DuVal Client Alert

Passing on Tribal Knowledge of FDA Law

Pre-Sub Series
Episode 2

Navigating The Interesting Sometimes Strange Pre-Sub Experience

#2 - The Technical and Strategic Aspects

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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 FDAs outside consultants who seem to have a hand in everything but frequently disappear only to reappear and attract attention-

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

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 walk 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.

To Pre-Sub or not to Pre-Sub —that is the question - It is not a foregone conclusion that everyone should request a Pre-Sub meeting before making a marketing submission. If the request is for a de novo or PMA approval, a Pre-Sub is necessary. If you do not have a predicate for a 510(k), it is likely you have a different intended use or your device is raising different

questions of safety and effectiveness and it is likely you will need clinical data (prospective or some version of real world data retrospectively mined), or animal data at a minimum. In either event, it behooves a sponsor to request a Pre-Sub to dialogue with the Agency about the data needed. That is not to suggest a sponsor asks the Agency what data it needs, FDA will not preform the role of being a consultant to the company and designing from the beginning what data it needs. A sponsor must propose to the Agency what it thinks it needs to obtain clearance of approval and then discuss it with the Agency.

While the FDA will not act as a consultant and design a study from scratch, do not be under the misimpression that FDA will have little to say about the design of the study. FDA's review staff won't say it out loud, but they want to be on your development team, and they think they know how to design trials better than the sponsor, in fact, anyone in industry. So put together you best foot forward on your study design and be ready to justify and debate it. But remember FDA's mentality is nothing is good or right unless and until they have had the opportunity to pontificate upon it—they can't help themselves. We don't know if its arrogance, regulatory boredom, fiefdom building, or all the above. Your proposed study may be, by all objective measures, the perfect study design, but they just have to comment on it and alter it, that's what they do.

If you are in pursuit of a 510(k), the question of whether to request a Pre-Sub is a closer call. By most objective measures, the predicate family has outlined by precedent what a subject device should be required to establish for clearance. FDA should not be re-inventing the wheel and asking for new and more data. We often tell our clients to be presumptuous about their position about what data are necessary and argue it upon submission rather then ask for FDA's feedback in a Pre-Sub. It is an exercise in calculating probabilities of winning the argument or not, or having FDA pass over it or not, versus the time and expense of a Pre-Sub. If FDA does not agree with

the data you have provided, you may have enough time on the 180-day clock to obtain it (unless it requires a prospective clinical trial—but real-world retrospective data and other testing often can be obtained). If you do not agree with FDA you can appeal. If you win the appeal you move on only having lost some time and money for the appeal.

It may be a close call timing-wise to do a Pre-Sub and, get FDA's feedback and then do the studies FDA requests, versus simply filing your 510(k) hoping to convince the review staff and getting your 510(k) or appealing the NSE if you can't convince them. If you lose the appeal, you must provide the data and you will have lost some time, but not that much considering how long the Pre-Sub process can take. So you must factor in four probabilities—first, the likelihood you will get your 510(k) upon the original data submitted; second, if you get an NSE, the likelihood of reversing that decision on appeal; third, the likelihood that if you lose the appeal how long the study and subsequent clearance will take; and finally, even if you lose the appeal, the likelihood upper management will fashion a compromise study that will not take as long or be nearly as expensive. ***It is the prospect of management compromise that often makes an appeal a viable option.***

Timing of the meeting - The FDA will attempt to schedule a normal Pre-Sub within 60-75 days after a request and will try to provide feedback 5 days prior to the scheduled meeting. The date is based upon mutual agreement. With a Submission Issues Request (SIR) FDA will try to schedule it within 21 days if the request is submitted within 60 days of FDA's marketing submission (Additional Information) letter or, if the request is outside of the 60 days of FDA's marketing submission letter, within 70 days.

How to write a Pre-Sub—Persuading FDA to your position - The new Pre-Sub Guidance was issued on May 7, 2019 and is entitled "*Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program*." It will give you everything the FDA technically requires of you to

obtain acceptance of your Q-Sub and get you an assigned "Q" number. But while FDA's guidance tells you what to submit to FDA, it does not tell you how to submit it or what to say in it. ***As with a 510(k), we find that good regulatory affairs professionals think of a submission as an evidentiary document***. As biomedical engineers or others with a technical/scientific background a submission is a compilation of strong data put together in a manner required by FDA and which looks presentable. As a regulatory law firm with lawyers and biomedical engineers and others with a technical background, ***we think of a 510(k) as an advocacy document, with evidence***. ***The same is true of any regulatory submission, including a Pre-Sub.*** Don't be locked into FDA's technical requirements. Ask yourself, what is your position on the regulatory pathway and the amount and type of information it will take to obtain clearance or de novo or PMA approval, and then advocate for it. ***Tell your story, make your argument upfront.***

