DuVal Client Alert

Passing on Tribal Knowledge of FDA Law

Volume 13
Issue 03

LITTLE RED RIDING HOOD AND THE BIG BAD WOLF:

BEWARE OF DENOVO

DuVal Client Alert -- Little Red Riding Hood and the Big Bad Wolf: Beware of De Novo, May 2013

DEAR CLIENTS AND FRIENDS OF THE FIRM,

You remember the story; the Wolf disguises himself as Little Red Riding Hood, alters his voice and demeanor, draws Grandma in and then devours her. The beginning of that story serves as a metaphor for the way in which the de novo program looks like—a benign substitute for the 510(k) program. And when a company is drawn into a *de novo* review by the FDA, the company gets devoured. Remember next that when the Wolf dressed up as Grandma and tries to draw Little Red Riding Hood, she becomes suspicious saying "What a deep voice you have," ("The better to greet you with"), "Goodness, what big eyes you have," ("The better to see you with") "And what big hands you have!" ("The better to hug/grab you with"), and lastly, "What a big mouth you have," ("The better to eat you with!").

This CLIENT ALERT reminds you that your company also needs to be suspicious of an offer to pursue the *de novo* path and ask yourself questions that may reveal the true danger of where you are headed. Know that FDA will disguise PMA-like data requirements in the form of the *de novo* program and those requirements may devour your company.

FDA favors the freedom it has to request additional data under the *de novo path*. FDA gets into many definitional battles with industry applicants regarding the interpretation over the elements of the 510(k) program, i.e. whether a device has the same intended use, same technological characteristics, or has different characteristics and/or the question of whether the new technological characteristic raises new types of questions

of safety and effectiveness. FDA is subtlety and indirectly redirecting many submissions that normally would have been effectively handled by the 510(k) program on to the *de novo* path. You might ask "why would FDA do that?" It is because the *de novo* path provides FDA more administrative control to dictate the quality and quantity of data than would otherwise be necessary under the 510(k) path. When FDA asks for data under the *de novo* path it is not tethered to the 510(k) standard of "substantial equivalence," which requires an applicant to demonstrate safety and effectiveness in a ***comparative sense*** to a predicate device.

The *de novo* path allows FDA to use the same standard as with a PMA, i.e. require that data be provided to establish safety and effectiveness in an ***independent and absolute sense*** by establishing "reasonable assurance of safety and effectiveness," albeit in the context of a moderate risk (Class II) device. By diverting as many 510(k) applications as possible to the *de novo* path, FDA can exercise more control over an applicant and require as much data as it wants for approval. Although FDA may disagree, the *de novo* path is PMA-like. Some would say it is PMA-lite. FDA finds it difficult to hold itself to a moderate risk (Class II) standard.

Beware: the request for de novo is really a disguised attempt to get more data ("the better to eat you with"). If you thought FDA's seemingly benign offer to pursue *de novo* to keep your device dream alive because your device was not going to survive the 510(k) path (i.e. an NSE letter), think again. The offer for a *de novo* "out" is often simply a way for FDA to justify a request for additional data, including animal and clinical data.

Let's face it, no matter what path your device is on—510(k) or de novo—FDA wants to ask for whatever information it desires, even if it exceeds the statutory construct for a moderate risk device; even if it exceeds the demands of good scientific judgment; even if it looks like a science project; even if it far exceeds what was required to obtain a CE Mark in Europe. Once FDA has an applicant in the *de novo* world the only limitation on its far-reaching administrative judgment is the well-intentioned, but often loosely defined and infrequently applied, Least Burdensome requirements. Some would say FDA is doing indirectly what it cannot do directly, i.e. require the "science project-like" data it prefers of many applicants of PMAs.

One also suspects that the real reason for asking for a clinical trial is that FDA, across the board, seems to be attempting to shore up past regulatory clearances where no clinical data was required. Today's FDA often feels the "old" FDA did not do its job and should have required far more data for clearance of the previous generation of 510(k)s. Never mind that the predicate devices have not demonstrated any safety issues or, in the rare case where there are some safety issues, they are not significant enough to merit a clinical trial as solution. FDA now seems to be asking for clinical data from new 510(k) applicants to create new predicates in the predicate family for which clinical data are required. This will, in turn, enable FDA to request clinical data of future device applicants, whether such data are truly needed or not. Frequently, that desire to have clinical data as the norm, where none was required in the past, seems to be another reason for pushing devices down the *de novo* path.

