DuVal Client Alert

Passing on Tribal Knowledge of FDA Law

Pre-Sub Series
Episode 1

Navigating The Interesting Sometimes Strange Pre-Sub Experience

#1 - The Idea Behind It

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INTRODUCTION/EXECUTIVE SUMMARY

In this three-part series, we will explore the strange world of FDA Pre-submission meetings through the metaphor of the Addams Family—the popular 1960's TV comedy. You remember the characters—the patriarch and matriarch, Gomez and Morticia, who play the Office and Division Directors at FDA who in their running of the household are completely unaware that their family just doesn't fit into the real world, that people are afraid of their ways, and don't understand their intentions---which are often out of sync with the world outside their home. Their children Pugsley and Wednesday, who are played by the reviewers at FDA, find creative ways to torture and play menacingly with sponsors. Then there is Uncle Fester as the Chief Medical Officer who explores creative new scientific theories for exploding a sponsor's submission. Cousin It is played by the biostatisticians who speak unintelligibly and scurry in and out of a submission distracting from the focus of what needs to be done. Thing is played by the FDA's outside consultants who seem to have a hand in

> *They're creepy and they're kooky, mysterious, and spooky, they're altogether ooky...*
>
> *The FDA Family*

everything but frequently disappear only to reappear and attract attention-grabbing ideas that derail the discussion. Grandma is played by the Ombudsman, eccentric and often not present or even that helpful, but always beloved. And then there is Lurch, the Consumer Safety Officer, your escort when you need to visit the Addams family home, who shows disapproval by shaking his head and communicating in grunts and groans. Finally, they live in this spooky mansion, Building WO66, filled with this odd cast of characters. The family gives sponsors a warm reception upon arrival, but they are thoroughly examined before entering and a sponsor walks through the halls with great trepidation holding a tense smile with unease not knowing exactly what is going to happen next, for the experience is strange and unfamiliar.

The idea behind this series. When we first wrote about the Pre-Submission (Pre-Sub) program in 2013 our Client Alert was entitled "*The Pre-Sub Meeting and Gilligan's Island: When a Three Hour Tour Can Turn Into a Shipwreck*." The Pre-Sub process has matured a great deal since then and they are now a fixture in our industry and are often quite helpful. The idea behind this series is to alert the reader to issues that crop up in the use of the Pre-Sub (Q-Sub) program, identify areas of improvement (should the FDA read them), and help the reader anticipate and proactively address these issues in the course of their Pre-Sub. We first explore the idea behind the Pre-Sub meeting and some of the overarching concerns we have with them. Then we cover the more technical aspects and strategies behind a Pre-Sub. Finally, we cover some anonymous but real-world examples of Pre-Sub issues we have encountered.

Do we need Pre-Subs? When FDA first conceived of the idea it was tempting to applaud it and we still do. But understand the Pre-Sub came about because FDA failed to meet its mission to review submissions in the time allotted—despite never-ending additional piles of cash awarded it by industry user fees and Congressional appropriations to allow it to hire more

and more people. Like a school district, the additional money FDA receives is generated by user fees and additional rising general appropriations. With that money FDA engages in mission creep, spends money on things the user fees were never intended to cover, and adds countless numbers of additional siloed positions of "expertise" and other administrative positions that add little to—and actually encumber—the user fee goals (i.e., to expeditiously clear and approve devices within Least Burdensome requirements). This extra money and personnel and siloed expertise allows the FDA to become increasingly academic and engage in scientific fishing expeditions that bog down the review process with incredible scientific minutiae. Many in industry believe that FDA is actually bothered by incremental innovation, and by the Pre-Subs that introduce them, because it interrupts the cloistered work life of so many at FDA who would rather operate without sponsor objection or debate and who prefer to do business without interacting on the phone or in person.

Pre-Subs came about to institutionalize and regiment what FDA was failing to do under the old process, i.e. interact meaningfully with the sponsor and make binding commitments to the sponsor to assist in the expeditious development of technologies. Pre-Subs represent yet another way for FDA to add review time to its review clock without being penalized for it by the Congress. Despite these concerns and criticisms, it is overall a good process. It is helpful to get both industry and FDA in one room to dialogue, debate and resolve matters (we address the resolution issue in our third Client Alert of this series). But like any bureaucratically created process, if not kept in check, the Pre-Sub process will grow (and has grown) over time and complexity and adds time, money and more burden to the clearance and approval process.

