Food and Drug Administration

Re-Evaluation of Case Report Forms Supporting the Initial Approval of the Essure System for Permanent Birth Control

Summary and Key Findings
February 29, 2016

1. Introduction

The FDA conducted a re-evaluation of the case report forms (CRFs) from the original clinical trials supporting the initial approval of the Essure System for Permanent Birth Control . This re-evaluation was performed to assess allegations of study misconduct that: (1) items on the CRFs had been inappropriately modified by study investigators and/or the manufacturer, and (2) the CRFs contain inappropriate discrepancies between the subject reported level of pain and the subject reported "comfort wearing the device."

FDA conducted an inspection of the current PMA holder, Bayer HealthCare, and obtained the available CRFs as well as the line item data for the pivotal study in digital format.

This document contains the summary and key findings of FDA's re-evaluation.

2. Regulatory Background

In November 2002, the FDA approved a Premarket Approval Application (PMA) for the Essure System for Permanent Birth Control , a Class III device. Conceptus, Inc. (subsequently acquired by Bayer HealthCare in 2013) submitted the original PMA (P020014) for the product in April, 2002.

The product consists of an introducer, delivery catheter, and microinsert. A microinsert, which is composed of nitinol, stainless steel, and polyethylene terephthalate (PET), is placed into each of a woman's fallopian tubes where it elicits an inflammatory reaction and response which, over time, leads to occlusion of the fallopian tubes by tissue ingrowth. Initial approval was based on both nonclinical and clinical data. Early clinical data consisted of "feasibility studies" to evaluate initial device placement, mode of action, and to confirm initial safety. The primary clinical studies which provided effectiveness and safety data, and upon which the PMA relied to demonstrate a reasonable assurance of safety and effectiveness were the "Phase 2" (STOP 10) trial, and the larger "Pivotal" study (STOP 2000). These latter two studies were the focus of this CRF re-evaluation. In total, 745 women underwent the device placement procedure, and 664 had successful bilateral placement. In November of 2002, following a review by the Obstetrics and Gynecology Panel of the Medical Device Advisory Committee, the PMA was approved.

3. *Methodology*

3.1 Case Report Form Review

The available CRFs were reviewed to identify modifications (cross-outs and/or changes) made to the recorded data elements. Modifications made to specific safety outcomes (pain, bleeding, and device placement/movement) and/or the primary effectiveness endpoint (pregnancy) were recorded. Re-evaluation focused on CRFs up to and including 2-year follow-up as these time points represented the primary data upon which the Advisory Committee made their approval recommendation and the FDA based their approval decision. Each case where a CRF had multiple cross-outs or changes affecting one of the key outcomes, was evaluated.

Each study (Phase II, Pivotal) required CRFs to be completed at each of the numerous post-implant follow-up office visits or phone calls. In addition, individual CRFs could have more than one item pertaining to the outcomes (pain, bleeding, device placement/movement, pregnancy). In total, the Phase II and Pivotal study CRF forms for the 745 women contained more than 100,000 data points pertaining to these four outcomes.

After identifying individual items that were modified, the potential impact of the cross-outs and changes was assessed by determining whether the change favored device safety or effectiveness, or not. CRF modifications were categorized as described in TABLE 1.

TABLE 1. Categorization of Case Report Form Modifications

DESCRIPTION	CATEGORY	EXAMPLE
Change Favors Device Safety or Effectiveness	Change Favorable	Severity of pain experienced changed from severe to moderate intensity
Change Does Not Favor Device Safety or Effectiveness	Change Unfavorable	Duration of pain event after device placement changed from 2 days to 7 days.
Change Is Neither Favorable Nor Unfavorable OR Cannot Determine	Change Indeterminate	Type of pain was changed from “dull” to “aching”.

3.2 Assessment of Relationship of Pain With Comfort Wearing the Device and Subject Satisfaction

Line item data from the original Essure pivotal study was used to assess the relationship between the subject's reported comfort wearing the device and the subject's responses to questions assessing her pain.

A question pertaining to the subject's comfort wearing the device was asked at several time points during the pivotal study follow-up. Subjects could report their comfort as: excellent, very good, good, fair, or poor. A formal study definition of "comfort wearing the device" was not included in the study protocol. Therefore, individual study investigators may have presented the question differently, and individual subjects may have interpreted the question differently. For example, some women may have equated the question with asking about the presence or absence of pain, while others may have interpreted the question to be asking whether or not they could "feel" the device inside their body.

Analysis was conducted to evaluate the relationship of the subjects' reported comfort wearing the device to contemporaneous reports (during the same follow-up contact) of pain duration (chronic or intermittent), severity (mild, moderate, severe) and location (abdomen/pelvis versus other).

