

REGULATORY UPDATE

Paclitaxel in 2020 and Beyond

An interview with representatives from the FDA's Center for Devices and Radiological Health on the current state of paclitaxel-coated device use, including safety, new data, and effects on the peripheral trial landscape.

WITH ELENI WHATLEY, PhD; SARA ROYCE, PhD; AND MISTI MALONE, PhD

We are now over 1 year out from the advisory panel meeting the FDA convened regarding paclitaxel-coated devices in peripheral vascular applications. What is the current status of the FDA's ongoing data collection and review of these products and their use? Are we any closer to a definitive answer on paclitaxel safety?

Signal refinement remains dynamic as new data and analyses from ongoing clinical trials and real-world evidence (RWE) have been rapidly emerging since the panel meeting in June 2019. FDA continues to evaluate these data as they become available to assess the potential impact on the benefit-risk profile of these devices. To date, we continue to believe that the benefits outweigh the risks for use of these devices in selected patients who are at high risk for restenosis as determined by their treating physicians. However, there is still uncertainty regarding the mechanism for the increased mortality observed in the randomized controlled trials (RCTs). FDA is collaborating with various groups and organizations—including the paclitaxel-coated device manufacturers, clinical researchers, and multistakeholder groups (eg, RAPID [www.mdpinet.net/rapid], VISION [www.mdpinet.net/vision])—to better understand the signal magnitude, mechanisms, and lessons learned.

What are some of the key lessons learned from the panel as well as the overall examination of existing trial data to determine the safety of these devices?

The key lesson from the panel is that the peripheral artery disease (PAD) community needs to do better in the execution of future trials, particularly to reduce the amount of missing data. Because high loss-to-follow-up rates in the RCTs limited the interpretability of the long-term results and consequently the significance of the observed mortality signal, minimizing loss to follow-up in future studies is essential to enhance our understanding of the benefit-risk profile of these products. Additionally, capturing key information such as concomitant medication usage/compliance and additional revascularization procedures would be valuable to address future questions. The RAPID Pathways Collaborative Paclitaxel Project Working Group, consisting of PAD experts from academia, industry, regulatory, and the clinical community, is in the process of characterizing the landscape of available data sources, trial designs, and analytic methodologies to further describe the lessons learned and suggest recommendations for future trials and analyses.

Paclitaxel products have remained on the market, and new iterations and applications of existing platforms have been approved since the safety concern was raised. Can you tell us how this reflects the agency's current understanding of the risks and benefits of these products?

As discussed at the panel, currently marketed paclitaxel-coated devices offer benefits of improved arterial patency and reduced repeat revasculariza-

tion procedures, which are important considerations for patients. As noted in our Letter to Health Care Providers dated August 7, 2019, we believe that clinicians have the most insight into their patients' disease characteristics to determine if the benefits of using a paclitaxel-coated device outweigh the risk of late mortality.¹ Given the uncertainty that remains regarding the late mortality signal, we continue to believe that for patients at high risk for restenosis, the benefits may outweigh the risks for these devices.

We recognize that this arena remains dynamic as newer generations of devices are being studied with the goal of improving care for PAD patients. The marketing application for any new product should include longer-term data and analyses that sufficiently demonstrate that the risk of late mortality is no worse than that of currently marketed devices.

Krishna Rocha-Singh, MD, and colleagues recently published the findings of the VIVA independent patient-level data meta-analysis, which found a safety signal regarding paclitaxel and mortality but a weaker one than that found by Katsanos et al in 2018.^{2,3} What is the agency's view on this finding?

FDA appreciates the continuing analyses that are being conducted on available and emerging data sets. In the same edition, FDA wrote a commentary on this article that provides our perspectives on these findings.⁴ In short, although some limitations of the analysis were apparent, we commend Dr. Rocha-Singh and colleagues for their high-quality analysis. By including additional follow-up mortality data, the VIVA study showed a smaller hazard ratio than previous analyses, but the late mortality signal was still present.

Certain registries, such as those pulling data from the Vascular Quality Initiative and Medicare databases, have gained prominence at the podium and in journal publications in the nearly 2 years since the *Journal of the American Heart Association* publication by Katsanos et al. How does the FDA view the quality of data from this type of registry? How do those registries fit in with data from RCTs, meta-analyses, and company-sponsored registries?

