDA would write warning letters for a modification that triggered a cascade of observations, e.g., a violation of Part 806 failure to report a correction or removal; failure to conduct and recall; and failure to file a new 510(k).

The concern is that the Agency already complains incessantly about a lack of resources and yet it wants even more command and control over approved devices that are merely being modified or changed. *FDA cannot and should not attempt to do everything and must prioritize its precious resources. We question if this is the best use of FDA's time and attention given other far more pressing priorities. FDA must resist the temptation to transform its intended role of regulatory oversight to performing the roles*

of an employee of a medical device manufacturer. Such an expansive view of FDA role would most certainly have a negative effect on the availability of safe and effective medical devices.

SOME QUESTIONS

Why is FDA proposing the Modifications Guidance? This is a great question. AdvaMed, MDMA and many other industry groups all felt the previous K97-1 guidance was serving industry well. But whenever FDA provides additional guidance it, like any other governmental agency, is not satisfied with the amount of discretion retained by industry. ***If you consider the scope and insidiousness of governmental regulation overall, FDA continues its creep into the management of a medical device company. FDA's authority never shrinks or fades, it continually invades and grows.*** Even though the proposed Modifications Guidance makes changes that seem small and incremental, the totality of the changes morphs the original intent, the balance, and the dynamic Congress originally intended to achieve. The concern of the trade associations is that the judgment of company personnel will be substituted with that of an FDA reviewer with little to no practical real-world experience and with an ideological predisposition to not entrust judgment calls to industry.

For example, on other fronts, FDA today wants to be on the developmental team of companies by having endless Pre-Submission meetings which are often little more than FDA's attempt to design and dictate clinical trial requirements and performance testing. FDA's inspections are increasingly prescriptive in their approach and the content of their recommendations, which seem to ignore the famous *Utah Medical* case in which the court stated there are many "roads to Rome" in how a compliant quality system can be built and operated. And FDA still can't figure how to accommodate the First Amendment in its proposed regulation of the promotion and dissemination of off-label information despite its many losses in court. FDA wants to direct our marketing efforts.

Similarly, how will the proposed Modifications Guidance work in practice? The bad part is that FDA, once again, has increased the stakes and the burden for documenting change. The good part is that it does seem to leave the initial decision and process up to the manufacturer for review by FDA in subsequent inspections. Yes, there is still manufacturer discretion to make these decisions under its risk management system, but it has been limited by examples found in the guidance document. ***We agree with most examples in the proposed Modifications Guidance, but disagree with many others. FDA has become very prescriptive about what is a change that can be documented by an LTF and what requires a 510(k). And the real problem is the liberal license FDA staff actually takes once a guidance document is released. The interpretive calls get increasingly conservative and prescriptive over time.***

How far does the guidance deviate from the original change? This is where we will give FDA some credit. They did attempt to follow K97-1 and some updating was helpful, but there are instances where FDA is outside the scope of the statute and regulation, the net effect of which will be to require more 510(k) submissions as opposed to LTFs. FDA from time-to-time loses its moorings from the original statute and regulations which we discuss below.

Why is industry leery of asking FDA whether a 510(k) is required? It is obvious to anyone in any regulated industry that if you go to an administrative agency with a problem, they will find a way to assume jurisdiction and authority and it will be a painful experience because in practicality, common sense judgment, and speed typically go out the window. It is axiomatic that industry would like to avoid filing a 510(k) for a change if possible primarily because FDA's 510(k) program has become unwieldy, unpredictable and impractical, which translates into extremely burdensome. ***Interfacing with FDA on an original 510(k) is often an extreme exercise in patience and restraint. A modified 510(k) is no different.*** It is a more burdensome process than Congress imagined, resulting in increased

costs, unacceptable delays, and a loss in therapies being available to patients and physicians in a timely basis. This has severely impacted the medical device ecosystem which relies on venture capital and corporate investors who no longer invest in early stage companies because the risk of going through FDA as well as obtaining CMS reimbursement is unpredictable. Venture capital has been decimated by government over-regulation, but that is a story for another time.

