

FDA Paclitaxel Safety Panel Preview

An interview with FDA CDRH representatives discussing the upcoming advisory panel meeting to review concerns and current data on paclitaxel-eluting device use.

WITH KENNETH CAVANAUGH, PHD, AND MISTI MALONE, PHD

The FDA's Center for Devices and Radiological Health (CDRH) has convened an advisory panel regarding the potential safety signal that associated paclitaxel use with early mortality. What does FDA aim to accomplish in this 2-day session?

On June 19 and 20, 2019, FDA will ask the committee to discuss and make recommendations on information related to recent observations of increased long-term mortality in patients with peripheral artery disease treated with paclitaxel-coated balloons and paclitaxel-eluting stents. Specifically, FDA will request panel input regarding the presence and magnitude of the signal, potential causes, the influence of missing data and covariates, and recommendations for future regulatory actions and clinical evidence collection associated with the findings.

How will this panel be assembled, and who will comprise it?

The panel will be composed of experts from pertinent clinical specialties (eg, cardiology, interventional radiology, vascular surgery), pharmacologists, statisticians and epidemiologists, and patient, consumer, and industry representatives.

Who will have the opportunity to present and speak?

Any member of the public may present and speak at the panel meeting. Typically, representatives from the affected industry, professional organizations and societies, individual/organizational stakeholders, and patients present data, information, and views.

What have you asked the device manufacturers to provide in advance of the panel?

In general, FDA has interacted with affected parties to further assess available data with particular focus on approved paclitaxel-coated devices (ie, drug-coated bal-

MEETING INFORMATION

WHAT:

FDA Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting

WHEN:

June 19, 2019: 8:00 AM–5:00 PM EDT

June 20, 2019: 8:00 AM–3:00 PM EDT

WHERE:

Gaithersburg Holiday Inn
Grand Ballroom
Two Montgomery Village Ave.
Gaithersburg, MD 20879

loons and drug-eluting stents) used to treat femoropopliteal peripheral artery disease. FDA's goal is to facilitate collaboration and additional analyses to efficiently utilize resources to address this important signal.

What will FDA be looking for in the data that are not already included in the trial and patient-level data required to be reviewed prior to device approval?

FDA intends to evaluate the available clinical data sets for the devices marketed in the United States, including patient-level data from the pivotal trials and other trials or registries.

Will FDA look at the technologies separately, both in classes of drug-eluting stents and drug-coated balloons, but also specific platforms?

FDA intends to discuss relevant data both in aggregate and by individual product.

Is it possible FDA will distinguish between applications and make separate decisions for each based on relative risk/benefit considerations?

FDA plans to request input from the panel on the expected benefits and risks for specific patient populations and other disease states.

In the recent FDA letter, it is suggested that paclitaxel-eluting products might be considered for patients at high risk for restenosis. Which patients would fall into this category?

The currently marketed devices have demonstrated a benefit in reducing restenosis and repeat procedures. Different patient populations have different needs and expectations regarding the benefit-risk profile of a device. The treatment decision is case-specific and should take into account the patient's history and characteristics of the lesion to be treated. We continue to recommend that, for most patients, alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents should generally be used until additional analysis of the data has been performed.

What is the range of potential outcomes from the panel and FDA's ongoing data collection and review?

The panel will discuss and make recommendations for addressing and mitigating the safety concerns. The discussion may include, but is not limited to, additional collection of nonclinical or clinical data, modifications to labeling and informed consent documents, and altering clinical trial design. FDA will use the panel's discussion to help inform any next steps.

How will FDA mitigate potential shortcomings inherent in cause-of-death reporting in attempting to determine a biological causal link?

The analyses conducted and presented publicly so far have highlighted the existing shortcoming associated with cause-of-death reporting, missing data, and uncollected covariates that have confounded interpretation of the mortality data. More systematic approaches to the adjudication process will also be discussed.

If no specific biological causal link is determined, but a statistical signal remains, how will this affect the FDA's decisions regarding paclitaxel product oversight?

This is an important topic of ongoing discussion.

Will the FDA consider both as-treated and intention-to-treat analyses of the major data?

FDA will analyze the clinical data for both the intention-to-treat and as-treated groups. Results from both groups may provide valuable information.

How will FDA address both known and unknown exposures of control patients to paclitaxel?

The pivotal clinical trials limited use of additional paclitaxel-containing devices prior to the 12-month follow-up, and such use was generally reported. Although we recognize the possibility that patients in either study arm may have undergone unreported new or repeated exposure to paclitaxel-coated devices beyond 12 months, assessing the impact of these treatments on the mortality signal could present challenges. This further underscores the importance of robust follow-up reporting even after the primary endpoint evaluation.

Will the panel conclude with a vote, as is the case with approval advisory panels?

The agenda will be available ahead of the meeting; however, the discussion during the meeting will be used to inform FDA's understanding of the benefit-risk profile for these devices and potential next steps.

Is there a target timeline for the completion of data review and subsequent decisions to be made?

FDA is committed to appropriate and timely communication and implementation of any additional clinical recommendations and potential regulatory actions following the meeting. ■

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