De Novo Proposed Rule: Regulatory Watchcat's Comments

…the device that was the subject of the original De Novo request can serve as a predicate device for a substantial equivalence determination.

Making De novo devices immediately available as predicates is likely to put patient safety at risk.

A 510(k) device is a known quantity.

When assessing the risk potentially associated with use of a medical device, CDRH has traditionally considered "prior clinical experience" (not to be confused with clinical data) with the device. This is the principle on which pre-amendment devices were accepted as predicates. Although pre-amendment devices had not been actively assessed for safety and effectiveness, there was prior clinical experience with these devices. They were not unknown to clinicians and patients. To the extent that a 510(k) device is "substantially" equivalent to a marketed predicate, clinical experience with the predicate is applicable to the 510(k) device. This is the rationale that underlies the entire 510(k) framework.

A De novo device is an unknown quantity.

The novelty of a De novo device impacts risk in ways that are not found in 510(k) devices. Because a De novo device has no predicate, there is no prior clinical experience with its device type. While CDRH may very reasonably classify a novel device as I or II based on an assessment of the information available to it premarket, as both the industry and CDRH have painfully learned (over and over and over again), there is only so much you can do to when it comes to assessing the safety of a medical device premarket. Postmarket, some devices are revealed to have more, different, and/or greater risks than anyone could have reasonably anticipated. This is inherently truer of a novel device than a 510(k) device.

De novo devices should have a postmarket "safe harbor" of several years, when they cannot be used as predicates. I'm not just talking about a harbor of commercial safety for the companies that develop them, although there is that. I'm talking about a harbor of postmarket safety for patients as well. If you want to put patient safety at risk, no better way to do it than to take a novel device for which postmarket safety has a degree of uncertainty and use it to start spinning off more devices that are "substantially" equivalent to it, meaning that their safety is also uncertain.

There is one exception to this safe harbor that I think might serve patient safety well. CDRH seems to be currently quite taken with the notion that innovation per se is the key to device safety. I beg to differ. While improving the safety profile of a device may well require "innovating" it, just any old innovation is as likely to endanger safety as it is to improve it.

No one understands a new technology better than the people who developed it, and no one is better positioned to improve it in a way that is likely to serve patient safety. Therefore, a reasonable exception to a safe harbor would be one that applies to the company that developed the device in the first place. That company probably already has plans on the table for future improvements, and it should be free to pursue them sooner rather than later. Letting another company start fiddling around with a novel device immediately upon approval is asking for trouble, IMO.

Making De novo devices immediately available as predicates is likely to put meaningful innovation at risk.

There seems to be a tendency to confuse the clinical risk that determines the regulatory classification of a medical device with the financial risk associated with its development. While there is some correlation between the two, the financial risk associated with the development of a novel medical device is determined by a number of factors, and will be inherently greater than the risk associated with the development of a 510(k) device. The

more that is invested in the development, the greater the risk. The longer the development process takes, the greater the risk. The more novel the device, the less certain the outcome, the greater the risk.

If CDRH wants to foster innovation that offers meaningful benefits to patients, then it would do well to give companies that are prepared to assume the risk associated with the development of a novel device a decent shot at recouping their investment before their device becomes a me-too target for competitors.

Subpart D--De Novo Classification

I don't think a separate subpart is needed simply to address classification of a low- or moderate-risk novel device, nor do I think that any of the information that was lifted from the PMA regulations belongs in Part 860. My general sense is that CDRH has classification and approval backwards, and is at times confusing what applies to a device type and what applies to a specific device.

Classification of a Device Type

I don't think it's possible to "classify" an individual medical device. It is only possible to determine which regulatory class and which regulatory classification a device belongs to. Sometimes CDRH seems to understand this:

> *Classification regulation* means a section under parts 862 through 892 of this chapter that contains the identification (general description and intended use) and classification (class I, II or III) of a single device type or more than one related device type(s).
>
> (b) De Novo requests can be submitted for a single device type

Other times, not so much. The Proposed Rule is clearly intended to apply to a single device, but at the end of the De novo classification process, CDRH should have created a new classification for "a single device type or more than one related device type(s)," not for a single device.

The proposed rule is asking for much more information than is needed to create a new classification regulation and to determine an appropriate regulatory class for that device type.

To create a new classification regulation, all CDRH needs is a very brief description of the device type, as is found in the existing classification regulations.

