Orthopedics This Week

1

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What's Up With New Post-Market Approval Studies?

By Walter Eisner

FDA has a new expectation about post-market approval studies for devices.

As anyone who has attended the last three FDA Orthopedic Advisory Panel meetings on ankles, hip resurfacing, and cervical discs has witnessed, there has been controversy about the new process that FDA staff have laid out to lead the panel through their deliberations regarding post-approval studies. This new process has been instituted after the transferal of oversight of post-approval studies from the Office of Device Evaluation (ODE) to the Office of Surveillance and Biometrics (OSB).

In short, the FDA has decided that orthopedic devices will now be required to have post-approval studies designed as part of the pre-market application process, and will, in effect, become a new condition for approval

Higher Cost, Less Innovation, and Fewer Advisory Options?

Some believe that this new condition will increase the costs of clinical studies and trials, serve to dampen the flow of new and innovative orthopedic products to patients, and tie the hands of the ortho panel as they recommend approval of devices, with or without conditions. The FDA believes this will improve patient safety.

We think device manufacturers may be paying the price for widely reported problems with pharmaceuticals and Congressional pressure on the FDA for more oversight and post-approval studies.

This week we bring you an interview with the person responsible within the FDA for post-approval studies, the chief of the epidemiology branch within OSB, Dr. Danica Marinac-Dabic. We also bring you the opinions of the industry representative on the ortho panel, Pamela Adams.

One Industry Perspective

Pamela Adams

Besides being industry rep on the ortho panel, Pamela Adams is also on the board of directors of the Orthopedic Surgical Manufacturer's Association (OSMA), an organization whose member companies market and sell over 85% of U.S. orthopedic medical devices. Adams is also senior VP and chief operating officer of the ETEX Corporation in Cambridge, Massachusetts.

"Industry understands and accepts that there is a need for valid scientific evidence to support product positioning in the marketplace," says Adams, "Companies are willing to conduct studies to collect such evidence. FDA's new focus on post-market [approval] studies may equate—we do not know yet—to more studies; an increase in studies equates to higher costs. The plain truth is that companies may chose not to bring products to market if the costs are too high. If barriers to U.S. innovation increase, patients will lose access to newer technologies."

Adams continues, "Industry needs predictability and consistency in the regulatory process. This new emphasis on post-market approval studies, reported publicly at advisory panels, has yet to be applied uniformly, or with suitable guidance. Companies are left to interpret and navigate on their own. What are the rules? How will it work? What might be the outcome of the Advisory Panel review?"

Concluding, Adams says, "This is a Center-wide initiative. But medical devices are different from drugs. Drugs represent billion-dollar markets and 10 – 20 years in the marketplace. Medical devices are usually outdated after 3 – 5 years, and represent far less potential revenue. Drug post-market study models are therefore not applicable to

medical devices: what value will be achieved by studying a device for 5 years, [then] presenting the study data to an Advisory panel, when the device is no longer on the market? Both OSMA and AdvaMed have expressed a desire to work closely with FDA to manage the change they wish to implement. This is critical to success. Industry wants to participate in the solution."

Dr. Marinac-Dabic Interview

For answers, we went to the person at the FDA responsible for overseeing the new FDA post approval process.

Danica Marinac-Dabic, M.D., Ph.D., M.M.Sc., is chief of the Epidemiology Branch, Division of Postmarket Surveillance, Office of Surveillance and Biometrics Center for Devices and Radiological Health (CDRH) at FDA. She spoke us to on June 13, 2007.

A New Oversight

OTW: Dr. Dabic, thank you for taking time to speak to our readers. There's been a change within the FDA in the way post-approval studies are handled. When did this take place?

Danica Marinac-Dabic
M.D., Ph.D., M.M.Sc.

DMB: Actually on January 1, 2005, there was a change in oversight of the post approval study [PAS] program and officially the program was transferred from the Office of Device Evaluation to the Office of Surveillance and Biometrics. Also, some review functions were transferred at that point as well—namely, epidemiology staff were included in the pre-market approval (PMA) review teams for "first-of-a-kind" devices.

During the last two years we've been working closely with our pre-market colleagues to fully implement the changes, leading to the full transfer of all post-approval studies to OSB that occurred on April 2, 2007. The full transfer includes oversight, tracking, and review functions for all open studies initiated by the Center since 1995 to this point.

The establishment of the [PAS] website demonstrates our commitment to transparency with post-approval commitments to make sure that all stakeholders have the most current information on how sponsors are meeting the post-market study commitments. On the web page you can find the reporting schedules as well as how the companies are complying with their reporting requirements. Also you can find the study progress. It does not divulge any confidential information. The website contains all information that can be shared with the public.

OTW: What was the purpose in making the change from ODE to OSB?

DMB: There was more than one reason. Several years ago, we performed an internal evaluation of the status of post-approval studies and looked at what actions we've been taking based on the results of the post-approval studies. Based on that internal evaluation, it was clear that we can better utilize the expertise that we have in OSB, namely, we have a staff of a dozen epidemiologists whose expertise includes the observational study design—the most frequent study design utilized in the post-market arena, as opposed to randomized clinical trials that are done pre-market. So we propose to utilize their expertise early in the pre-market review process in order to improve the quality of post-approval studies. That's one thing we felt we could do better.

