United States Regulatory Perspectives on Paclitaxel in PAD

Moderator Dr. Gary Ansel asks representatives from the FDA's Center for Devices and Radiological Health about controlling for ascertainment and investigator bias in future vascular device trials, potential changes for drug-based device approvals, how the agency weighs the level of data required for approval of new vascular devices, the statistical strength of the data from general use studies, and the level of data needed to update FDA's position on paclitaxel-containing devices.

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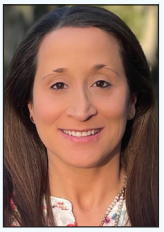

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Ascertainment bias as well as the potential for investigator bias appear to be evident when evaluating new devices, and these factors may have played a role in the paclitaxel data generated to date. How does FDA suggest trying to control for this in future vascular device trials?

FDA acknowledges the potential biases that are present in clinical trials. As always, FDA recommends prospectively taking efforts to control and minimize bias. One way to control for ascertainment and investigator bias is to blind the treatment physician and follow-up physicians of the treatment arm. Minimization of loss to follow-up is also important. FDA understands the difficulty in taking these measures in some circumstances and continues to recommend that individual investigators implement measures to control for biases.

Will there be any changes by FDA regarding drug-based device approval evaluations, and if so, will this be for all antiproliferative drugs or just paclitaxel? If so, what is anticipated in terms of effects on device approval (eg, time to approval) if more or different data are required?

FDA's evidentiary standard for drug-based devices remains a reasonable assurance of safety and effectiveness. For devices containing paclitaxel, given the late mortality signal, FDA has begun to review additional premarket longer-term clinical data in order to ensure that no additional increase in risk for late mortality is present. Evidentiary expectations for peripheral devices coated with drugs other than paclitaxel are still evolving because no such products have yet been approved. The community has published lessons learned from the experience with this signal and a retrospective look back at the previous peripheral interventional trials.[1] Our hope is that these recommendations are considered for future trials to support efficient device evaluation in which past issues with data, such as potential bias and missing data, are minimized. FDA recommends companies with drug-coated devices speak with FDA (eg, via presubmission) to discuss the data expectations for their specific device, drug, intended use, and patient population.

Did the industry/academic/FDA working group yield the outcomes FDA had hoped for?

FDA believes that the external collaborations that have been working on this safety signal have been very beneficial to date. FDA will continue to work with external stakeholders to continue to facilitate data development associated with this safety signal and to communicate with the public as new information becomes available.

During the recent FDA panel evaluating Lutonix (BD) below the knee (BTK), Dr. Bram Zuckerman voiced concerns the agency still has regarding paclitaxel. Since a mortality signal has occasionally also been seen in non–drug-based devices, how does the agency weigh the level of data required for approval of all new vascular devices, regardless of whether they involve a drug?

FDA believes that drug-based devices can offer different risks and benefits due to the presence of the drug. However, for any class 3 (highest-risk) medical device, reasonable assurance of safety and effectiveness must

be established regardless of whether the device contains a drug component. FDA is not holding drug-based devices to a different evidentiary standard but assesses the benefits and risks of each device and combination product separately based on the device design, intended use, and patient population. Both short- and long-term safety and effectiveness data are evaluated and considered as part of the benefit-risk profile of a device.

What follow-up point for drug-based BTK devices does the FDA consider optimal or necessary for device approval, and does this differ from non–drug-based devices?

FDA believes that short- and long-term time points are both important in evaluating the safety and effectiveness of drug-based BTK devices. Given the complexity and heterogeneity of patients with critical limb ischemia (CLI), typically with multiple comorbidities, FDA agrees with the consensus reached during the recent February 17, 2021, meeting of the Circulatory System Devices Advisory Panel that a 6-month primary endpoint can be appropriate.[2] However, as determined by the panel, FDA expects that additional long-term safety and effectiveness data (12 months and beyond) are provided to support a reasonable assurance of safety and effectiveness in the marketing submission, with additional follow-up to continue out to 5 years. As noted previously, evaluation of drug-based devices should consider the additional potential risks and benefits of the drug component. Hence, the endpoints and time points may differ between drug- and non–drug-containing devices, depending on the device design, intended use, and patient population.

We now have > 200,000 propensity-matched patients in general use studies (both claudication and CLI) without any evidence of elevated early or delayed mortality compared to plain old balloon angioplasty. What is the view of the FDA on the statistical strength of these data?

FDA acknowledges that additional, robust, real-world evidence (RWE) is available that does not demonstrate an elevated risk for late-term mortality for drug-coated devices compared to uncoated devices. These data do suggest an acceptable safety profile for these devices in real-world clinical use. However, there remain limitations with the current RWE as compared with the pivotal trials due to differences in patient population, limited duration of follow-up, missingness, and biases. Given the limitations to both the RWE and randomized data sets, it is difficult to identify the reason for the discrepancy in late-term mortality results. FDA continues to evaluate all available data with regard to this safety signal. As the RWE infrastructure becomes more robust with reduced missingness and longer-term data, FDA hopes that signals such as these may be addressed more quickly.

We have been studying and evaluating the paclitaxel safety concern for several years now, which I believe is affecting care delivery, as evidenced by a continuing lower level of drug-coated balloon (DCB) and drug-eluting stent (DES) usage in the United States. Japan's Pharmaceuticals and Medical Devices Agency officially stated that there are not enough data to limit use of paclitaxel-containing devices. What level of data will be needed for the FDA to either confirm its concern for a delayed increase in mortality for paclitaxel devices or provide an updated safety statement?

Patients should receive the best available medical therapy, with all options carefully considered based on the patient and lesion characteristics. The effectiveness of DCBs and DESs to improve blood flow to the legs in accordance with the devices' intended uses has been demonstrated, and FDA continues to work with physicians, industry, and other external stakeholders to facilitate data development to better refine the signal magnitude and cause. FDA will continue to communicate with the public as new information is available to provide additional answers regarding these open questions. ■

1. Lottes AE, Whatley EM, Royce SM, et al. Important considerations for trials for peripheral arterial disease: lessons learned from the paclitaxel mortality signal: a report on behalf of the registry assessment for peripheral interventional devices (RAPID) paclitaxel pathways program. Am J Heart. 2021;232:71-83. doi: 10.1016/j.ahj.2020.10.070
2. US Food and Drug Administration. 24 hour summary of the Circulatory System Devices panel meeting: Lutonix 014 DCB: February 17, 2021. Accessed August 18, 2021. https://www.fda.gov/media/146128/download