DuVal Client Alert

Passing on Tribal Knowledge of FDA Law

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FDA Fails to Review Data in the "Stage-Gated" Review of a 510(k)

FDA Often Sees No Data, Speaks No Data, Hears No Data—A Failure to Review Data in a 510(k)

EXECUTIVE SUMMARY

Is FDA not reviewing your data in a 510(k) submission? Have you ever received a Not Substantially Equivalent (NSE) letter from FDA stating your device does not meet of the definitional elements of "substantial equivalence?" Did FDA do this without even looking at your data when your data may have helped your device meet the SE definition?

Well join the club; where FDA sees no data, speaks no data, hears no data.

When FDA does this it is called a "stage-gated" review—FDA makes a legal/regulatory definitional interpretation that your device does not: 1) have the same intended use, 2) same technological characteristics, and/or raises different questions of safety and effectiveness. It does so without ever looking at your data and earning its user fees.

The issue of course is whether FDA in a stage-gated review should look at data submitted by the sponsor in making a determination of whether a device is substantially equivalent (SE) or not. Stated another way, is it acceptable for FDA to make a legal/regulatory determination in a stage-gated review of the SE status without looking at any data? We know that FDA for decades did not apply "stage-gated reviews" as they are being

interpreted and applied by FDA today. Today FDA averts its eyes, ears and does not even speak about data if it can avoid it.

Last week our firm submitted comments to the Docket for FDA's recently finalized 510(k) Guidance, for which it is seeking new input: "*The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications; Guidance for Industry and Food and Drug Administration Staff; Availability*," dated July 28, 2014. You can get our comments sent individually to Christy Foreman, Director, Office of Device Evaluation (ODE), and to the FDA's docket, by *clicking here or going to our website @ www.duvalfdalaw.com*.

The statute and regulation actually require that FDA consider all "the information submitted" to it, not some of it, or the amount FDA chooses in its discretion to review. For confirmatory analysis, we also show how the remainder of the statute and regulation (and as a last resort FDA guidance), support the view that FDA must look at your data. You can use these arguments to hopefully convince FDA to look at your data and not get short-changed in FDA's review. We will make sure that Congress is aware of this FDA practice for future user fee negotiations.

EXCERPTED FROM THE SUBMISSION TO THE DOCKET

Here is the short version of our analysis for you to use when working with the Agency. Our hope is that it will persuade them, compel them and/or simply shame them into looking fully at your data when reviewing your 510(k). These are selected portions cut and pasted from our submission:

STARTING WITH THE STATUTE AND REGULATION

Overarching starting point—the mandate is more straightforward than FDA thinks

As we must, let's start analytically with the statute and regulation. First the statute, "substantial equivalence" means:
...that the device has the same intended use as the predicate device and that the Secretary by order has found that the device—

(i) has the same technological characteristics as the predicate device, or

(ii) (I) has different technological characteristics ***and the information submitted*** ***that the device is substantially equivalent to the predicate device contains information,*** including clinical data if deemed necessary by the Secretary, ***that demonstrates that the device is as safe as a legally marketed device, and (II) does not raise different questions of safety and efficacy than the predicate device.***

21 U.S.C. 360c(i) (emphasis added). The regulation states as follows:

A device is substantially equivalent if, in comparison to a predicate it:

has the same intended use as the predicate; and has the same technological characteristics as the predicate; or

has the same intended use as the predicate; and has different technological characteristics ***and the information submitted to FDA***;

does not raise new questions of safety and effectiveness; and

> demonstrates that the device is at least as safe and effective as the legally marketed device.

In the normal course of statutory construction, we should really have to go no further than the direction to look at **"the information submitted."** The statute and regulation refers to all the information submitted, not some of it, or the amount FDA chooses in its discretion to review. For confirmatory analysis, we can look at the remainder of the statute and regulation (and as a last resort FDA guidance).

It doesn't say, FDA should do a stage-gated review and determine, on its own without ever looking at data, whether the device meets the statutory definition. There is no qualification for the data that must be reviewed—it says "the information submitted to FDA." The statute and regulation ***do not say*** that the review of the device is to be based upon: "a ***superficial review*** or a ***partial review*** or a ***selective review*** of the information submitted to FDA, to show the device does not raise new questions of safety and effectiveness; and demonstrates that the device is at least as safe and effective as the legally marketed device." It is to be based upon a review of "***the*** information submitted to FDA," without limitation or qualification. So FDA must look at ***all*** the information submitted to it in making its determination of whether the new technological characteristic raises different questions of safety and effectiveness and the data support a clearance.

The inquiry is greater and more holistic than FDA is trying to make it out to be. It is tempting and even laudable to think FDA is trying to be administratively efficient and help companies by mercifully making an early call on this issue using the stage-gated approach to avoid reviewing data where FDA deems it unnecessary. FDA's view is that it would rather deliver the bad information earlier, rather than later. But actually FDA is short-changing the applicant and itself, because FDA may actually learn

something from the data. Moreover, sponsors are paying for the more thorough review.

