FDA Activities

September 2015 Advisory Committee to discuss Essure Safety and Effectiveness

The FDA has been examining safety concerns about Essure raised by patients and cited in Medical Device Reports (MDRs). We convened a meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee on September 24, 2015 to:

- discuss currently available scientific data pertaining to Essure's safety and effectiveness,
- hear expert scientific and clinical opinions on the risks and benefits of the device, and
- hear concerns and experiences of women implanted with Essure.

Meeting participants and the panel also discussed recommendations for:

- Additional prospective clinical data collection to better understand adverse events such as allergic reaction and autoimmune response, persistent pain, device removal, migration, perforation or fragmentation and bleeding;
- Improved physician training and education;
- Improved patient counseling and education to facilitate informed decision-making; and
- Labeling modifications.

The Advisory Committee meeting provided valuable information and perspectives the FDA considered to inform our next steps.

FDA's Review of Available Information after the September 2015 Advisory Committee Meeting

After careful review of concerns identified by the public speakers and the feedback and recommendations provided by the panel (See Advisory Committee meeting summary and panel transcript), comments submitted to the public docket, and

additional medical literature and adverse event reports that have been published or received since the Advisory Committee meeting. The FDA:

1. Ordered Bayer to conduct a postmarket surveillance study to obtain more data about Essure's benefits and risks.

Like the Advisory Committee panel, the FDA believes more clinical data is needed to better define and understand certain outcomes and events that may be associated with Essure when compared to women who undergo tubal ligation. Findings from the study will inform any future FDA action.

On March 29, 2016, Bayer submitted a postmarket surveillance study plan to the FDA for the Essure device and the agency approved an updated plan on September 2, 2016. The FDA believes that results collected from the approved study plan will help the agency better understand complications associated with the Essure device, as well as the underlying reasons inhibiting the completion of the three steps of the Essure System method (device insertion/gplacement, use of alternative contraception for three months, and a confirmation for proper location/occlusion). Additional details on the postmarket surveillance study are available on the 522 Postmarket Surveillance Studies webpage.

2. Intends to require a boxed warning and Patient Decision Checklist as part of the labeling to help ensure that a woman receives and understands information regarding the benefits and risks of this type of device. In addition, FDA issued the draft guidance, "Labeling for Permanent Hysteroscopically-Placed Tubal Implants Intended for Sterilization" to provide the public an opportunity to comment on the proposed language to be included in these warnings.

Advisory Committee meeting and comments received through the public docket indicated that patients are not reliably receiving and/or understanding appropriate information about the device and associated risks prior to making a sterilization decision – for Essure as well as other sterilization methods. Panel members recommended changes to the patient and physician labeling and more aggressive methods to ensure patients are well-informed of risks. FDA intends to require a boxed warning and Patient Decision Checklist as part of the labeling to help ensure that a woman receives and understands information regarding the benefits and risks of this type of device. The FDA issued draft guidance on the content and wording to be included in the product labeling for permanent hysteroscopically-placed tubal implants with respect to:

- A boxed warning with safety statements to better communicate to patients and providers the significant side effects or adverse outcomes associated with these devices and information about the potential need for removal;
- A Decision Checklist with key items about the device, its use, and safety and

effectiveness outcomes, which the patient should be aware of as they consider their sterilization options.

The 60-day comment period on the draft guidance ended on May 3, 2016, and the FDA is in the process of reviewing all comments submitted to the public docket before issuing a final guidance

3. Is in the process of completing its evaluation of the trade complaint.

The Office of Compliance within the Center for Devices and Radiological Health (CDRH) is in the process of completing its investigation of the trade complaint regarding allegations initially made in a Citizen Petition. These allegations include clinical trial misconduct, notably that clinical trial participants' medical records were altered to reflect more favorable data about participants' experiences, and that the sponsor violated the terms of the PMA approval order and violated laws that relate to the manufacturing and marketing of Essure.

The FDA inspected Bayer as part of the complaint investigation. In addition, Bayer provided the FDA with the available case report forms that documented patient experiences during Essure clinical trials.

The FDA analyzed these forms to evaluate the incidence of cross-outs and discrepancies regarding patient-reported pain, comfort and satisfaction ratings to assess whether modifications favored Essure safety and effectiveness. The Agency found that less than 1 percent of case report form data pertaining to pain, bleeding, device placement/movement and pregnancy were changed during the clinical trials. Although modifications to the case report forms were identified, our analysis did not find evidence the sponsor purposefully modified patient responses to reflect more favorable data for Essure. More information about the Agency's case report form analysis can be found in the Summary and Key Findings document.