And a prediction: the user fee/appropriations-insatiable-FDA will soon ask for specific user fees for the Pre-Sub process, adding to rising registration fees, submission fees, and other ever-expanding, and rarely-decreasing fees, which bog down and make immeasurably more

expensive to bring to market the innovation that fuels the medical device industry. But fighting the expansion of user fees and increase in FDA appropriations and mission creep is better left for another day.

The original idea—expand the discussion - The idea behind the original Q-Submission Guidance came about as a result of the Medical Device User Fee Amendments of 2012 (MDUFA III) which included a commitment to institute a structured process for managing interactions with industry. Industry formerly relied on the pre-IDE program which had more limited value because the type, size and complexity of the clinical studies clearly needed to be tailored to the regulatory expectation of whether the study was to support a substantial equivalence determination, a Class II moderate risk de novo grant or a PMA approval. As a result, the program, of necessity, needed to expand to include regulatory pathway discussions. ***Industry finally had a mechanism to discuss both the regulatory pathway and the quantum and the quality of the data to support clearance or approval.*** This can now include performance data (e.g., engineering bench testing, biocompatibility testing, human factors, animal testing, and clinical data). The initial Pre-Submission Guidance, published on February 18, 2014, implemented the broader Q-Submission (Q-Sub) Program, which includes Pre-Submissions (Pre-Subs), Submission Issues Meetings, as well as additional opportunities to engage with FDA. The new Q-Sub Guidance was issued on May 7, 2019 and is entitled "*Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program*." The Q-Sub Program expanded the pre-IDE program to include options for many types of communications between sponsors and FDA including Pre-Subs, Submission Issue Requests, Study Risk Determinations, Informational meetings, and other types of Q-subs (i.e. PMA Day 100 meetings, Agreement and Determination meetings, and Breakthrough Device Designations). In this series, we will focus only on Pre-Subs.

Don't fall into the suggestion to use the 513(g) request - Despite the idea of expanding the discussion to include the regulatory pathway, when the Pre-Sub process was introduced, the FDA began, ironically, to deny the sponsor the opportunity to discuss the regulatory pathway. In our first handful of Pre-Subs with FDA, after the guidance was first issued in 2014, FDA incredulously tried to deny our clients the opportunity to discuss their chosen regulatory pathway, usually because FDA had a different idea on which pathway the device should take. We had to create a boilerplate email to convince the FDA review staff that we were entitled to discuss the regulatory pathway with FDA in a Pre-Sub—using FDA's own words against them. Once we regurgitated FDA's own words back to them, we were allowed (reluctantly) to join the regulatory pathway discussions with the amount and type of data needed. Our letter mostly solved the problem, ***yet from time to time today FDA still wants to bifurcate and relegate regulatory pathway discussions raised by sponsors to the 513(g) process.*** Sponsors should reject this suggestion and point out that it is critical to any discussion of how much data are needed to get a device to market is to first agree upon the appropriate regulatory pathway. The 513(g) process has shown itself to be rather useless, a waste of time, and almost always slanted towards an FDA finding of a more difficult pathway for the sponsor. The 513(g) process is not a collaborative process and has shown itself to be impractical and of little utility because it does not allow face-to-face discussion and debate. It is also far from Least Burdensome because it is time consuming and impractically divorces itself from the discussion about data which should be inextricably intertwined.

The Pre-Sub arises in several different contexts

A. The first is when a Pre-Sub is truly a collaborative meeting held early between FDA and the sponsor before the data are developed. In many cases the sponsor uses the Pre-Sub meeting to try to persuade FDA to its desired regulatory path and clinical program. In this situation, the Pre-Sub is truly performing the role it was designed to play (i.e. an early dialogue with FDA to prevent missteps in the sponsor's development program). The problem with the pre-IDE meeting in the past was that it became a protracted approval path unto itself and did not result in definitive, but rather couched and qualified, advice. FDA was non-committal and introduced enough disclaimers to render the meetings unhelpful. Adding insult to injury, when the company would finish its trial and provide the data to FDA, the Agency would frequently state that the trial did not meet its expectations for clearance or approval (often calling for another trial). With the Pre-Sub, FDA gives feedback and it is memorialized in agreed-upon meeting minutes. The issues that remain are ensuring the Agency takes a realistic view of clinical trials and faithfully applies standards for an SE determination, de novo, or PMA approval without FDA imposing its often dictatorial or misplaced view on what a clinical trial should look like and what the regulatory pathway should be. Although the current Q-Sub program has not resolved these issues with Pre-Sub meetings, there are strategies that can be used to make this type of early meeting the most beneficial for a product commercialization experience. We will discuss those in the second part of this series.

