First Impressions

In November, I attended the second meeting of the Patient Engagement Advisory Committee (PEAC). I attended a lot of regulatory meetings last year. I can only take so much time "inside the bubble," so this year I was inclined to attend none. However, the PEAC meeting was easily the most interesting of the lot, and finally I couldn't pass on attending the second one, to see how things were progressing.

A few general observations:

I was especially interested to see who showed up for the second one, since the first of any type of event tends attract a lot people who are more curious than committed. My impression was that the overall turnout was a bit smaller than last year, but still respectable. I thought the digital crowd was less in evidence…perhaps smaller, or maybe just quieter…and that those who showed up this time seemed a bit more in touch with the actual "real world." The patient advocacy crowd seemed more in evidence, which I hoped was a good thing. The registry crowd was pretty lightly represented, I thought.

Given this is a CDRH advisory committee, not an ACRP advisory committee, I was relieved to see that the industry representative was now from the medical device industry. At the first meeting, it was someone from the CRO industry. As to how that happened, I don't even want to know.

Since many of issues raised by the efforts to link patient engagement to the postmarket surveillance of device safety are statistical issues, I was not pleased to realize that none of the Committee members is an epidemiologist or a statistician, but maybe that too will change next year.

I also realized that the methods followed in a traditional clinical trial came out of years of struggling with how to wrest some kind of meaningful (i.e., scientifically valid) result from "real world" evidence. I began to wonder if the ultimate result of all of this deliberation might not be the realization that the answer to these questions is "a clinical trial."

Scientific Evidence

This year's meeting got off to something of a wobbly start with me. The Federal Register notice indicated that the Committee would discuss and make recommendations on the topic "Connected and Empowered Patients: E-Platforms Potentially Expanding the Definition of Scientific Evidence."

I wonder a lot about the extent to which CDRH knows what it is doing; I regrettably chalk this one small piece of evidence into the Science-No column. I'm of the strong opinion that the definition of scientific evidence falls within the domain of science, not within the domain of government regulation of medical products, and certainly not within the domain of e-anything.

On the other hand, it's just an FR notice; could be just a verbal hiccup. Maybe I'm making too much of it.

Next I wonder whether CDRH has a definition of scientific evidence, since I take it as a given that you can't expand upon a definition that you don't have. Thus, I am further discouraged when CDRH distributes a Glossary of Terms to inform the Committee's discussion on expanding the definition of scientific evidence, and "scientific evidence" is nowhere to be found among them.

But then I find some comfort in the introduction to the questions that CDRH wants the Advisory Committee to address, as it seems to be driven by the regulations, which include a definition, not of scientific evidence, but of "valid scientific evidence." 21CFR 860.7(b)(2)

I am happy enough for CDRH to take ownership of what it considers "valid" scientific evidence in its regulations, because I think "valid" is sort of like "significant" as used to refer to a statistical outcome, in that you can define it however you like for your purposes. (Hopefully with careful consideration of how well your definition will serve that purpose, but perhaps I can only expect so much.) However, when the term "valid" is dropped…not happy.

Scientific evidence, like the difference between two groups in a clinical study, is what it is. Neither the actual ("real world"?) nor the statistical difference between two study groups changes just because you change the level you will accept as significant. Nor does the difference between the two populations the study may have attempted to sample. Similarly, evidence does not become "scientific" or "un-scientific" just because someone says so.

Next I look at the questions FDA wants the Committee to address. It seems that the issue has now been reformulated a bit:

> *Some challenges with the use of patient-generated health data include the statutory requirement that information used in regulatory decision-making be valid scientific evidence. To address some concerns about whether this information could be used as valid scientific evidence, FDA is requesting your recommendations about whether patient-generated health data could be fit-for-purpose in a regulatory context.*

I am not exactly sure what FDA is trying to say here, but I think it wants to know if, and perhaps under what circumstances, patient-generated data might meet the statutory definition of valid scientific evidence, or if the statutory definition would have to be revised to allow FDA to consider these data as scientifically valid. Or, who knows, maybe do away with the constraint altogether and just let FDA call it from its gut.