Suffice it to say companies fear the gauntlet they will face when the increasingly academic-minded, risk averse, Ph.D. and physician-driven, FDA gets its hands on a simple 510(k) where the device is already cleared and a small modification has been made. Today's FDA drills down into levels of granularity unheard of in previous years and turns most everything into a science project. So even if there was an inclination to go to the FDA to ask about small changes to devices, FDA's answer to the question whether a 510(k) is needed is predictable—an invariable "yes"—while the 510(k) review process is anything but predictable.

Is this a solution in search of a problem? To those steeped in this industry for several decades or more, we ask what is it that led to more guidance? With the exception of a few devices, no one we know who has been around industry for decades have ever seen FDA or anyone suggest that a new modifications guidance is a pressing need due to product problems. There will always be anecdotes and one-offs with modified products. ***But FDA must resist regulating to the rare exception because it means they will over-regulate the vast majority of devices on the market at great cost to society.***

If you were to ask field investigators, local FDA District Offices, and the Office of Compliance, they want the authority to dig deeply into modifications during inspections. They have a command and control mentality and want the discretion of the industry to make LTF/510(k) filing decisions limited in scope. FDA's true colors were revealed in the July 2011

draft that was required to be withdrawn by the Congress. The trade associations estimated it would have required a three hundred percent (300%) increase in 510(k) filings. FDA had to be shocked when industry stood up for itself and pushed back. Despite FDA's stated desire for more guidance, there doesn't seem to be any objective and pressing trend supporting the unnecessarily disruptive need for more guidance—73 pages worth. ***Why FDA feels the need to rewrite a policy that has worked so well can only be explained by understanding the never-ending growth of a bureaucracy not willing to entrust any level of judgment to the industry it regulates.***

LET'S START AT THE BEGINNING—A VERY GOOD PLACE TO START, THE STATUTE AND REGULATION

The statutory language employed by Congress and embellished upon in regulations deliberately chose the words "major change to the intended use" and "significantly affect safety or effectiveness" to trigger the threshold requirement for a new 510(k). FDA has, ever since, been trying to shift that balance to require more and more changes to be subject to new 510(k)s. Industry has justifiably asked FDA to maintain the balance that has been maintained for decades, especially under the previous guidance famously known as Blue Book Memorandum K97-1. Industry and FDA shared responsibility under this guidance and equilibrium was struck that served FDA, patients, physicians and industry well.

FDA renews its attempt to refresh its K97-1 guidance and distance itself from its disastrous July 2011 draft. While this proposed guidance maintains a better balance there are still some opportunities for improvement. FDA also introduced a separate guidance "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" which addresses a specific type of device change but reveals with more granular details FDAs most recent thinking on the application of risk management in filing decisions. We will address this guidance in a subsequent Client Alert.

The new guidance rightfully starts with the standard in 21 CFR 807.81(a)(3), which states that a 510(k) must be submitted when:

> (i) A change or modification in the device that *could* ***significantly*** *affect the safety or effectiveness* of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process.
> (ii) A ***major*** *change or modification in the intended use* of the device.

THE OLD AND NEW MODIFICATIONS GUIDANCE

FDA in the old guidance, K97-1, rightfully focuses on the words "significantly" and "major." It states:

> The key issue here is the phrase 'could significantly affect the safety or effectiveness of the device' and the use of the adjectives '***major***' and '***significant***' sometimes lead to subjective determinations. Because of this manufacturers have frequently expressed the need for more specific guidance in applying the regulatory standard for their decision-making.

The proposed Modifications Guidance starts well and re-states the underlying balance that the original K97-1 Guidance promoted. In it FDA reiterates the K97-1 quote above and adds (emphasis in bold, italics and underlining added):

> This draft guidance preserves the basic format and content of the original, with updates to add clarity. The added clarity is intended to increase consistent interpretations of the guidance by FDA staff and manufacturers....***The net effect of the QS regulation is to require that, when manufacturers of a finished medical device make a change in the design of a device, there is a process in place to demonstrate that the manufactured device meets the change in design specifications (or the original specifications, if not change was intended).*** They must

keep records, and these records must be made available to an FDA investigator (see section 704(e) of the FD&C Act). ***For many types of changes to a device, a new 510(k) may not be required per 21 CFR 807.81(a)(3).***