There is no harm in basing the description on a single device, but neither is there any need to do so. CDRH staff could just sit around making up classification regulations for imaginary devices, but there would not be much point in doing that. The device that is the inspiration for a De novo "request" is not an imaginary device. It provides confirmation that a device of this type exists, and therefore that establishing a regulatory classification into which the device will fit is likely to be a worthwhile exercise. But the regulatory classification should be for a device type, not for the one device.

CDRH could also assign a risk class to the new device type with the flip of a three-sided coin, but again, there is not much point in doing that, if it turns out that there are no non-imaginary devices of this type which present the level of risk associated with that class. It makes more sense for CDRH to base the risk class on the level of risk associated with a non-imaginary device of this type; in this case, again, the device that inspired the De novo "request." All CDRH needs to do this is a detailed formal risk analysis (e.g., FMEA, fault-tree…see my comments on § 860.234(a)(11) below) and a thoughtful and thorough discussion of all clinical risks associated with that device. If special controls are needed, they will be identified in the formal risk analysis. The discussion of clinical risks should be adequate to determine whether these controls will provide adequate assurance of safety and effectiveness, but the content requested in § 860.234 (10) would undoubtedly be helpful also.

Approval of a Specific Device

A lot of the regulations in the Proposed Rule have been pulled directly from the PMA regulations, with a modest bit of "modernizing." The PMA regulations are ***not*** classification regulations. They describe premarket approval of a specific device that has already been classified. Regulations that describe the same process for a specific low- or moderate-risk device, based on the same information, are also premarket approval regulations, and they belong in a separate regulation, just like the PMA regulations:

§ 813 Premarket Approval of Novel Class I and II Medical Devices

All of the text lifted from the PMA regulations should go here, not in Part 860. And, what the heck, it's way past time to liberate the 510(k) regulations, which aren't classification regulations either, nor are they registration, listing, or "notification" regulations:

§ 811 Premarket Clearance of Substantially Equivalent Medical Devices
§ 812 Investigational Device Exemptions
§ 813 Premarket Approval of Novel Class I and II Medical Devices
§ 814 Premarket Approval of Class III Medical Devices

(How's that for "modernizing"? And "innovative"?)

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§ 860.3 Definitions.

Many people working in the industry have frequent need to cite the regulatory definition of a specific term. It would be helpful if these definitions were in an outline format like those used in 803.7 and 814.3, so that they can be cited individually, e.g.:

(a) Class I means…

(b) Class II means…

(c) Class III means…

De Novo request…De novo requester… grant or decline…

Is it really necessary to create a whole separate lexicon for each regulatory path?

"Cleared" versus "approved" can be reasonably justified on the argument that the standard for clearance (substantially equivalent) is different than the standard for approved (safe and effective). Not that this has ever done much to discourage people from using the wrong term half the time, but still, reasonably justifiable.

As far as I can tell, this is simply an application for both De novo classification and premarket approval of a medical device. If the application is successful, the device will have been classified and approved for marketing in the US.

Most of the requirements for "granting" a De novo "request," especially those for the data and information needed to support a regulatory decision, have been lifted verbatim from the PMA regulations. PMAs are neither "requested" nor "granted."

CDRH approves both "De novo devices" and "PMA devices" for marketing in the US based on its determination that they are safe and effective for their intended use, right? It bases both decisions on the exact same criteria (§ 860.7), right? So why not call an approval an approval? I appreciate that use of the term may strike terror in the hearts of some, but one can only hope. Maybe they will run away screaming and not come back.

860.5(g)(1) The existence of a De Novo request may not be disclosed by FDA before an order granting the De Novo request is issued, unless it previously has been publicly disclosed or acknowledged by the De Novo requester.

For years I've tried to come up with a reason for this, other than to spare CDRH from being transparently accountable for each and every submission it receives. I haven't been able to come up with one, but I'm still open to the possibility. It seems clear to me that CDRH is not going to endanger confidential or proprietary information (or "national security") by disclosing the mere existence of a De novo request, e.g., by posting a DEN number and date received. The same is true when it comes to posting the date it was accepted for review or the date it was refused or declined or whatever. This is accountability in its most basic form; why not do it?