B. The second context in which the Pre-Sub is used is after the company has completed its clinical program and decided upon its regulatory path and is now trying to persuade FDA to agree to both. This can be a dangerous position to be in and FDA is the first one to tell a sponsor that

fact. FDA often feels slighted when it has not been consulted before a clinical trial has started even though industry is not obligated to do so (unless it is a significant risk trial conducted in the United States). This is because FDA has developed a bit of an arrogant mindset that it should be on the development team because it knows better than industry how to develop devices. This is not meant to be a caustic or unfair comment; it simply is the natural evolution of any bureaucracy to believe it knows more and better than those it regulates. Never mind that there is a world of very, very bright, experienced, capable people who reside in chairs outside government buildings. It may be an uphill battle for a sponsor to convince FDA to accept data when FDA has not contributed to the study or trial design. So, hence, the dilemma—involve FDA at great risk of a big delay and an FDA proposal for an extraordinarily large, unnecessarily complex trial—or conduct the trial without FDA's input and take your chances later.

C. The final context in which a Pre-Sub arises is when FDA interrupts/stops a 510(k) or de novo review midstream to discuss the regulatory path and performance data requirements (which predictably include clinical trial suggestions (read: demands)). We've seen it many times. A submission is reviewed, FDA wants more data, and suggests that the sponsor utilize the Q-Sub program to discuss the data needed. If the sponsor agrees to this, the available response clock will often be used up trying to complete a Q-Sub, rather than completing the required response. When the response clock is going to run out, FDA may suggest that the sponsor voluntarily withdraw the submission (think of the imposing arm of Lurch waiting to throw you out) to prevent a negative decision and allow collection of the additional data. FDA says it does this to be benevolent because it does not want to reject the sponsor's submission (e.g., issue a Not Substantially Equivalent (NSE) decision or non-approval for a de novo or PMA) and FDA implies this is a better, less negative, way out for both parties. In reality, it

is best for FDA's user fee metrics to not have to report too many NSE or non-approval decisions. FDA gets credit from Congress, i.e. increased user fees and appropriations, for collaboration and de-merits, if you will, for saying "no" to new technology too often. It's sad to say, but often the Pre-Sub process seems more about FDA's ensuring its ever-increasing operating funds than speeding innovations beneficial to patients to the market. FDA is a master at playing the clock to ensure it is never faulted for delays and Congress usually buys it because it doesn't understand the process.

But the strategy of accepting a Q-Sub mid-submission just delays the inevitable pain of accepting the disagreement between the parties, i.e. FDA is attempting to dictate a clinical study designed in its own image to which the sponsor does not agree. The NSE decision is substituted with an excruciatingly long and difficult clinical trial negotiation (or possibly other performance data) upon which the parties do not agree. Again, the skeptic might think that FDA does this because it does not want to report another NSE or non-approval decision which negatively influences the metrics it reports to Congress under user fee legislation, or does not want to create a significant decision that could be appealed (and often overturned), or both.

One reason FDA states why a Pre-Sub is needed during the middle of a submission review is FDA's view that the sponsor has not provided enough data, or their device does not meet the definition for a 510(k). Not infrequently, today's FDA review staff will tell a sponsor that they do not have the quantum or quality of data needed to get a PMA, 510(k) or de novo. Or they will tell a sponsor for a 510(k) that they do not meet the definition of substantial equivalence (i.e. the a) same intended use, b) same technological characteristics, and/or c) the differences in technological characteristics do not raise different questions of safety or effectiveness).

When FDA, unilaterally, believes one or more of these definitional elements are not met, they leap ahead to the conclusion they are right, the sponsor is wrong, and suggests to the sponsor that it should save face by going to a Pre-Sub meeting to figure out what is needed to please FDA's desire for data. ***What that presupposes is that FDA is right about the regulatory pathway and data needed without any meaningful discussion with industry.***

When our firm discusses these matters with the Division Chief, Office Director or appeals to higher-level management, we frequently overturn the reviewer or find compromise. Sometimes we attempt to overturn the Division Chief (and sometimes the Office Director), on one or more of those questions and keep the device on the chosen path. When the review staff forces the sponsor into a Pre-Sub meeting, it takes the device off the review clock and derails the submission. The FDA does this based upon the belief that their view of the world is correct, i.e., the sponsor's submission is deficient because it does not have enough data or fails the definitional requirements in the case of a 510(k), and the Pre-Sub meeting will take them to Nirvana. That view is inappropriate, premature and presumptuous.