The proposed Modifications Guidance also restores the cherished flowcharts, which were absent from the 2011 draft to the disappointment of many. The latest draft reiterates many of the concepts from the original 1997 guidance: always compare a change with the 510(k)-cleared version of a product, changes must be assessed both individually and in aggregate, and document your filing decision. It adds some helpful guidance for documenting decisions and insightful examples that illustrate the boundaries between some key criteria (and will likely require some fine tuning to be consistent). It seeks to clarify the longstanding confusion between the meaning and significance of ***intended use*** (what a device does) and ***indications for use*** (when and where to use it). ***Most profoundly, it endorses the concept of applying risk management to make the 510(k) filing decision. This changes the flowchart. The new, and often repeated, question in the proposed Modifications Guidance is now: "Does a risk assessment identify new or significantly modified risks?"***

The New Standard—Safety is Freedom From Unacceptable Risk

FDA logically construes from the regulatory language "could significantly affect the safety or effectiveness" to mean changes in risk may affect safety. The newly proposed standard states that safety is "freedom from unacceptable risk." ***The question we have is how does "freedom from unacceptable risk" compare with and, more importantly does it alter, the statutory and regulatory standard of whether it "could significantly affect safety or effectiveness?"*** Our concern that is it does, but only time will tell with concrete applied examples. It may be a perfectly benign way of interpreting the regulatory standard through risk management, but we aren't sure how it will play out. Risk management provides the most complete repository of known risks for a product and answers both what

changes impact risks and the significance of these risks to safety. Therefore, the manufacturer's risk management file is the logical source for determining regulatory questions significantly affecting safety. We welcome this change, grounding any safety analysis in the comprehensive risk management files maintained by device manufacturers over the life of a product. This is an excellent use of FDA's only consensus standard on risk management for devices, ISO 14971, and well within its scope. It provides for a consistent process, cross-functional involvement, and manufacturer ownership of risk management decisions.

Risk Management Enables Distributed Decision-making by Manufacturers

This guidance expands the risk management file's influence as a pivotal input for determining when to file 510(k)s for introducing a change to an existing device. Relying on manufacturer risk management files provides a real foundation to make risks assessments by measuring the impact of changes against preexisting risk analysis and prospective criteria. This elevates the analysis from being a merely subjective opinion separately produced for each product change or retrospectively imposed during an inspection of records. Risk management enables the consistent analysis of varied and at times subjective inputs to produce a single discrete conclusion. Without the decision-making framework and basis for known risks that risk management provides, there is no resolution when reasonable people may disagree. Differences can become protracted when there are no criteria to judge between two valid perspectives. Leveraging manufacturers' ISO 14971 risk management processes ensures the same rules apply to each change assessment and provides the nomenclature for interpreting their significance to ensure a consistent outcome. FDA's consensus standard, ISO 14971, puts the responsibility squarely on the device manufacturer to define the risk acceptability, thresholds, parameters, and review processes.

This applies risk management to a regulatory decision-point, as with recalls and adverse events, industry is again confronted with complex inputs that must be distilled into singular outcomes: i.e., either the change significantly impacts our risk assessment and we file a 510(k), or it does not and we move onto our old familiar questions from K97-1. The outcome of this decision entirely relies on the manufacturer. ***The new challenge is that the analysis must be supported by the risk management file, and not just a free form letter-to-file. But we still recommend stand-alone LTFs dedicated to analyzing the modification in the context of the statute and regulations to ensure the risk management analysis is consistent with the requirements of the statute.***

Manufacturer Risk Management Files Will Determine 510(k) Filing Decisions

In practice, what does this mean? It primarily means your risk management process and the structure of your existing risk management files will now drive 510(k) filings. The guidance provides generally that a change that creates any new risks or significantly modifies existing risks should result in filing a 510(k). A significantly modified risk is described only at a high level as increased probability or severity or changes that "significantly affect a device's risk profile." FDA's companion guidance "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" reveals with much more nuance the small shifts in risk parameters that may result in 510(k)s. Expounding on the same regulatory standard in the software change guidance, FDA requests a new 510(k) for new or modified:

- causes leading to a hazardous situation,
- hazardous situations, or
- risk control measures,

when these may lead to significant harm. FDA acknowledges that this assessment starts with the risk parameters "as identified and defined by the manufacturer in the risk management file for the device." With the

proposed guidance, manufacturers will evaluate the impact upon risk (and safety) of a change against its own risk management file using its own processes and procedures. The manufacturer defines the thresholds between categories for risk acceptability, severity, probability, etc. The risk assessments, the precision (or generality) of the causes and hazardous situations will now be decisive factors when to file a 510(k) for all of your current products. The quality of this risk management file has always been essential, now it will be visible. Beyond ensuring safe products, your risk management file and program will also determine the latitude your company has to improve products on its own. We think this is the right place for this vital responsibility. However, it requires thoughtful preparation to do accurately and well.