860.5(g)(2) After FDA issues an order granting a De Novo request, the data and information in the De Novo request that are not exempt from release under § 20.61 of this chapter are immediately available for public disclosure.

The fact that these data and information are "immediately available for public disclosure" leaves open the question of how and when they will be disclosed.

CDRH discloses 510(k) Summaries and PMA Summaries of Safety and Effectiveness reasonably soon after a decision is made. The 510(k) and PMA summaries are prepared by the applicants, following the format and content requirements in § 807.92 and § 814.20(b)(3), respectively, and are included in the original application.

The Proposed Rule does not require a similar summary for De novo requests. It includes a definition of a Supplemental Summary Data Sheet (§ 860.3), but this data sheet is not listed as part of the content of a De novo Request. And "Supplemental" carries with it the connotation of sometimes yes, sometimes no. The draft De novo acceptance checklist CDRH issued in October 2017 references an Executive Summary, but an Executive Summary is not included in § 860.234.

As written, the Proposed Rule describes two different types of decisions, classification and approval, which suggests two different types of summaries:

1. A summary of the information that was submitted to CDRH to support the development of a classification regulation for a device type, and to determine the appropriate regulatory class for that device type.

   This information would undoubtedly be of interest to any company planning to submit a De novo "request." These classification summaries could be posted in CDRH's Product Classification database. CDRH is the expert on device classification, and therefore it should write these summaries.

2. A summary of the data and information that was submitted to CDRH to support the safety and effectiveness of a specific medical device.

   This information is likely to be of keen interest to a number of constituencies, including, first and foremost, healthcare providers and patients. These summaries would presumably be posted in CDRH's De novo database. I hope that CDRH would stop referring to these summaries as Decision Summaries and instead follow the convention previously established for 510(k)s and PMAs, and call them De novo Summaries. I would also hope that the applicant is the expert on the safety and effectiveness of its device and on the data that support it. I would like to see CDRH incorporate these summaries into the content of a De novo, and let the applicant write them.

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§ 860.234 De Novo request content.

Kudos to whoever replaced "patient" with "subject" in the sections on clinical investigations that were lifted from the PMA regulations.

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§ 860.234 De Novo request content.

Looking at all the summaries CDRH is asking for in the De novo "request," it appears CDRH has decided that the best way to address lower risk is by a more cursory review of less detailed information. I appreciate why CDRH might find this appealing, pressed as it is by its MDUFA commitments, but I beg to differ.

I think the information needs to be as detailed, and the review as thorough, for all devices, regardless of regulatory class. Where I think there should be flexibility is in CDRH's standard for "valid scientific evidence." To give a statistical example, $p < .10$ is every bit as "valid" as $p < .001$, although the latter is far more compelling than the former. The lower the risk, the less compelling I think the "valid scientific evidence" needs to be. But it still needs to be valid, it still needs to be presented in full, and it still needs to be reviewed in full.

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§ 860.234 De Novo request content.

CDRH has been talking a lot about "modernizing" lately, but it cannot seem to modernize itself. Most of the contents of this section are taken directly from § 814.20, much of which is vintage 1986. The Design Controls regulations were passed in 1996, 22 years ago and counting. It is way, way past time for ODE to start acting like it ever even read them, much less understood them, much less lifted a finger to implement them. Step 0 would be to tailor the format and content of all premarket submissions to be consistent with design controls. All premarket applications should include the design and development plan, design input, output, reviews, verification, validation, transfer, and every single design change since V&V was started.

CDRH can't say enough about how clinical trials are inadequate to assess safety, which is to say, inadequate to keep unsafe devices off the market. This is very true, but neither can you postmarket surveil safety into a medical device. CDRH keeps letting unsafe horses out of the barn then racing helplessly after them, waving warning letters and black boxes, and not even shutting the barn door afterwards.

I think ODE's failure to assure the application of design controls premarket is a big reason that device safety is still a major issue after all these years. And I don't think chasing after the horses faster and faster, with more and more technology and more and more postmarket data, and scouting more and moredatabases for more and more "signals" (a term of art if ever there was one) is going to make a single medical device safer.

The only thing that will improve the safety of medical devices
is for industry to DESIGN SAFER MEDICAL DEVICES in the first place.

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§ 860.234(a)(11) Summary of risks and mitigations.