The other reasons we instituted these changes was to ensure more effective and timely epidemiology input in the PAS design. In the past, the design issues of the post-approval studies were happening at a time when the device was about to be approved, or shortly after approval.

What's happening now is that we added the epidemiologist to every PMA review team in the pre-market phase as early as the filing date. So that epidemiology has a role to review the PMA submission with an eye towards identifying remaining post-market questions and rationale for post-approval studies. This early involvement gives the epidemiologist sufficient time to learn about the product area, to educate themselves about that particular product

and also work very interactively with the sponsor to design a good post-approval study while the device is still being reviewed pre-market. The PAS program goal is to complete this post-approval study protocol by the time the approval of the device is issued. Those changes also ensure the least burdensome approach, meaning that the sponsors will have easy access to our expertise as we interactively work with them to design a post-approval study.

OTW: You said that you'd be involved early on after the company has submitted their PMA. But it sounds like you see companies coming to you before they even design their clinical studies.

FDA Post-Approval Study Expectation in PMA

DMB: Many of the PMAs do not contain post-approval studies protocol when the PMA is submitted. We now communicate to the sponsor, even before the PMA is submitted, that the Center expectation is that each PMA should have at least the outline of a post-approval study at the time the PMA is submitted.

OTW: What will be the impact of this on the ortho panel discussions? What if the panel determined in their recommendation that they didn't think there was a need for a post-approval study?

DMB: As I mentioned, we work together with our pre-market colleagues to prepare the best possible presentation for our advisory panels. As a part of this presentation, epidemiologists present the rationale for the post-approval study based on our review, but we have specific questions for the panel, so we take their comments very seriously and we incorporate their opinions and recommendations into our final decision. The final decision is made by the FDA after all components of the review and panel input are obtained and taken into consideration.

New Advisory Panel Procedures

OTW: I'd like to ask about three (ankle, cervical disc, and hip resurfacing) PMA applications that are in the process of being decided upon by the FDA after recommendations of approval with conditions from the ortho panel. During those three panel deliberations there appeared to be different post-market approval processes. There was a lot of conversation between FDA ODE and OSB staff during those deliberations. Where you testing out various post-market strategies that you wanted to follow?

DMB: As you know we cannot speak publicly about the specific submissions that are currently under our review. What I can share with you is that our approaches to various submissions are different, because the submissions are to be evaluated based on the uniqueness of the device and the quality of the pre-market data. There are notable differences between the device groups you have mentioned, so one can't use the same post-approval study approaches for all of them. That is not a reasonable expectation and this approach would not serve either the sponsor or the public. We need to apply the most appropriate and least burdensome methodologies to the specific submissions. We are also committed to developing product specific epidemiology expertise that will add value to methodology expertise of our epidemiology staff

The approach we used to present the data to the panel slightly differed in the last three panel meetings. For example, the reason for this is that we are constantly looking into better ways of how to present to panel members and how to give them the most complete and objective information. Most of the panel members indicated that they prefer post-approval study presentations as part of the FDA talk in the morning rather than after the panel's motion to approve with conditions as happened in some of the panel meetings you described.

Addressing Objections

OTW: We notice that there have been some objections raised, particularly by the industry representative on the panel, regarding the new expectation of post-approval studies.

DMB: The Center is committed to raising the bar for post-approval studies (well-designed, science-based post-approval studies) to answer important post-market questions. Studies that are reasonable, that can be conducted effectively and that will lead to results that can be interpretable—results that we can act upon. The Center has demonstrated this commitment toward all

post-approval studies to better utilize this important post-market tool.

When we talked about some of the accomplishments, we talked about changes in the oversight, changes in the review process, we talked about the web page and we talked about the tracking system. The other important change is that we are proposing post-market updates for the advisory panels. This change, along with other changes, was presented at the OSMA meeting in April, and we had a chance to hear the industry concerns and to engage the outside experts and stakeholders in these kinds of discussions.

We hear back from our panel members that they make all those recommendations and they don't hear back about how the FDA acted in terms of asking for post-approval studies, what the status is of those studies and if there was any action taken based on those results.

New Challenges for Sponsors

OTW: What do you say to those who claim that these changes will make the approval process more expensive and difficult?

DMB: I don't know how this could be more difficult because we are not asking for the randomized control trials data post-market. We are seriously taking into consideration the least burdensome approach. The difference is that we would like to see the studies that have a specific post-market question defined. We'd also like to see the studies that have hypothesis built around those questions and adequate samples size, control group, and optimal length of follow-up.

OTW: If the communication is good between the sponsor, the ODE, and OBS, the sponsor should not be put in a position, in a post-market study, to create a new study or data. The post-approval study would simply be a continuation of observations of the existing data in place when they submitted their PMA?

DMB: That is partially correct. And there are reasons why it cannot be extrapolated to all submissions. Some of the reasons for doing the PAS are to study device performance in broader patient population under general condition of use as the device technology penetrates the market and moves from highly-trained physicians in best clinical sites to average clinicians and community hospitals. These general principles of post-approval studies are not new, we've been asking for these things before. We are focusing now on the orthopedic community. What we are trying to do now is to be sure we clearly have the post-market questions, but we are now being more consistent in our application of these principles.

OTW: Thank you Dr. Dabic. We're eager to see how the next panel meeting on July 17th plays out.

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