Risk Management is Ongoing, Different Conclusions Are Not Wrong

FDA field investigators reviewing documents perhaps years later will have the benefit of hindsight, where the manufacturer making the original decision is always dealing with incomplete information. The Greek philosopher Heraclitus said, "No man ever steps in the same river twice, for it's not the same river and he's not the same man." This is true for medical devices and the FDA regulatory environment as well. The prevailing "current" we encounter is always changing as FDA intersects with our devices. FDA is always evolving, with new people, new information, new policies, new priorities, and new guidance documents. FDA has an immense challenge in keeping its staff trained and moving in the same direction, with the added complexity of both Center and distributed District field-based staff. Devices are changing too, incrementally improving and evolving clinical applications, which is what this guidance permits within certain regulatory parameters.

It is likely that FDA field investigators will be the first to review these 510(k)-filing decisions with the supporting risk documentation. The variability in interpretations and outcomes in these reviews could be disruptive. ***Risk***

management does not depend on perfect decisions. Rather, it provides a means to make a good decision followed by a continual process of monitoring and refining over time. This is closed-loop risk management. We are pleased to see FDA acknowledge this in the proposed guidance:

> In general, the assessment of risk in deciding whether to submit a new 510(k) should identify all possible risks, and then focus on risks whose existence and characteristics are supported by objective scientific evidence. *It is not necessary to focus on hypothetical risks that are not supported by scientific evidence or those that are determined to be negligible due* to both the low probability of occurrence and low severity of harm.

The FDA reminds us here that we are not to unnecessarily speculate on risks, but to focus on what we know and can assess at the time the risk is reviewed. Later reviews may bring new perspectives and information, but these new inputs do not mean past decisions were incorrect. This is an excellent insight, that risk determinations associated with a modification to a 510(k) device should exclude hypotheticals and negligible rates of occurrence, as well as require a scientific basis to be included in an analysis – this removes a great deal of distractions from real analysis. Any challenges to risk-based conclusions should meet these criteria as well. Based on the above, we are optimistic that FDA will respect decisions made that are consistent with its own ISO 14971 consensus standard, i.e. that the decision can avoid hypotheticals and negligible rates of occurrence and apply the ISO 14971 standard of "reasonably forseeable consequences or combinations of events that can result in a hazardous situation…."

Manufacturers are Responsible for Safety, but Must Show Their Work

Manufacturers following their own ISO 14971 risk management procedures and thresholds should be given great deference in their filing decision related to risk. Risk management provides the only FDA-recognized

process for managing the impact of device changes on safety. It is the right process to endorse industry ownership of risk and its first responsibility to make reasoned decisions for safety. Where industry makes the decision, FDA still has oversight of both the design changes, risks assessments and 510(k) filing opportunities. Manufacturers must prepare for more scrutiny of their risk management files. These need to be ready to demonstrate that 510(k) filing decisions are consistent with their existing risk management positions. Is your risk management file ready?

An example where FDA's interpretation does not meet the spirit of the law and regulations. Take the example of a change to a contrast injector manufactured by a major company that has years of experience in the business. One of the major issues is bubbles in the injector line which can cause a safety issue for patients. The company provides a better sensor and makes the same injector with the new sensor available to customers. The old sensor was the best in the industry and certainly was not a safety issue. The new sensor is an improvement, an enhancement. The manufacturer did the verification and validation studies it always does to substantiate its safety and effectiveness.