The de novo program was never expected to be a reclassification option or an escape valve for the 510(k) program. Remember if a device fails to receive a 510(k) clearance it is automatically reclassified, by operation of the Food, Drug and Cosmetic Act, into a Class III, high risk device. The request for *de novo* review is both a request for reclassification of the device into a Class II, moderate risk device and an "approval" of that device by FDA. The

subject device then becomes a new 510(k) predicate for all future devices that claim it as a predicate, even though the lineage of the reclassified device is not from another 510(k) device. The process of reclassification is simple enough to understand. The standard FDA applies to make that decision is not and, therefore, inevitably can be and is used to FDA's advantage.

CDRH has misapplied Congress' initiative to use the *de novo* clearance process more frequently as a true alternative to premarket approval (PMA). Instead, this initiative has adversely affected the objective review of scientific data and the application of established 510(k) principles in certain 510(k)s. ***Specifically, instead of being a substitute for premarket approval when appropriate, de novo reclassification is becoming a substitute for 510(k) review.*** This distinction is important to understand since it was wholly unintended by the Congress and industry. To restate it: the *de novo* process has become a substitute for 510(k) review, instead of a way to allow a moderate risk device to avoid being unfairly over-classified as a PMA device.

Industry often disagrees with a review team regarding the appropriate marketing pathway for a device. Industry is often in the position of making its case to FDA that its device has a legitimate predicate(s) and deserves to be considered under the 510(k) path. And it seems there are also internal disagreements within the Agency about whether a device belongs on the 510(k) path. It is industry's impression that when internal disagreements occur, management will tend to side with the most conservative view, in many cases regardless of the merits of the various arguments. The dynamic at play with the *de novo* path is that it has become something it was not intended to be—a convenient "out" for the Agency. What seems to happen is that review staff and management truly debate internally whether a device belongs on the 510(k) path and as they struggle with the definitions of same intended use, same technological characteristics and does it raise new questions of safety and effectiveness, FDA often comes to an internal

stalemate. Rather than management having the courage to break the stalemate and leave the device on the 510(k) path, they simply punt and suggest or direct the applicant to pursue the *de novo* path. In this fashion, *de novo* becomes an escape valve for internal disagreement and potential strife. The *de novo* program was never intended to be a default position for making tough decisions or a tie-breaker for moments when there is internal controversy over whether or not a device belongs on the 510(k) path. It was not meant to be an easy out for handling such tough decisions. It was intended to be applied when a predicate truly does not exist and the device was not so risky that it required the PMA pathway.

This is one of the reasons why Congress recently passed Section 603 of the FDASIA. It requires FDA to produce documents to show the various internal opinions expressed during the review process. It is industry's hope that this provision will help to reduce bad decisions whose aim is directed more to minimizing internal controversy than in making the correct decision. These bad, politically motivated, decisions frequently lead to the use of the *de novo* process as an escape valve for internal disagreement and controversy. In doing so, the *de novo* process becomes a *de facto* substitute for 510(k) reviews.

The FDA does not seem to understand, or misapplies, the standard for a *de novo* review. Once a device is no longer on the 510(k) path and is on the *de novo* path, our experience is that FDA inevitably defaults to a PMA-like standard of review. The standard of review for a 510(k) is "substantial equivalence." The standard of review for a PMA device is "reasonable assurance of safety and effectiveness." That leaves open the question of what is the standard of review for a *de novo* medical device. A petition for *de novo* review and classification of a device into Class II must be evaluated under the criteria in section 513(a)(1)(B) of the FD&C Act, which defines a Class II low to moderate risk device as (emphasis added in bold and italics):

> A device which cannot be classified as a class I device because the general controls by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, ***and for which there is sufficient information to establish special controls to provide such assurance….***

In evaluating the safety and effectiveness of a device, FDA considers, among other things, the probable risks and benefits of the device. See FD&C Act Section 513(a)(2)(C).

This is the essence of the *de novo* standard. It is not a PMA-like standard of whether there is safety and effectiveness in an absolute sense, i.e. where there is statistical significance in a pre-specified outcome measure in a trial; it is whether the benefit outweighs the risk and there are sufficient controls that will make the device (and subsequent devices using it as a predicate) safe and effective. ***By analogy, it is not whether the device is deemed safe and effective beyond a reasonable doubt. It is whether the device is safe and effective as demonstrated by a preponderance of the evidence – a fifty-one percent standard, if you will.*** The benefit of the device must outweigh the risk and that determination is more permissive and tolerant in a *de novo* standard of review. FDA's guidance states the following:

> ***Because devices classified under this pathway (de novo devices) are low to moderate risk devices, they may not need to confer as substantial a benefit to patients in order to have a favorable benefit-risk profile.*** Devices granted marketing authority under *de novo* petitions should be sufficiently understood to explain all the risks and benefits of the device such that all risks can be appropriately mitigated through the application of general and/or special controls to provide reasonable assurance of safety and effectiveness. ***Further, devices classified under de novo petitions may serve as predicates for future devices which can be appropriately regulated through the 510(k) program;*** therefore, FDA carefully considers the benefit-risk profile of

> these devices in the determination that there is reasonable assurance of safety and effectiveness.
>
> …
>
> In these circumstances, in order to facilitate patient access to new devices important for public health and to encourage innovation, ***we may tolerate greater uncertainty in an assessment of benefit or risk than for most established technologies, particularly when providers and patients have limited alternatives available.***

Guidance for Industry and Food and Drug Administration Staff - Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and de novo Classifications; Document issued on: March 28, 2012 (emphasis added in bold and italics).

FDA in the guidance document quoted above looks at "Additional Factors in the Assessment of the Probable Benefits and Risks of Devices." These include, but are not limited to: the patient's tolerance for risk and perspective on benefit; the availability of alternative treatments or diagnostics; and if it is a novel technology addressing an unmet medical need. ***This makes the de novo standard something more than a 510(k) substantial equivalence determination, but less than a PMA standard of review. Yet FDA does not yet seem to have a handle on this fact and without proper guidance and training, reviewers will invariably default to PMA-like reviews because they are already doing that in 510(k) reviews.***

The CoAxia NeuroFlo example. As an illustration of how FDA misapplies, intentionally or unintentionally, the *de novo* standard, the CoAxia case is a recent example of the offer of the *de novo* path which devoured a company, in the metaphor of the Big Bad Wolf disguised in sheep's clothing. CoAxia was offered and accepted the first ever *de novo* panel having once failed a *de novo* approval with divisional staff alone. The prospect of an independent expert advisory panel was appealing to the company. That was before we discovered out how manipulated it could be by Divisional

staff. For full disclosure I was on the team that appealed, obtained the panel meeting, and lost. The device did not get approval for the labeling the company sought (see below)—first as an extension of the 510(k) labeling as discussed below, second, as part of a *de novo* reclassification and approval.

The device and its clinical and regulatory history. CoAxia has a dual balloon catheter, twice 510(k)-cleared for use in the descending aorta to divert blood flow from the lower extremities to the upper extremities, such as in the cerebral, cardiac and pulmonary vasculature. In addition to two 510(k) clearances, the device has a Humanitarian Device Exemption (HDE) for use in patients with cerebral vasospasm. Accordingly, this device would be used in patients who need more blood in the head, such as those with cerebral ischemia or, arguably, ischemic stroke. After its two clearances and HDE approval, CoAxia conducted a 500+ patient randomized trial showing safety in using this device in ischemic stroke patients.

The study also showed, on a post-hoc basis, a safety benefit, i.e. a substantial reduction in mortality (2 to 1 over standard of care). But the company missed its efficacy endpoint based upon an endpoint pushed by the Agency, i.e. a measurement of "return to normal." This is a very difficult endpoint to demonstrate and one to which the company, in hindsight of course, should not have acquiesced. Even though the Company narrowly missed its efficacy endpoint, the body of clinical data still had substantial worth which demonstrated the safety of the device and reduced mortality as a benefit. Based upon this very solid data, the manufacturer abandoned its hope to make a reduction in stroke and other potential outcomes claims in a PMA submission. Instead, it regrouped with this large and very good safety data set and sought a modest extension of the current 510(k) labeling for use in ischemic stroke patients. FDA's review staff, almost inexplicably, fought this requested 510(k) labeling for several years.

The failed 510(k) path. The question the FDA considered was whether the manufacturer should be able to clarify the labeling to state the device is a "tool" that could be used safely in ischemic stroke patients as long as the manufacturer did not claim the device as a "treatment" making treatment/outcome claims for reduction of ischemic stroke symptoms. CoAxia argued that since patients with ischemic stroke are a clear subset of patients with cerebral ischemia, the tool claim is a specific indication logically and rightfully falling under the general intended use. In this therapeutic segment there is a lack of treatments available for patients with ischemic stroke (less than 10% of the 650,000 stroke patients each year benefit from acute treatment). Consider the cost to society if FDA does not allow such a device to be used to treat stroke patients who have few to no options. CoAxia argued that FDA should: a) examine FDA's "Decision Making" criteria in FDA's General/Specific Use guidance to determine if the claim could fall under the intended use, and b) assess the sponsor's data to see if the new use raises any different questions of safety and effectiveness that are not answered by the data. If the use could plausibly fit under the general use and the data support the use, the 510(k) path should have been available to the manufacturer.