If CDRH is concerned about device safety, a summary doesn't seem adequate. CDRH's guidance for feasibility study IDEs requires inclusion of "a thorough risk analysis." A feasibility study puts a small number of subjects at risk; market approval will put many patients at risk. How can CDRH ask for less risk information in a premarket submission, than in an IDE for a single small study?

Any competent medical device design team will follow a formal process to do a detailed analysis of risks associated with a new medical device. The FMEA is the most popular, but other approaches, such as fault-tree analysis, are used. Design engineers often have strong preferences for one over the other, but any of these would be preferred over a summary.

The feasibility study IDE shows some Device Evaluation Strategy Tables (p. 15, and 30-32) that would serve this purpose quite adequately as well. These tables have the advantage that they don't try to quantify the severity, frequency of occurrence, or likelihood of detection of each risk, a fairly pointless exercise that is typically part of the FMEA/fault-tree approaches.

The submission should also include a discussion (not just a summary) of the clinical risks and mitigations identified in the formal risk analysis. This discussion is the appropriate place to address severity, frequency of occurrence, and likelihood of detection for each clinical risk, because a any given clinical risk is likely to occur at different levels of severity with different frequencies, and may be more or less likely to be detected, depending on a number of factors.

§ 860.234(a)(15)(i) and (iii)

These sections seem inconsistent and confusing, starting with the reference to protocols being included in results, and the reference to a protocol for the clinical investigations, but not for the laboratory studies. All tests and studies should have a protocol and a report, even a mundane bench test. Why not just ask for them?

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§ 860.289 Granting or declining a De Novo request.

(a)(1) says that FDA will grant the request if none of reasons in (b) apply.

(b) says FDA may issue written notice to the "requestor" that the De novo has been declined. "May" suggests there is an alternative to issuing written notice. What is it?

(d) says FDA will use the criteria in 860.7 to determine safety and effectiveness in deciding whether to grant or decline a "request" but the lack of a determination of safety and effectiveness does not seem to be one of the reasons listed in (b), so it doesn't seem like FDA has the authority to use these criteria for that purpose. Does this make the De novo a pathway by which a device that FDA has not determined is safe or effective, or has determined that it is not, will be given access to the US market anyway?

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§ 860.289(d) FDA will use the criteria specified in § 860.7 to determine the safety and effectiveness of a device in deciding whether to grant or decline a De Novo request. FDA may use information other than that submitted by the requester in making such determination.

And so here we have it, the determination of safety and effectiveness, addressed at the very bottom of the Proposed Rule, as is appropriate for a mere footnote, or an afterthought.

Much of the Proposed Rule reads as if CDRH thinks that all it has to do is create a classification regulation that describes a device type consistent with the device that is presented in the De novo "request," assign it a regulatory class, and its job is done. The device is ready for the market. Maybe that is exactly what it thinks, I don't know.

I went back and read the De novo sections of FDASIA, to see if the language might provide some insight into what Congress thought. Heh. Mostly I got the impression that Congress thought the De novo addressed only classification. While I read nothing to suggest Congress assumed that, once a classification decision had been made, the De novo device was then free to go to market, without a clear and separate determination of its safety and effectiveness, I didn't see any language to suggest otherwise, either.

I think it must be very hard for CDRH to put together a coherent Rule that usefully addresses the regulation of medical devices within the confines of the FD&C Act, because I think the original Act did a poor job in establishing a framework for medical device regulation. I expect that many of my comments trample on the Act, to the point that CDRH could not implement them even if it wanted to. No matter. I think a bit of tramplikng might do the Act a world fo good.. I also think it's way past time someone said a lot of this stuff out loud. It's not like no one has been thinking it for decades already. Plus, I'm getting old, so there's a bit of "if not now, when" to my perspective on this as well.

Beyond that, I waited my entire career for the De novo. No point in considering all the good it might have done both patients and the industry, had it arrived sooner, or, even more so, had it been part of the original framework, as it obviously should have been. It's here now, and I can only hope that it hasn't arrived too late. It seems to me that a lot hinges on whether or not CDRH can get it right the first time, if it can get it right at all. Or if we will have to wait until patients are harmed by some De novo devices, and then go through another investigation, another high-octane committee issuing another weighty report, another purge at the top, another reorganization, yet more bad legislation band-aided on top of bad legislation, rinse and repeat.

I regret that I think there is only so much CDRH can do here, but I will ask it to please try harder.