Two years later FDA conducts a routine inspection of the company and discovers the design modification. The investigator alerts CDRH Center office staff and Office of Device Evaluation and the Office of Compliance get involved. CDRH issues a warning letter arguing that a) the device is adulterated and misbranded, b) there is a violation of Part 806--failure to make report of corrections and removals, c) the company must commence a recall, and d) the company must file a new 510(k). The company argues that the Agency should not be disincentivizing companies from making such safety improvements.

The company is in a position where the new device has replaced almost all pre-modification devices and FDA now takes the position that the current device cannot be distributed and sold because it is adulterated and

misbranded. FDA wants a recall communication to be sent to all customers. The pre-modification device has been discontinued so this presents a big problem for the manufacturer. This is an example where FDA does not see the forest for the tree in front of it. The big picture screams "no problem here." But FDA acts as if it is a major violation of the Act. This is always what concerns industry as FDA gets more prescriptive in guidance. Field investigators are often not very practical and can be very black and white in their interpretations. The company eventually negotiated a successful resolution, but these issues could have been avoided with a more common sense application of the old K97-1. One can only assume it will only get worse under the proposed Modifications Guidance.

SOME ISSUES WITH THE PROPOSED MODIFICATIONS GUIDANCE

Requesting manufacturing and quality information. ***There are a few areas in which we take issue with the proposed Modifications Guidance.*** The first is that the Agency has made a fairly sweeping inclusion of manufacturing process changes, the need for sterilization data has been expanded, and the issue of whether a modification alters a medical practice. These are all areas that under FDA's Least Burdensome Guidance would not, in most cases, be relevant to a 510(k) determination, yet they appear in the proposed Modifications Guidance as important and seemingly non-negotiable for device changes. For example with respect to manufacturing, FDA's Least Burdensome guidance states as follows:

> ***Manufacturing and quality control information should not be part of a 510(k) submission unless the information relates to the equivalency determination.*** The 510(k) process focuses primarily on the end product of the manufacturing process rather than the manufacturing process itself. The Quality Systems (QS) regulation requires device manufacturers to perform design verification and validation testing, as appropriate, on new devices as well as on modifications to existing devices.

If manufacturing and quality control information is not to be part of the original 510(k), then it certainly should not be part of a modifications decision. To request manufacturing information continues FDA's inexorable march to close the gap between a PMA and a 510(k) which completely distorts the intent Congress had in mind for the 510(k) program. The 510(k) is supposed to be limited to asking does the device 1) have the same intended use, 2) does it have the same technological characteristics, and 3) if it has different technological characteristics (which are allowed), do those difference raise different questions of safety and effectiveness? The subject device is to enjoy the underlying regulatory presumption that the predicate has established the fundamental safety and effectiveness of the predicate family. The standard is one of comparison to a known entity. With a modification, the starting point of the device is even closer in lineage, it is the same device that has been modified. The request for manufacturing and quality control information is even more PMA-like.

Requesting sterilization information. *Another area is sterilization which has become a fixture in 510(k) submissions, due to the demands of today's FDA, but that was not contemplated in the Least Burdensome guidance.* The data are supposed to be maintained by the manufacturer, not submitted in the 510(k). The guidance states as follows:

> In the updated guidance, a least burdensome approach to sterility in 510(k) submissions is employed which relies on a manufacturer's legal obligation to comply with the Quality Systems requirements, including the assurance of the sterility of finished devices. This policy applies to 510(k)s for all devices labeled as sterile, regardless of the method of sterilization that a manufacturer chooses to employ. Sterility of the finished device is addressed through the regulatory requirement that a manufacturer conduct proper process verification and validation studies. These studies ensure the adequacy of the manufacturing process, including the sterilization process, to produce a device which meets the specifications described in the manufacturer's 510(k). *The*

> *data resulting from these studies, however, would not be submitted in the 510(k), but rather would be maintained by the manufacturer.*

See, The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry, see Hyperlink #12 (October 4, 2002).

If it is FDA's position that data from sterilization studies should not be submitted in a 510(k), then a modified device should not have to submit such data either. Again, like the request for manufacturing and quality control information, the request for sterilization data is more PMA-like and unnecessary given the spirit of the Least Burdensome requirements, especially for modifications which are a step removed from the original 510(k).