For example, in the case of a 510(k), make sure you make an argument why you meet the criteria of same intended use, same technological characteristics and if the technological characteristics do differ, why your device does not raise different questions of safety and effectiveness. This requires using the statute, regulations and FDA's own guidance documents against them. Then argue that the data you are to submit are not required to demonstrate safety and effectiveness in an independent and absolute sense as with a PMA, but in a comparative sense in comparison to a predicate, as with a 510(k). Without the sponsor demonstrating and applying knowledge of the statute, regulations and guidance—again ***old and new*** guidance—FDA will always default to data it wants instead of what it actually needs to establish substantial equivalence or the standard for a moderate risk de novo device. In short, advocate for your position from the beginning.

Use an executive summary - The best place to start your advocacy and to simply encapsulate your story is to use an executive summary. While this is a very practical and seemingly obvious suggestion, it is hard to believe how

many Pre-Subs and other submissions we review do not use an executive summary when we are asked to review and edit them. Remember your Pre-Sub may be lengthy. Do the reader a favor and summarize your position and then elaborate on it in the body of the submission. Follow the old adage, "tell them what you are going to tell them, tell them, and then tell them that you told them." This is especially helpful for upper management who may only read the executive summary before a Pre-Sub meeting or they may have read the entire body of the Pre-Sub a week before the meeting and may need to quickly refamiliarize themselves with it. An executive summary is invaluable for those reasons.

Limit your questions to the majors - It is imperative that you use your time wisely within a Pre-Sub. Do not ask subsidiary questions the answers to which are nice-to-have's but are not critical to the outcome of the meeting. FDA's Pre-Sub guidance states that it is presumed most meetings can be tackled within one hour. To obtain more time you must make a specific request and justify it, but additional time is not easy to come by. If other questions can be asked and answered interactively do so. Or if tests can be performed without too much additional time and expense, do them without using another Pre-Sub to address them. Focus on the majors that take major time and money and, if not done to FDA's expectations, may not be considered acceptable upon completion—like animal or human studies.

Formulate the right questions - Another important tactic is to formulate the right questions. FDA's guidance document is helpful on this. You cannot, for example, ask FDA the penultimate question that "Will this data lead to a clearance or approval?" That is the very purpose of the data to be developed and that is always a complicated answer as data are never perfect and without some questions. What you can ask is that will this study if implemented as proposed be likely to lead to clearance, subject of course to possible unknown results or new information that may confound the data? What we typically propose is that before the actual question you want

answered is asked to use an introductory set up paragraph which sets forth facts and qualifiers and limitations to the questions asked. These qualifying introductory paragraphs allow the sponsor to shorten and simplify the actual question and obtain a simpler answer.

Requesting a face-to-face or conference call - If the Pre-Sub is your first meeting with the FDA on your device, it is advisable to meet with FDA unless it is unaffordable to do. Every time you can actually meet with FDA you have the chance to improve your relationship with them and help them to better understand your device (through show-n-tell), which will impact their understanding of the regulatory pathway you've chosen and the type and amount of data you propose. There is no substitute for face-to-face interaction so greater understanding can be achieved and more opportunities for misinterpretation can be avoided. You would not believe how many times progress is not made because FDA does not understand the device or has misconceptions about it. Showing the device can be very helpful. It is amazing how many misconceptions of what a device is and does can be avoided if it can be shown. Demonstrations can be another thing. Take care that if you demonstrate a device it does not fail or otherwise raise new questions. In early Pre-Subs the device design is often not yet locked in and can reveal problems or raise questions in FDA's mind. So be careful. After the first meeting subsequent meetings can easily be done by conference call.

Who to take along; who to request at FDA - The company should take only the number of people it needs to assist in the discussion of the regulatory pathway, the technology, the medical issues, etc. that are in play. As a rule of thumb five people might be appropriate—with management, biomedical engineering, regulatory, clinical, biostatisticians, outside medical and/or regulatory consultants as possible attendees. We've taken as many as nine, but that was an outlier including multiple medical consultants and a patient advocacy representative. It really depends on the issues and who FDA

might invite to attend which may reveal, correspondingly, along with FDA's response, the issues that FDA believes are most important.