FDA's questions for the Committee are not put to it until fairly late in the day, after a lot of presentations and other activities. When they are, things take a strange turn. A lot of the questions are not related to scientific evidence, valid or otherwise, nor even "fit-for-purpose," which I haven't figured out if it is supposed to be an alternative to valid scientific evidence, or another, maybe broader, way of saying it. The full discussion is documented in a little over 40 pages of the transcript, starting on page 137. On page 145, a Committee member comments that "I guess we are beyond the question of whether this is scientifically based data." I would say mostly they skipped right past it, and that they never really come back to it.

I'm not sure what to make of this. I'm inclined to think CDRH is still finding its way when it comes to how to work productively with this type of Advisory Committee, including figuring out who should sit on it and what questions can be reasonably put to it.

It was my impression that relatively few of the Committee members had the background needed to tackle the topic of valid scientific evidence. Maybe CDRH concluded the same thing between the time it crafted the topic of the meeting and the time it sat down to develop its list of questions for the Advisory Committee to address, and therefore it took its questions in a different direction. As a result of this shift, I think the few members who had the background were given an opportunity to bring that background to bear on the topic. Since this was my interest, I found it a bit frustrating, and I imagine those Committee members may have found it frustrating as well. I worry that they won't come back next year.

All that said, the fact that I found the topic of interest to me personally doesn't mean that it was the best topic for CDRH to bring to this Committee. I will be interested to see what topic it settles on for this year's meeting, and if that seems to be a better fit.

Surveillence

It's my long-standing opinion that the US has no meaningful postmarket surveillance of medical devices. Postmarket surveillance was a key topic at this PEAC meeting, and one statement by Jeff Shuren caught my attention:

"One of the areas that…we believe we are poised to move forward on, is active surveillance here in the U.S., where we take large datasets, electronic datasets, and apply analytical software to more quickly look for safety issues."

My first reaction was maybe this was more like active surveillance of the results of some else's passive surveillance than actual active surveillance. This promptly led me to ask, what is active surveillance, anyway? I realized I was very clear on passive surveillance, but when it came to active surveillance, not so much. I googled, and soon found out why. Turns out there are a lot of definitions and descriptions of passive surveillance out there, but when it comes to active surveillance, not so much.

The other twist is that there is surveillance as it applies to public health, and there is surveillance as it applies to medicine. Public health tends to have given much consideration to passive surveillance, where medicine has focused on active surveillance. Moreover, medicine views active surveillance as an alternative to active treatment, rather than as an alternative to passive surveillance.

The authorities on passive surveillance are, not surprisingly, the CDC and WHO. Their descriptions of passive health surveillance are pretty much like MAUDE, if it were done well. Possibly more like MedSun, but I haven't looked at it much.

> Regular reporting of disease data by all institutions that see patients (or test specimens) and are part of a reporting network is called passive surveillance. There is no active search for cases. It involves passive notification by surveillance sites and reports are generated and sent by local staff.
>
> A passive surveillance system relies on the cooperation of health-care providers — laboratories, hospitals, health facilities and private practitioners — to report the occurrence of a vaccine-preventable disease to a higher administrative level. Once the data have been received, they must be compiled and then analysed to monitor disease patterns and identify possible outbreaks. Passive surveillance involves the regular collection and reporting of surveillance data and is the commonest method used to detect vaccine-preventable diseases. In most countries with a passive surveillance system, every health facility is required to send a monthly (sometimes weekly/daily) report of all cases of vaccine-preventable disease (and sometimes other diseases of interest) on a standard form.
>
> Passive surveillance is less expensive than other surveillance strategies and covers wide areas (whole countries or provinces); however, because it relies on an extensive network of health workers, it can be difficult to ensure completeness and timeliness of data.
>
> Some countries might not have the capacity or resources to identify all cases of a disease, either because the diagnosis of the disease requires specialized clinical skills or because laboratory resources are not available throughout the country. Under these circumstances, passive surveillance can be adapted in a number of ways, depending on the completeness and quality of data required, financial constraints and the availability of specialist skills and services
> *https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/en/*

The National Cancer Institute's definition of active surveillance is somewhat interesting to apply to postmarket surveillance of medical devices:

> *A treatment plan that involves closely watching a patient's condition (*in Shuren's statement, not watching actual patients, but large datasets*) but not giving any treatment (*not taking any regulatory action*) unless there are changes in test (*software analysis*) results that show the condition is getting worse. Active surveillance may be used to avoid or delay the need for treatments (*recall or market withdrawal*) which can cause side effects or other problems (*patients not experiencing side effects suffering health consequences after being deprived of an effective treatment*). During active surveillance, certain exams and tests are done on a regular schedule*. Shuren didn't say anything about a schedule, but I wouldn't be surprised.
> *https://www.cancer.gov/publications/dictionaries/cancer-terms/def/active-surveillance*

I think for surveillance to be truly active, you have to actively ask about what you want to know, not just actively look at datasets. The problem with my model is that it's a certainty that, the more you ask, the more you will hear. Most manufacturers don't find the prospect of hearing about more and more adverse events associated with their devices very appealing. The model that Shuren describes…eh, don't know nothing about those datasets, but I guess it's better than just sitting there.

Data Access

When it comes to healthcare as it has devolved in the US, one of the few things I still care much about is patient access to their records. So naturally my interest was piqued when Jeff Shuren said, in a particularly adamant tone that "we believe patients can and should have access to their own records, period."

I think "believe" is the operative word here, because I can tell you from personal experience that patients do not have access to their own records. But I accept that Dr. Shuren believes this. He can probably speak from personal experience too, since it seems a virtual certainty that he can and does get access to his own records whenever he pleases.

The statement was in the context of NEST, which he described (not adamantly) as "a little bit unique because it's not an FDA system." He also also happily announced that they had already gotten access to nearly 500 million patient records, a revelation that did not inspire any happiness in me. Nor did the revelation that among those involved in this unique little venture include representation from the patient community, healthcare professionals, healthcare systems, payers, industry, and government.

With all these players potentially getting access to all those data, I started to wonder, if NEST isn't an FDA system, what does that imply about transparency and data access? And did Shuren just answer that question?

Did “period” convey “…and that’s that,” or did it mean “…and that’s all the data patients can and should have access to”? Even though apparently the rest of the known universe may have access?

My spirits were lifted considerably when one of the Committee members took up the issue of data access, although not with respect to NEST:

> *…if the manufacturer is collecting any data, I think that data needs to be transparent, not just to the Agency but also to the broader community, and there are different ways that you could do that to make it safe.*
>
> *I know that there are competitor issues, but I don't think issues related to competitor advantages are sufficient to explain or excuse restricting access to data. That has been done, or they come up with other constructs for, you know, restricting access to certain datasets to patients versus physicians. And that, to me, is insane.*
>
> *I think if the Agency is going to be able to use real-world evidence, we should be able to be able to access that structured data in a usable format, be able to pool that data as a patient population and do our own analysis, and be able to compare that with what the company is actually coming out with and what the Agency is acting on.*

Of course I’m thinking how enthusiastic both industry and CDRH are likely to be about this plan, especially since she had just revealed that some of her patients are hackers who could help her do all kinds of great things. This left me wondering how many people would be lying awake that night, letting their imaginations run wild, lol.

If anyone has been following NEST closely enough to know whether data access has been discussed, I’d be very interested to hear. If not, I expect that eventually we will all find out what that “period” really meant.

As at the previous PEAC meeting, the public attendees were seated at roundtables and one part of the meeting was dedicated to roundtable discussion of a scenario provided by CDRH:

> *You are employed by a medical device company that manufactures Device C. Device C, designed to cure lung cancer, has completely changed how physicians treat this disease and has exponentially increased survival rates for lung cancer patients.*
>
> *In your position, you are responsible for conducting postmarket surveillance on Device C (that is, evaluating potential safety concerns for the marketed device). You received an email from one of your field technicians that Device C may be causing strokes in patients by causing an irregular heart rhythm like atrial fibrillation.*
>
> *Your boss does not want to pull Device C from the market (for example, issue a voluntary recall) unless there is evidence of a true safety concern; however, your boss is concerned about possible lawsuits and patient deaths if Device C is associated with strokes. You would like to explore the issue a bit more before making your recommendation.*

At this point, I am nearly lost to the rest of the conversation. I realize it’s only a discussion scenario, but…seriously? This is a device that has exponentially increased lung cancer survival rates. How could a stroke possibly be a true enough safety concern to warrant a recall?