Deciding if it alters a medical practice. ***With respect to whether a modification alters a medical practice,*** FDA through its Office of Chief Counsel (OCC) long ago had this to say about FDA's attempted use of clinical utility and standard of care in making a 510(k) determination in the ReGen Report quoted below:

> The first issue was the appropriate review standard for a 510(k) submission. ***OCC advised that review of a 510(k) involves a comparison of a device to a predicate rather than to a standard of care and that there was no legal foundation for requiring a company to demonstrate clinical benefit in a 510(k).***

See, Preliminary Report "Review of the ReGen Menaflex®: Departures From Processes, Procedures, and Practices Leave the Basis For a Review Decision in Question," in September 2009, page 9 (emphasis added in bold and italics).

Again, the point is if FDA cannot require a comparison to a standard of care in medical practice then it should also be irrelevant in a modification decision. The key is the statutory language "could it significantly affect safety or effectiveness," which is a far different standard than "does it affect medical practice." ***Comparison to a standard of care is distinctly not part of the substantial equivalence determination, so it should not come in through the back door under the analysis of a modification.***

When a labeling change is not a change to the intended use and when is it not "major." ***The main area in which the proposed Modifications Guidance seems to struggle, and with which there may be controversy, is determining what is a "major" change to the intended use.*** This is where FDA's proposed Modifications Guidance runs headlong into issues with the First Amendment and cases like the Howard Root/Vascular Solutions case, discussed below. First, we have had experience with FDA on this matter. We have found from time-to-time FDA review staff "stuffs" the intended use statement upon clearance with words that are beyond the scope or the purpose for the intended use or indication statement. Then if it is later changed by the company with verification and validation activities, the Agency takes the position that a 510(k) is required because the change was a "major" change to the intended use statement.

A case study example—Pharma Tech. In the case of Pharma Tech, we had a situation in which the Office of In Vitro and Radiologic Devices ("OIR") at the 11th hour, after a difficult clearance that went on appeal, "stuffed" the intended use statement with the following additional highlighted (and underlined) statement for a glucose test strip:

> *GenStrip Test Strips with calibration codes 4, 10 and 13 are for use with OneTouch Ultra, Ultra2, and UltraMini Meter purchased before July 2010.* They are used to quantitatively measure glucose in fresh capillary whole blood samples taken from the finger, forearm or palm. Testing is done outside the body (in vitro diagnostic use). They are

indicated for use by people with diabetes in their home as an aid to monitor the effectiveness of diabetes control. The system is not intended for the diagnosis of or screening for diabetes mellitus and is not intended for use on neonates.

Because the large retailers thought consumers would be confused by the limiting dating, they refused to carry the product which they had committed to putting on their shelves. The company decided to do another validation study that updated the labeling to read:

> *GenStrip Test Strips with calibration codes 4, 10 and 13 are for use with OneTouch Ultra, Ultra2, and UltraMini Meter purchased before July 2013.* They are used to quantitatively measure glucose in fresh capillary whole blood samples taken from the finger, forearm or palm. Testing is done outside the body (in vitro diagnostic use). They are indicated for use by people with diabetes in their home as an aid to monitor the effectiveness of diabetes control. The system is not intended for the diagnosis of or screening for diabetes mellitus and is not intended for use on neonates.

This was submitted in a LTF and not a 510(k) because we believed it was not a major change to the intended use statement. Upon a subsequent plant inspection, the field investigative staff and review staff at the Center would not consider whether the change was actually a change to the intended use or indications for use. FDA also gave no import to the word "major" in making its assessment of whether the change to the intended use involved a major change to the intended use. OIR essentially took the position that any change to any words appearing in the intended use statement is a major change to the intended use. They sent the company a warning letter. Dr. Maisel, Deputy Director for Science and CDRH Chief Scientist, in his decision overturning OIR's definitional determination, agreed with our argument that when Pharma Tech obtained its clearance order it had the

same intended use as the predicate, which did not include any date limitation. Dr. Maisel's rationale is set forth below:

> ***To determine whether the change to the date limitation is a major change or modification in the intended use, I reviewed the indications for use for the GenStrip.*** In clearing GenStrip via K103542, FDA found that it had the same intended use as the predicate device (LifeScan OneTouch Ultra Blood Glucose Monitoring System – K002134). This predicate device did not have a purchase date limitation in the Indications for Use statement or in the labeling. Under Section 513(i)(1)(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), a finding of substantial equivalence means that the indications for use of the new device fall within the intended use of the predicate device and, therefore, the two devices have the same intended use. ***When I reviewed the clearance decision for the GenStrip in K103542 and the predicate to which it claimed substantial equivalence, I concluded that the intended use for these devices does not include a date limitation. Therefore, the change to the date limitation is not a major change or modification in the intended use.***[1]

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[1] Dr. Maisel also accepted our argument that the change to labeling did not "significantly affect the safety or effectiveness of the device" because it did not expand to another patient population, and even if it did, FDA's K97-1 guidance permits such a change. Dr. Maisel used FDA's definition of "indication for use" and discussion of "patient population" to conclude as follows:

> "***Even if the date limitation were considered a part of the indication for use and a change to it an expansion to a new patient population***, FDA's Guidance, "Deciding When to Submit a 510(k) for a Change to an Existing Device," issued on January 10, 1997, notes:
>
> > '***If the expansion is to a population*** with similar demographics, diagnosis, prognosis, comorbidity and potential for complications as the original, ***then a new 510(k) is not ordinarily expected***.'
>
> ***Ultimately, the modification to the date limitation does not introduce a new patient population distinct from that which was cleared via K103542***. This conclusion is based on the fact that the limitation in date of manufacture applies to the device and not the intended patient population."

This case illustrates, and we have had many more like it, the liberty investigators and review staff can take with the statute and regulations. Investigator and review staff argued strenuously this constituted a major change to the intended use, yet upper CDRH management did not agree. The point is that even with guidance, FDA has broad interpretive freedom which it frequently exercises and sometimes abuses.

FDA has created a new blended standard that is not faithful to the statute and regulations. The proposed Modifications Guidance seems to blend the standard for labeling here by combining two separate standards into one, i.e., whether the modification "could significantly affect the safety or effectiveness" with the change for labeling, i.e., whether a change is a "major change in the intended use of the device." We believe it is inappropriate for FDA to combine these. But in the proposed Modifications Guidance FDA does just that to come up with a new standard:

> *Rather than referring to "intended use" as a determinant* in deciding when to submit a new 510(k), *this guidance identifies several types of labeling changes or modifications that have a major impact on intended use* and thus would require the submission of a new 510(k). *FDA interprets major changes in intended use to be a type of change that could significantly affect safety or effectiveness.*

FDA has taken two disparate standards and created a new one that it admits is different than the statutory standard. FDA explicitly states "***Rather than referring to intended use as a determinant*** in deciding when to submit a new 510(k)." FDA admits to an extraordinary and deliberate departure from the statute. FDA is explicitly rejecting the standard created by the Congress and inserts its own "major impact" standard in its place. FDA also blends it with the standard applied to physical changes to the device, i.e. that the change "could significantly affect safety or effectiveness."

The standard of whether a change is a major change to the intended use is a different exercise than deciding if the change has a major impact on the intended use of a type of change that could significantly affect safety or effectiveness. One examines if an indication is consistent with (i.e. properly subsidiary to) the intended use statement, using the criteria found in FDA's General/Specific Use Guidance (1997). The approach proposed by FDA in the Modifications Guidance is agnostic to the consistency of the indication; it focuses on impact. So even if a device has the same intended use under the examination of an indication, if it has a major impact (whatever that means) on the intended use, it could be a "major change" to the intended use. ***One standard looks for sameness in general purpose, the other looks for a major impact in safety and effectiveness. The key is not in examining the impact, but in determining if the use is subsidiary to the general intended use statement.*** Remember FDA defines intended use and indications for use as follows:

> "***intended use means*** the general purpose of the device or its function [or what the device does] and encompasses the indications for use…. ***indications for use …*** describes the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended.'"

See "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]" (February 2014) at page 16. [Emphasis added in bold and italics.]

When we discuss "indications" in relationship to a general "intended use" statement cleared by the FDA, we use the analogy of an umbrella. A general intended use statement is, in reality, a bundle of specific indications for uses, albeit not stated specifically in the cleared general intended use statement. Specific indications fall under the protective reach of the general intended use umbrella and are deemed on-label. Without specifically stated indications, a device seemingly could be used for everything under

the general intended use, and yet could be promoted for nothing specifically.