Who you take also depends upon the strength and vocality of the FDA representatives in attendance. For example, some chief medical officers within FDA divisions are more vocal, dominant and inflexible than others and may need a higher level of academic expert (read: lofty pedigree), versus a practicing physician, to overcome their objections. Other chief medical officers want to hear from a practicing physician who has done thousands of procedures to gain a more practical perspective. Sometime both an academic and an experienced physician is needed. Some biostatisticians at FDA like statistics for statistics-sake and miss the practical realties of what is trying to be proven by a trial. The bottom-line is gauge who you take to FDA by what issues FDA raises and who they will bring to the meeting.

You can also request certain FDA personnel be in attendance, especially if they have previous background with your device or in the field in general or might be helpful in mediating the discussion between FDA and industry.

Who will attend from FDA? - Before the reorganization of FDA along life cycle lines, the number of FDA attendees had started to fall into a more realistic and sensible range. With the recent reorganization the number of pre- and post-market personnel in the room has swelled again. **As a taxpayer, the number of FDA personnel in a room on any given device is appallingly large. It is unnecessary, inefficient and expensive especially for an organization constantly clamoring for more money.** Industry understands if the FDA is using certain meetings to train others, to let them watch and learn. Our firm does the same thing, we bring newer personnel to FDA with our client's permission. But FDA overdoes the number of attendees. FDA is also far too egalitarian in its management style—always opting for some form of scientific political correctness, i.e. no idea is a bad idea, even when it is. Everyone seems to have an equal voice at the table

and can stop a submission or impose ridiculous requirements. And unlike management in many private sector organizations, middle managers do not have (or do not assume) the power to override employees who are often asking for information the agency might not need or require, e.g., it might be irrelevant to a 510(k) determination or the quantity and quality of the data request may clearly be overkill (not Least Burdensome) for the device under consideration. It is often only at the first or second level of appeal to management that common sense gets applied and compromise is possible.

FDA often brings in people with the correct substantive background, but as FDA gets increasingly academic, it brings in people with siloed expertise. This increases the number of people who "must" be in attendance and contribute to the dialogue. FDA is increasingly insisting upon hiring people with Ph. D.'s which is the worst development at FDA since most Ph.D.'s a) want to apply their dissertation to their work, if at all possible, b) want to demonstrate their superior level of knowledge, fresh out of graduate school, to everyone else in the room, and c) are often too granular and too narrow in their outlook and too inexperienced to make the practical judgments and balanced risk taking required to allow a medical device to be cleared or approved. In addition, FDA usually cannot hold on to a Ph.D. for too long since they will often move on to the private sector to command a higher salary. That attrition really hurts FDA and industry. ***FDA needs personnel who approach problems from a larger, more wholistic and practical approach, who can see the forest from the trees.*** If it's a Ph.D., great, but often it is a biomedical engineer with a four-year degree or masters who is more practical.

Preparing for the Pre-Sub - Finally, preparing for the Pre-Sub is important and should not be underestimated. The written submission is the first step turning an evidentiary document into an advocacy document with evidence. While a Pre-Sub meeting is the most collaborative and often relaxed meeting you will have with FDA (unless FDA is completely off-base and ridiculous in its positions), do not take preparation too lightly. It is your

chance to tell your device's story and get FDA to agree with your pathway and/or approach to the data development. The PowerPoint slides must track the written submission but go into greater detail and emphasis on points that might be particularly in contention. ***For that reason, it is wise to do an opposition analysis trying to discern what FDA has objected to and why or what FDA may object to and why.*** By anticipating potential questions/issues, you can add points and information in your slides to preemptively address them.

Then plan rehearsal sessions to finalize the slides and practice delivering them. It is when you finally have everyone together in one room, often the day before the actual FDA meeting, that the sponsor finalizes and freezes their slides to send them to FDA. Without that kind of concentrated, uninterrupted thought with the team, it is difficult to produce your best work product in the slides. You will invariably find points of emphasis or refinement that were not made in the written submission sent to FDA weeks or months before the meeting with FDA.

Generally, plan no more than 20-25 minutes for the presentation, 30 minutes at the outside. Devote as much time to discussion as possible. Remember that anyone who presents must be briefed on their role. For example, physicians or even executives without preparation can single-handedly derail a meeting because they often feel they are being called upon to save the sponsor in their management role or role as consultant. Without an understanding of the regulatory framework and their role in the meeting, which is usually circumscribed, they may venture off into unhelpful tangents that will detract and distract from the strictly defined objective for the meeting.

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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