



Paclitaxel Post-Panel: FDA Discusses What's Next From a Regulatory Perspective

An interview with representatives from the FDA Center for Devices and Radiological Health on the key updates to the letter to health care providers, lessons learned for future trials and follow-up protocols, and additional plans for monitoring in the future.

WITH ELENI WHATLEY, PhD, AND ANDREW FARB, MD

What are the key updates in the current (August 7) notice on peripheral artery disease (PAD) treatment with paclitaxel-coated devices compared with the previous communication?

The FDA's letter to health care providers on August 7, 2019, updates findings and recommendations following the June 2019 FDA Advisory Committee panel meeting. This letter communicates the conclusion reached by the panel members and the FDA that paclitaxel-coated devices used to treat femoropopliteal disease are associated with a late mortality signal. One key recommendation is that for many patients, alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents provide a more favorable benefit-risk profile based on currently available information. The letter also emphasizes the importance of collecting additional long-term safety and effectiveness data to ensure that the benefit-risk profile of these devices remains appropriate. Lastly, we indicate that we are working with manufacturers on labeling updates for paclitaxel-coated devices and informed consent documents to include information about the late mortality signal.

How will the lessons learned in reexamining the paclitaxel trial data affect the design and follow-up protocols of future PAD trials? Will timelines to approval be affected as a result?

A key limitation of the current clinical trials is the amount of missing data, and device manufacturers have been working to address this problem by gathering additional follow-up information. Going forward, the FDA will place additional emphasis on device manufacturers and study sites, minimizing the number of

patients who are lost to follow-up. Regarding timelines for device approval, the FDA will continue to consider the totality of safety and effectiveness data in regulatory decision-making, which includes both shorter-term (eg, 6 months–1 year) and longer-term (≥ 2 years) follow-up.

Will future trials be more uniform in comparison to one another (for like products) in terms of endpoints and definitions?

The FDA works collaboratively with device manufacturers to design the most appropriate clinical trial to evaluate device safety and effectiveness to support the proposed indications for use. Often, the FDA provides sponsors with study design considerations that the agency believes will enhance the quality of the trial. Although the FDA does not mandate identical clinical trials for like products, it can be expected that key study elements (eg, enrollment criteria, primary endpoints, patient follow-up, event adjudication, study monitoring) will share many similarities. The FDA has also found that uniform clinical event definitions are helpful in interpreting study data, and we appreciate the collaboration of investigators with the professional societies in crafting these definitions. Even though clinical trial designs may be similar, one must be very cautious in attempting to draw conclusions based on a comparison of the results from different trials.

Does the FDA have guidance as to the patients it considers to be at high risk for restenosis, or does the agency defer to the physician?

In the letter to health care providers, the FDA noted that, "for individual patients judged to be at particularly high risk for restenosis and repeat femoropopliteal



interventions, clinicians may determine that the benefits of using a paclitaxel-coated device outweigh the risk of late mortality.” Because patient comorbidities, extent of disease, and lesion characteristics play a role in clinical outcomes, the FDA believes it is important for physicians to determine which patients are considered to be at a high restenosis risk and may have a favorable benefit-risk profile from treatment with paclitaxel-coated devices.

With trial data continually being collected in the United States and other countries, does the FDA believe there is potential that the growing/future body of evidence could either amplify or reverse the signal found by Katsanos et al should a future meta-analysis be conducted?

The FDA encourages the continued collection and evaluation of clinical data. As additional data become available and are analyzed, we are hopeful that this information will aid our understanding of the presence and magnitude of the late mortality signal, which will help clinical decision-making. The FDA is collaborating with device manufacturers, professional societies, and clinical investigators to support further analyses of previously collected and ongoing clinical trial and registry data.

What additional plans does the agency currently have to monitor for the presence of the signal?

As noted in our August 7 updated letter to health care providers, the FDA is continuing to work with device manufacturers, professional societies, and clinical investigators to monitor ongoing clinical trial and evaluate new data. If new information alters the current assessment of the late mortality signal or the benefit-risk profile of these devices, the FDA will communicate our conclusions to the public and take appropriate regulatory actions. ■

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