The General/Specific Use guidance applies to a major change to the intended use. That leads us finally to the interpretive implications of whether an indication is on-label and therefore not a major change to the intended use. Let us look no further than the Howard Root/Vascular Solutions case to see how different the government's interpretation can be from industry's interpretation. In U.S. v. Vascular Solutions (2016), a federal jury acquitted a medical device manufacturer and it's CEO of all charges, which included misbranding products due to alleged "off-label" promotion. This case is about the Vari-Lase device cleared for treating varicose veins which was launched in June 2007. It was cleared with a broad intended use statement for use in ablating varicose veins and for the incompetence and reflux of superficial veins in the lower extremity. A "Short Kit" version was promoted for use in short vein segments, which includes perforator veins. The main question in the case was whether the claims and conduct of the sales representatives in promoting for use in perforator veins constituted off-label promotion in violation of the Food, Drug & Cosmetic Act. The device had a general intended use statement for the following:

> "The VARI-LASE Bright Tip kit (and Console) is indicated for the treatment of varicose veins ***and*** varicosities associated with the Great Saphenous Vein, ***and*** for the treatment of incompetence ***and*** reflux of superficial veins in the lower extremity."

Emphasis added in bold, italics and underlining.

The irony in this case is that the FDA Branch Chief Neil Ogden under cross-examination essentially testified that the use in perforator veins was on label, emasculating the government's off-label case, because the specific use in perforator veins fell under the umbrella of the general intended use. Vascular Solutions and Root were acquitted of all charges. The point is that

the government took a fanciful and arbitrary decision that the indication for use was not under the general intended use and required a new 510(k), and brought a CEO to a criminal trial for it. The jury did not agree, cutting through the government's flimsy and overly-technical logic, and acquitted him on a unanimous vote.

This is precisely what industry should fear the government doing when it applies the "major impact" standard in the proposed Modifications Guidance. In the Vascular Solutions/Howard Root case, the government was essentially arguing a theory similar to major impact, but didn't prevail. Applying the logic of the case to a modification, instead of simply focusing on whether this was a "major change to the intended use," which it was not, the government posits an alternative theory which allows for more subjectivity and FDA discretion, i.e., major impact on intended use. This standard is not true to the statute or regulations and doesn't consider all the recent First Amendment cases in which an independent arbiter came to a different conclusion than FDA about labeling.

CONCLUSION

The bad part is that FDA, once again, has increased the stakes and the burden for documenting change in the proposed Modifications Guidance. The good part is that but it does seem to leave the initial decision and process up to the manufacturer for review by FDA in subsequent inspections. Yes, there is still manufacturer discretion to make these calls under its risk management system, but it has been limited by examples found in the guidance document. We agree with most examples in the proposed Modifications Guidance, but disagree with many others. FDA has become very prescriptive about what is a change that can be documented by an LTF and what requires a 510(k). And the real problem is the liberal license FDA staff actually takes once a guidance document is released. In practice, the interpretive calls get increasingly conservative and prescriptive over time.

The application of risk management principles is helpful in the context of modifications and, even though risk/benefit is not part of the 510(k) determination, it is useful in assessing the import of modifications. The proposed Modifications Guidance offers many examples, most of which seem to make a logical and fair conclusion on whether a device is subject to a LTF or new 510(k). Other examples are questionable. Only time will tell how FDA applies this guidance.

We do think FDA strays a bit from the statute and regulations in looking at manufacturing and quality control issues, sterilization, and whether any change alters the practice of medicine. The place where the proposed Modification guidance seems to stray the most is in the area of labeling changes, i.e. whether the modification results in a "major change to the intended use." We discuss an example of FDA's misinterpretation of what is a change to the intended use statement by chronicling an FDA appeal we made on behalf of a client. In that appeal we challenged OIR's interpretation of whether a change was a major change to the intended use, and won. FDA's thinking on labeling (intended use versus indications for use) is fairly rudimentary and seems to avoid its General/Specific Use Guidance, the First Amendment, and the developing case law. Again, we will have to see how this guidance works when used in real life.

DuVal & Associates
Drug, Device and Food Law

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