RWE generated from high-quality data sources, including registries, can provide information on a large number of patients and represent a broad patient population. However, RWE has several limitations, including the potential for inconsistent and incomplete capture of data elements, potential biases,

and limited long-term follow-up. FDA recognizes the efforts to improve the quality of data collection and analysis of these RWE sources and appreciates these efforts. However, we believe that prospectively designed RCTs provide the most robust data because randomization minimizes bias by attempting to enroll treatment groups with matched baseline characteristics. FDA views registry data sets as important complementary sources of information that should be considered in totality with the other data sets. It is important to note that the late-mortality safety signal identified in the pivotal RCTs has not, to date, been identified in registry or claims data sets, although many of these data sets have limited long-term follow-up. Therefore, further research is needed to understand the discordant results between RCTs and observational data.

Have there been any modifications to the FDA's approach to ongoing and new PAD trials, specifically those involving paclitaxel, since the safety signal was raised and the panel was held?

Sponsors of ongoing trials for paclitaxel-coated devices have been requested to maintain study subject follow-up through 5 years and to update their informed consent forms to include language on the late mortality risk. New trials for these devices have adapted the lessons learned from the safety signal, such as incorporating flexible options to improve patient follow-up, collecting detailed information on new revascularization procedures and concomitant medications, and incorporating additional statistical analyses.

How do you think the examination of this controversy will positively influence the peripheral trial landscape? What are the priorities of the FDA moving forward?

Although the examination of this safety signal has been challenging because of limitations of the existing data, these challenges are already shifting the trial landscape in a positive direction. Changes include emphasizing the importance of complete follow-up and collaborative crosstalk between stakeholders (ie, industry, regulatory, academia, clinicians, patients) to ensure consistency in data capture and event definitions while also capturing patient perspectives and patient-reported outcomes. The RAPID Pathways Collaborative Paclitaxel Project Working Group has connected multiple stakeholders and facilitated a better understanding of the trial landscape, the limitations of completed or ongoing trials, and critical

areas for improving collaborative efforts to streamline future studies.

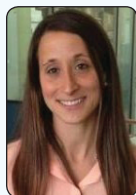
Does the safety concern regarding paclitaxel raise the bar for proving safety of all devices that incorporate antiproliferative agents, such as limus-based devices? If so, how might this be seen in the clinical trial setting?

Marketing applications for the highest-risk medical devices, including those that incorporate antiproliferative agents, require a reasonable assurance of safety and effectiveness based on the totality of available data. Given this safety signal, increased emphasis may be placed on the availability of sufficient long-term data to demonstrate the robustness of effectiveness as well as continued safety. Therefore, expectations regarding trial design and minimization of missing data continue to be stressed. These changes may be reflected in options for follow-up by telephone, the

collection of additional device procedures, concomitant medication usage and dose, and standardization of death and adverse event data capture.

FDA recognizes the evolving clinical and medical device landscape. We strive to be collaborative to further understand this signal and create the least burdensome path for future device iterations and generations to help bring high-quality, safe, and effective medical devices to patients. ■

1. US Food & Drug Administration. August 7, 2019 update: treatment of peripheral arterial disease with paclitaxel-coated balloons and paclitaxel-eluting stents potentially associated with increased mortality. Accessed August 19, 2020. <https://www.fda.gov/medical-devices/letters-health-care-providers/august-7-2019-update-treatment-peripheral-arterial-disease-paclitaxel-coated-balloons-and-paclitaxel>
2. Rocha-Singh KJ, Duval S, Jaff MR, et al. Mortality and paclitaxel-coated devices: an individual patient data meta-analysis. *Circulation*. 2020;141:1859-1869. doi: 10.1161/CIRCULATIONAHA.119.044697
3. Katsanos K, Spiliopoulos S, Kitrou P, et al. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2018;7:e011245. doi: 10.1161/JAHA.118.011245
4. Royce S, Chakraborty A, Zhao Y, et al. US Food and Drug Administration perspective on "mortality and paclitaxel-coated devices: an individual patient data meta-analysis." *Circulation*. 2020;141:1870-1871. doi: 10.1161/CIRCULATIONAHA.120.047376



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