The analysis of the statute and regulations really should stop here, because the language is clear and unambiguous, but we've provided some additional policy arguments below. Congress also listed the two additional items to be reviewed in the order of the reviewing the data first and, presumably, to see if the data raise different questions of safety and efficacy, second. Let's break those constituent elements down.

First prong—"the information submitted" to FDA demonstrates that the device is at least as safe and effective as the legally marketed device

It is interesting that Congress chose this criterion as the first prong. It suggests that Congress intended the second prong (does the device (data) raise issues of safety and efficacy) as subsidiary to the first prong (a review of the data). We believe this was intentional and, indeed, FDA acted as if it was intentional for decades before it created the "stage-gated" review. FDA wanted a review of the data and if the data revealed different questions of safety and efficacy, the device would not be eligible for the 510(k) path. We also believe that when read in conjunction with Least Burdensome requirements Congress wanted FDA to make determinations in favor of the 510(k) path where necessary and remedy deficiencies through a request for additional data, not by bouncing devices off the 510(k) path through fanciful regulatory interpretation employing a "stage-gated" review. Congress used both prongs as conjunctive, not disjunctive, requirements, i.e. both must be considered together. FDA cannot dissociate the two.

Second prong—"the information submitted" to FDA does not raise different questions of safety and effectiveness

To determine if a device raises **different** questions of safety and effectiveness, without the benefit of data, FDA must make that decision in the abstract. That is why Congress wanted the review to first review the data itself and in that data review may reveal different questions (or not). To interpret it in any other way not only does a disservice to sponsor, but the FDA as well. FDA as an organization is normally data-driven, but FDA seems to want to be able to make a judgment call on whether different questions are raised FDA based upon its lone impression, without the benefit of data.

There are three issues with this approach—first it results in FDA guesswork; it relies on regulatory intuition and instinct. This can vary by CDRH divisions and the individuals whom FDA employs—some with vast experience and some quite naive and inexperienced. Even with mature, experienced reviewers, they are not infrequently overturned by management on such issues. Sometimes they are unaware of facts and data which may change their minds and or give them the comfort level they need to conclude a device truly does not raise new questions of safety and effectiveness. FDA is continually trying to improve and make more routine, consistent, predictable and transparent how it makes quality decisions. Would it not be better to require a data-driven agency to review an entire file, routinely, instead of exercising judgment file-by-file and deciding this application should be bounced off the 510(k) path and this one can proceed?

By allowing a decision to be made without reviewing data gives FDA far too much academic freedom to create issues where none may exist.

FDA in its vast repository of institutional knowledge has seen most of the issues before it and FDA knows that often those issues can be tested through existing means or methodology. FDA has even attempted to accommodate this approach by allowing for FDA to consider "reference" devices in its review of a 510(k) device. See Draft Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating

Substantial Equivalence in Premarket Notifications [510(k)] (December 27, 2011). This is a good idea. In looking at whether questions are the same or different, FDA is not limited to the predicate device itself, it can look at "reference" devices, a device that serves as precedent for issues seen by FDA before in non-predicate devices. So FDA should employ this knowledge base when reviewing a device instead of attempting to silo its thinking and deliberately shrink its analysis and avert its eyes to avoid looking at the data. It becomes mechanistic and gives the appearance is that FDA is trying to avoid doing its work. This is an issue/perspective (reference devices) with which you and I have seemed to agree over the years.

The system and incentives become skewed when FDA can avoid reviewing a device by engaging in a stage-gated review, avoid doing the heavy lifting of reviewing the data submitted, and then summarily conclude it "raises different questions of safety and effectiveness." This would lead to FDA obtaining user fees, but never earning them. This is clearly not what Congress intended, either for the standard of review or in enacting user fee legislation.

Finally, under Least Burdensome requirements, the applicant should be given the benefit of the doubt and the data reviewed and the final judgment should err toward allowing a 510(k) path if at all possible. These are Class II moderate risk devices being reviewed (in the vast majority of cases) and as stated above a review of the data may help smooth over FDA concerns and give FDA a comfort level with possible and more tangential "different" issues, so that a device under review may not appear so different to FDA once the data are reviewed. If they were high risk devices with truly novel therapies, it would make sense to take a more cautious approach.

In sum, it is clear Congress wanted FDA to review all the information submitted, not just enough to make a legal/regulatory determination the device does not belong on the 510(k) path. In addition, on the first prong

of determining whether information submitted to FDA does not raise new questions of safety and effectiveness, FDA must consider the data submitted to it. To avoid doing so relies too much on FDA intuition. Without that approach, it is not a data-driven exercise. It also does not employ FDA's own strength of institutional knowledge and experience and ability to look at reference devices, but sidelines them. The incentives also become skewed and if it is not improper, it at least leads to the appearance of impropriety by taking user fees and not earning them through an actual review of data. Finally, Least Burdensome principles would suggest FDA make every effort to help an applicant stay on the 510(k) path if possible.