FDA's Review of Reported Problems

Problems that were reported during clinical studies are addressed in the Essure product information (labeling for physicians and patients). Some women have reported to the FDA that they have experienced pain or other health problems after Essure placement. Other reports that are not included in the labeling, were not observed in post-approval studies, or described in the clinical literature include extreme fatigue, depression, weight gain, allergy and hypersensitivity reactions. Many of these outcomes were discussed at the Advisory Committee meeting and cited in docket comments.

The FDA relies on a variety of postmarket surveillance data sources to monitor the safety and effectiveness of medical devices. The FDA conducted a thorough review of the available information about Essure and the experiences of patients who have had

Essure since the FDA approved it in 2002. This includes experiences of patients who have had positive outcomes with Essure as well as those who have experienced problems. For this review, the FDA:

- ***Analyzed Essure patient reports of problems (including Web-based testimonials) and reports of problems submitted to the FDA from other sources, including doctors, patients, and the manufacturer of Essure.***

  Adverse event and product problem reports submitted to the FDA are one source we use to monitor marketed medical devices. These reports may contribute to the detection of potential device-related safety issues as well as to the benefit-risk assessments of these devices. While such reports are a valuable source of information, this type of reporting system has notable limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. Complaints or adverse event reports do not necessarily directly indicate a faulty or defective medical device, and adverse event reports alone cannot be used to establish or compare rates of event occurrence. Additionally, we may receive multiple reports related to the same event making it difficult to determine actual numbers of events.

  The FDA conducted a search of the Manufacturer and User Facility Device Experience (MAUDE) database. From Nov. 4, 2002, Essure's approval date, through December 31, 2015, the FDA received 9,900 medical device reports related to Essure. The majority of reports received since 2013 have been voluntary reports, mostly from women who received Essure implants.

  The most frequently reported patient problems during this period were pain/abdominal pain (6989), heavier menses/menstrual irregularities (3210), headache (2990), fatigue (2159), and weight fluctuations (2088). Most of the reports received listed multiple patient problems in each report. The most frequent device problems reported were patient-device incompatibility (2016) (for example, possible nickel allergy), migration of the device or device component (854), device operating differently than expected (490), device breakage (429), device difficult to remove (280), malposition of the device (199), and device difficult to insert (187). Multiple device problems can also be listed in each report.

  There have been 32 reports coded by the submitter as death. Six of these were incorrectly coded, as there was no indication of death in the report. Of the remaining 26, six relate to four adult deaths; 18 reports relate to 15 incidences of pregnancy loss; and two reports related to two incidents of a death of an infant after live birth.

  FDA has received 631 reports of pregnancies in patients with Essure. Of these, 150 were reported to result in a live birth; 204 did not indicate whether the pregnancy resulted in a live birth or pregnancy loss; and 294 resulted in

pregnancy loss.

Among the 294 reports of women who experienced a pregnancy loss, 96 were reported as ectopic pregnancies; 43 were reported as elective terminations of pregnancies, and 155 were other pregnancy losses.

Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report.

- ***Reviewed the results from two Post-Approval Studies (PAS) conducted by Conceptus as part of the product's 2002 approval.***

  PAS I was conducted to gather five-year follow up information on the participants in two groups of patients that were part of premarket clinical trials (known as Phase 2 trial and Pivotal Trial). The study evaluated:

  - how well Essure prevented pregnancy;
  - the safety of the procedure used to place Essure; and,
  - the safety of Essure once implanted, including patient comfort.

  Although there is evidence of complications, as there are with many medical devices, overall results from this study did not demonstrate any new safety problems or an increased incidence of problems since the time of device approval.

  PAS II was conducted to evaluate bilateral placement rate (insert placement in both the right and the left Fallopian tubes at first attempt) for newly trained physicians in the U.S. Data from this study were used to evaluate the training procedures and to update labeling.

  You can view a summary of Essure PAS results for the two studies ordered in conjunction with the PMA approval, which have been extracted from the Post-Approval Study Status web page.

  Subsequent to the product's approval in 2002, three PMA supplements were approved with post-approval studies required as conditions of approval. One supplement was related to device modifications; the other two supplements supported labeling modifications. Details on the study protocols and status are posted on the Post-Approval Study Status web page.

- ***Evaluated the available clinical literature to better understand long-term complications.***

  FDA sought to determine what long-term complications may be associated with Essure more than five years after placement, because the post-approval study evaluated safety and effectiveness only up to five years. To date, we have found

no conclusive evidence in the literature indicating any new or more widespread complications definitely associated with Essure occurring more than five years after Essure placement.

The Executive Summary prepared for the Advisory Committee meeting provides a comprehensive overview of Essure and the FDA's review, including post-market information, clinical literature and information from ongoing studies. FDA continues to monitor the safety of Essure to ensure it does not pose an increased risk to public health and that its benefits continue to outweigh the risks.

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