FDA's review division (DONED) ruled that the device was NSE because the proposed use constituted a new intended use. FDA found, according to FDA's General/Specific Use guidance, that the proposed indication for use in ischemic stroke "involve the diagnosis, therapy or prevention of a particular disease or entity or entities, especially where such entity carries clinical implications not normally associated with other general uses of the device." In other words, the additional claim took the device from simply being a "tool" to being a "treatment" under FDA's General/Specific Use guidance. FDA's decision with the CoAxia device shows how subjective this determination/interpretation is because this device certainly can be used by physicians today in ischemic stroke patients and the anatomic placement and physiologic purpose is identical for both

the general use (redirection of blood flow to the cerebral vasculature) and specific use (redirection of blood flow for ischemic stroke). Indeed, the FDA also approved the HDE for the device for use in the head, i.e. for cerebral vasospasm. Importantly, FDA made its NSE decision without ever formally reviewing the clinical trial data in the 510(k).

If FDA wanted to embrace the 510(k) program and Least Burdensome requirements, it could just as easily justified a decision to find that the proposed use fell comfortably within the general use and made a substantial equivalence determination. The amount of clinical information was more than satisfactory to support the proposition that the device is safe for use in ischemic stroke. ***Instead, FDA used its NSE decision to treat the device – twice cleared and once HDE-approved – to force the device onto the PMA path (with a de novo stop in between) and to support a request for yet another large clinical trial, thus effectively killing the company and the use of its technology in stroke patients.***

FDA's offer of the *de novo* path and the misapplication of the standard of review. The important thing about the *de novo* panel meeting is that FDA never trained the FDA panel in the *de novo* standard of review and the panelists were largely drawn from FDA's general pool of PMA panelists (because there had never been a *de novo* panel before). The panel also did not have any trained clinicians on the panel who treat stroke patients on an emergency interventional basis. FDA did have two physicians who treat stroke patients in therapy after a stroke has occurred. The rest of the *de novo* (read: PMA) panel was populated with well-intentioned, but misdirected, clinical trialists, biostatisticians, generalists and those well outside of the stroke neurology arena. The two major medical societies, representing physicians who actually treat these patients, appeared at the panel meeting requesting that this device be made available for their patients because they have so few choices available after tissue plasminogen activator (t-PA) is administered in the first three to four hours

of a stroke. The company had three of the best stroke experts in the world representing them.

As such the panel was comprised of people who were last in a world of "P" values, i.e. statistics and statistical significance, detached from the actual clinical benefit versus risk ratio of this device. This statistical mindset was a waste of time for CoAxia and the panel since CoAxia had conceded to FDA two years earlier that its study did not achieve statistical significance in the effectiveness study parameters.

Important to this CLIENT ALERT, is that the panel was not trained on the *de novo* standard of review discussed above using my analogy of a preponderance of the evidence (*de novo*) versus beyond a reasonable doubt (PMA). The FDA stated the panel was trained but the industry representative said they were not. When we saw the "training" the panels received it was a paragraph in the panel packet they received from FDA describing the difference between a 510(k), *de novo* and PMA. It was elementary and had nothing to do with the actual standard of review. ***The point is that context is everything in a proceeding like this. Without the proper standard or review for de novo, the panel resorted to the instincts of statisticians and professional clinical trialists, not searching for clinical benefit which simply outweighed the risk of the device, but looking for statistical significance—a standard too high for a de novo review. The panel meeting became an abstract statistical exercise in establishing how the device in the study did not statistically meet its effectiveness study parameters at a very high confidence interval.***

Conclusion to CoAxia

Remember, this device is, after all, on the market today with two 510(k) clearances and one HDE approval all of which target the use of this device to the cerebral vasculature. The Divisional staff stubbornly refused over

many years to grant a modest extension of the labeling to permit its use as a tool, in the armamentarium of stroke neurologists and other stroke experts, for use in ischemic stroke. *The Divisional staff began with its end in mind—i.e. get more clinical data—and then used the process to get there. CoAxia went out of business as a result; another company in the growing FDA graveyard and another sad victim in an era of FDA over-regulation.* This case demonstrates 1) how FDA can use its interpretive decision making, power and control over the process and dialogue, to support a request for more and more data and make a decision that is more Class III, PMA-like than a Class II, moderate risk *de novo* decision; and 2) how the panel process can be manipulated by Divisional staff to achieve the end they desire. *Watch out for the Big Bad Wolf, de novo may not be what it seems.*

DuVal & Associates
Drug, Device and Food Law

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

CALL ON US FOR ASSISTANCE WITH YOUR REGULATORY NEEDS

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