Sometimes review staff must be told by upper management that the amount of data provided is adequate or there is an acceptable compromise to a lesser amount of additional data. We once had a reviewer ask for a prospective 150 patient-plus trial, only to have management on appeal agree to accept a completed European study of 49 patients. Another time we had a request for a drug-device trial for a Class I device, with a Class II claim, resolved by agreeing to a Section 522 post-marketing surveillance trial. Yet another time we had the request for a 150-patient trial resolved by a 92-patient retrospective chart review from three sites in Europe where the device was approved and being sold (as valid scientific evidence). We

also have another example (and many more) where upper management agreed that a clinical trial was not required because the predicate (the company's own device) had been cleared two years earlier without clinical data. Yet another time additional mechanical bench testing and cadaver data replaced the need for a clinical trial. The bottom line is that a sponsor may be needlessly shoved off the normal path and into a Pre-Sub where a clinical trial may be demanded, when time (following an appeal to management) may show the sponsor was correct all along. These examples demonstrate the review staff's beginning premise may not be correct, e.g., that industry does not have enough data, or their device does not qualify for 510(k) treatment, and hence FDA's reason for proposing a Pre-Sub.

And note, when the FDA gets a sponsor off the review path and into a Pre-Sub meeting, the response clock for the underlying submission does not stop. Clients must be aware that the FDA can waste enough time simply trying to set up the Pre-Sub meeting that the response clock can run until it expires. The sponsor then gets a "Notice of Withdrawal" letter that its submission has been withdrawn because the review clock has expired. This is particularly aggravating for industry when they agree to do a Pre-Sub meeting as a meaningful gesture to FDA that they agree to a forum to candidly discuss issues with FDA. Often, we tell our clients not to acquiesce to a mid-review Pre-Sub meeting. It can be unnecessary and dangerous—a frightful monster dressed in a suit. Anything FDA wants to say to you in a Pre-Sub can be said in normal review negotiations. ***Sometimes forcing FDA into the prospect of issuing an NSE decision brings them to the table and results in a softening in their position. FDA is ever mindful of their user fee metrics.*** Beware of the pressure, however, that FDA will bring to bear upon a sponsor to go into a Pre-Sub meeting.

The Pre-Sub plays to FDA's advantage in a number of ways: a) it doesn't have to give the sponsor an NSE, nor report the NSE to Congress as part of user fee metrics, b) it gets credit in user fee metrics for having a Pre-Sub dialogue, c) the Pre-Sub puts the sponsor where FDA wants them—in discussions about a clinical trial or going from a 510(k) to a de novo or even PMA, and d) the response clock continues to run and if it expires FDA issues a Notice of Withdrawal, which does not look like a negative NSE/non-approval decision in user fee metrics with Congress. The system is gamed to FDA's advantage.

SUMMARY

The Q-Sub process often provides a useful mechanism for discussion about the regulatory pathway and data needed to commercialize a product in the United States. It has been a helpful and often used expansion of the original pre-IDE program. The Q-Sub process can be used early in the product development program to obtain feedback on the data needed to support a future submission. In our experience, this is the most helpful time to utilize the Q-Sub process, not mid-submission. The process can also be used to talk with FDA about plans for a submission after data have been collected. This often results in a challenging discussion and review process. Finally, the Q-Sub process can be utilized during review of a submission and is often recommended by FDA within requests for additional information. Be wary of acquiescing to a Q-Sub at this stage, as it can very efficiently eat up your response clock, quietly ticking away in the background, resulting in a submission withdrawal (either voluntary or imposed by FDA) if you cannot complete your response in time.

In Part 2 of this Q-Sub series, we will explore the technical aspects and strategies for Pre-Subs to make the process a bit less creepy and ooky, should you decide to enter the creaky gates of the (White Oak) mansion to meet with the Addams Family (aka FDA).

While they may be creepy and kooky, mysterious and spooky, and all together ooky, they are our FDA family. And though their house is a museum, when people come to see 'em, they really are a scre-am, our FDA Family. Don't forget to snap your fingers…

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.

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