MOVING TO THE GUIDANCE

In the proper sequence of interpretation, one only looks to FDA guidance after it is clear there are or may be ambiguities in the statute or regulations and any guidance must be read to ensure consistency with the plain reading of the statute and regulations. We do not believe such ambiguity exists. Having said that, we believe FDA guidance is consistent with our view as well. In reviewing the K86-3 Blue Book memorandum, it first starts out with a position that, at first blush, superficially supports FDA's current reading of its responsibilities in reviewing 510(k)s, i.e. to do an initial review, but that review is limited to certain circumstances.

FDA's Guidance on the CDRH Premarket Notification Review Program 6/30/86 (K86-3) 510(k) Memorandum #K86-3 that says:

> ***If it is clear from an initial review*** that a new device has a technological feature that makes it NSE, the Center will not review or require performance information in the 510(k). Instead the applicant will be notified that the device is NSE, and any performance data will be reviewed in a PMA or reclassification petition.

We have two thoughts for the Agency on its reading. First, while the thinking behind K86-3 is still relevant on so many fronts, K86-3 was written at a time when it was heavily disputed whether ***any*** data were needed to demonstrate substantial equivalence. FDA did not intend, and indeed did not use, this phrase in the manner in which FDA is attempting to use it today, i.e. as a gated approach to reviewing 510(k)s. FDA was just stating the obvious; if it is ***so*** clear from an initial review that a device does not belong on the 510(k) pathway because the technological characteristics are ***so*** different, FDA should send an NSE letter to the applicant. Stated another way, I think the Agency at the time meant "if it is **abundantly** clear" from an initial review. As support for this position, the FDA's K86-3 guidance also says:

> **The Center normally will require performance testing data** to substantiate equivalence ***if a new device has an important descriptive difference*** in comparison to marketed devices within its type, ***and it is not clear from an initial review*** that the device has an intended use or technological change that makes it NSE….

The word "normally" implies in almost all cases, FDA ***will require*** performance data. This creates a presumption that FDA should review the data and not the other way around. In 1986 FDA would avoid looking at data and issue an NSE only if it was so clear (read: obvious) from an initial (read: superficial) review. So, only obvious calls stemming from a superficial review would qualify for this abbreviated and abrupt treatment, which is so upsetting to industry, i.e. a stage-gated NSE determination. This extreme exception, built into K86-3, has been turned by FDA today into a standardized stage-gated review which it was clearly never intended to be. That is why FDA's newly-instituted stage-gated approach is so ill-conceived and wrong. It is built upon and erroneous premise and reading of K86-3 and certainly ignores the plain meaning of the statute and regulation which states that FDA must look at "**the information** submitted to FDA…."

One thing is clear—the exemption FDA created in K86-3 for devices with data that do not need to be reviewed is where it is ***abundantly*** clear (read: obvious) from an initial (read: superficial) review that the device raises different questions of safety and effectiveness. As the guidance also states the "Center ***will normally require*** performance testing data" to be reviewed. And to exercise "reasonable scientific judgment" the Agency must look at the scientific information available to it. The Center cannot exercise "reasonable scientific judgment" if the Center is not allowed to review, evaluate, and consider valid scientific evidence and/or performance data.

It cannot be "clear from an initial review" when FDA itself, in the context of implant materials acknowledges that "such a rule would be too encompassing." It would indeed be "a mechanistic application of rigid formal criteria" to avoid looking at data in a 510(k) submission. Data would help, and indeed are necessary for, FDA's review.

CONCLUSION

FDA's current interpretation is 1) not true to either the statute or its promulgated regulation which requires that FDA considers all "the information submitted" to it, and 2) even if one moves to reviewing the guidance, FDA misapplies the original thinking for K86-3. With respect to the statute and regulation, they do not say that the review of the device is to be based upon a superficial review or a partial review or a selective review of the information submitted to FDA. A review is to be based upon all "the information submitted." With that caveat in mind, the guidance still supports this reading. A fair reading of K86-3 (and other guidance documents) and its application of when devices can be summarily dismissed from the 510(k) path is that it is a reserved for extraordinary cases in which "it was clear from an initial review" that the technological characteristics were different. We would suggest this means "abundantly clear." In fact, the guidance states the norm is to ***require*** a review of such data. We know

that FDA for decades did not apply "stage-gated reviews" as they are being interpreted and applied by FDA today.

Our hope is that the thinking in this submission is, hopefully, applied to all 510(k)s and so FDA might reconsider its use of "stage-gated" reviews. To not do so is a disservice to the applicant/sponsor and FDA and results in FDA not earning their user fees.

DuVal & Associates
Drug, Device and Food Law

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