To make matters worse, several people clearly asking themselves the same question immediately raise the question of how soon after treatment these strokes occur. Off the cuff, the FDA discussion leader says “well into the future,” probably without consideration of the clinical implications of this statement, but because the questions are about registries, which are being looked at as an alternative to a long-term postmarket study.

At this point, I am completely gone. (You all know how I can get.) I express my astonishment that anyone would even consider a recall of this device, regardless of when a stroke might occur, but if it is going to occur at some time well in the future, the idea of a recall is just, just…mind boggling.

I ask, what patient would say, “Oh no, I don’t want the treatment that exponentially increases my chances of surviving this cancer, because if I do survive, then someday I might get a stroke? Noooo, I want the treatment that exponentially reduces my chance of survival now, so I won’t risk getting a stroke in the future.” What doctor would ever recommend this?

Across the table, a millennial RA professional from one of the large device companies is bobbing her head in enthusiastic agreement with my every word. I take a breath and she jumps in and starts talking about reviewing manufacturing records. I have no idea why, but since she was so enthusiastic about my comments, I bob my head reciprocally at hers.

Later I realize that she and I were probably making different assumptions about the potential source of the problem. She was thinking more along the lines of the traditional manufacturing failure leading to the recall of

one or more lots. That actually wouldn't have been so bad for patients, only the affected lots would be recalled and would still have had access to the treatment. Premarketer me, on the other hand, was thinking of a potential design problem, so I talked about looking at principles of operation and mechanisms of action. And a design issue would mean all units recalled and no more shipped until it was addressed. In theory, any way. On the whole, I think Premarket Me and Postmarket Her would have made a great team and gotten the matter straightened out in no time.

I finally came in for a landing, and we proceeded to discuss the scenario and the specific questions that FDA wanted us to address, which regrettably did not include "Would you be out of your mind to recall this device," lol. One question was the potential use of registries in this scenario. I was skeptical you need a registry to find cancer patients, because they are typically followed very closely for years. I would just contact oncologists. But I decided it was high time I got with the program, so I let this go.

After the allotted time for discussion, the FDA discussion leaders summarized the comment at their tables. I was reassured to learn that I was not alone in my reaction to the idea of a recall. No one addressed this directly, since it wasn't one of the questions, but the general theme found its way into the summaries, nonetheless:

> *There was less discussion about doing a randomized clinical trial than the ethics of denying treatment to a group that could potentially benefit from the therapy…*
>
> *We actually took a little bit of a different route…looking at the benefit-risk assessment overall, given that this was a breakthrough treatment for lung cancer, versus the risk of stroke*
>
> *…may not even be that important to patients with lung cancer if they've had such an exponential improvement…*

My favorite summary comment was on the issue I had let go:

"How could you use the internet to find patients with the condition to participate in your clinical trial?"

> *Why use the internet, right? Why not directly contact the oncologist?*

I especially liked this answer, not because it validated my instincts on how to best contact cancer patients, because there is a crowd out there that is drooling over "patient engagement" via the internet as a get-rich-quick scheme, and I want them to go just away.

The Committee Speaks

This meeting had so many different facets. It included a number of different presentations and public comment periods; I could probably continue writing about it until the next one. Anyone interested in registries should check out the presentation by Paul Coplan. But it's time I wrapped this up. My frying pan is ready for other little fishies.

I will fast forward to the end of the meeting, when it was time for the Committee to provide input to FDA's questions. CDRH asked the Committee to address five questions, of which three were multi-part. Too much text to post all of it here. And, although some of it was interesting, I didn't find it all that enlightening with respect to the issues of the day, to the point of being somewhat anticlimatic.

I am inclined to think that CDRH may have bitten off more than the Committee could chew, and might have done better to ask the Committee to give twice the consideration to half the questions. Some of the questions strayed a little or a lot from anything to do with "valid scientific data," such as how would the Committee like FDA to communicate to the public.

Perhaps it's just as well. I estimated that no more than half the Committee members had the background needed to address concerns about valid scientific data, and I wonder if the drift in the focus the questions might indicate that, somewhere between announcing the topic of the meeting and finalizing its list of questions, someone at CDRH also came to that realization.