A similar evaluation was performed for pivotal study data to assess the relationship between the subject's reported satisfaction with the device and their responses to questions assessing their pain. Subjects could respond to questions assessing their satisfaction with the device with one of the following answers: very satisfied, somewhat satisfied, neither satisfied or dissatisfied, somewhat dissatisfied, or very dissatisfied.

4. Results

4.1 Case Report Form Review

Among the 745 subjects enrolled in the Phase II and Pivotal Studies supporting initial Essure approval, 268 CRF modifications to the individual data elements involving the four outcomes reviewed (pain, bleeding, device placement/movement, pregnancy) were identified (TABLE 2). In total, this represents modifications to less than 1% of the more than 100,000 data items comprising these outcomes.

Key additional observations include:

- Among the four outcomes (pain, bleeding, device placement/movement, pregnancy), CRF modifications affecting pain-related items were most common and accounted for approximately half of the changes observed. Approximately equal numbers of the pain-

related modifications were categorized as favorable to the device, unfavorable to the device, or indeterminate.

- Data elements pertaining to bleeding, device placement/movement, and pregnancy were modified less frequently.

- Overall, 35.1% of the observed CRF modifications were changes that were favorable to the device, while the remaining changes were either unfavorable to the device or indeterminate.

TABLE 2. Summary of Case Report Form Modifications

	Pain	Bleeding	Placement	Pregnancy	Total
	Items (Subjects)	Items (Subjects)	Items (Subjects)	Items (Subjects)	Items (Subjects) [% of all items]
CHANGE FAVORABLE TO DEVICE	46 (43)	31 (28)	15 (15)	2 (2)	94 (82) [35.1]
CHANGE UNFAVORABLE TO DEVICE	43 (40)	25 (25)	12 (12)	1 (1)	81 (76) [30.2]
CHANGE INDETERMINATE	46 (40)	19 (17)	23 (20)	5 (5)	93 (73) [34.7]
TOTAL	135 (112)	75 (65)	50 (40)	8 (8)	268 (184) [100]

Summary of Key Findings – CRF Modifications

Less than 1% of CRF data items pertaining to key outcome measures were modified during the conduct of the Phase II or Pivotal Essure clinical trials. A pattern of CRF modifications favoring the device was not observed.

4.2 Relationship of Pain With Comfort Wearing the Device and Subject Satisfaction

A summary of the analysis related to pain and comfort wearing the device is shown in TABLE 3.

Overall, approximately 96-98% of study subjects reported very good or excellent comfort wearing the device in the pivotal study. Among this subset of subjects, 10.4-14.1% reported some pain at follow-up with a smaller percentage of subjects reporting continuous pain, or moderate or severe pain. A small percentage of women reported excellent or very good comfort wearing the device despite moderate or severe continuous pain.

TABLE 3. Relationship of Pain With Comfort Wearing the Device in the Pivotal Study

SUBJECTS	**Comfort Wearing Device Rated as Excellent or Very Good**					
	Months following Discontinuation of Alternative Contraception					
	3	**6**	**12**	**18**	**24**	**Range**
Subjects Rating Comfort as Excellent or Very Good (%)	96.4	98.0	97.7	96.1	96.2	96.1-98.0
Any Pain (%)*	14.1	10.7	13.7	10.4	13.2	10.4-14.1
Continuous Pain (%)*	8.1	3.2	3.5	5.6	4.8	3.2-8.1
Moderate or Severe Pain (%)*	10.3	7.5	10.4	8.5	9.4	7.5-10.4
Moderate or Severe Pain AND Continuous Pain (%)*	6.1	2.7	3.0	5.1	3.0	2.7-6.1
Moderate or Severe Pain AND Continuous Pain AND Abdominal or Pelvic Location (%)*	4.0	1.1	2.8	4.3	2.3	1.1-4.3

* Percentage of subjects reporting symptom since last scheduled contact among those rating comfort as excellent or very good.

A summary of the analysis related to pain and subject satisfaction is shown in TABLE 4.

Overall, approximately 94-96% of study subjects reported their satisfaction as “very satisfied” in **t**he pivotal study. Among this subset of subjects, 9.8-14.1% reported some

pain at follow-up with a smaller percentage of subjects reporting continuous pain, or moderate or severe pain. A small percentage of women reported that they were very satisfied with the device despite moderate or severe continuous pain.

TABLE 4. Relationship of Pain With Subject Satisfaction in the Pivotal Study

SUBJECTS	Subject Satisfaction Rated as Very Satisfied					
	Months following Discontinuation of Alternative Contraception					
	3	6	12	18	24	Range
Subjects Rating Satisfaction as Very Satisfied (%)	94.4	95.9	94.6	96.1	94.1	94.1-96.1
Any Pain (%)*	14.1	9.8	13.9	10.6	13.5	9.8-14.1
Continuous Pain (%)*	8.1	3.0	3.3	5.6	4.6	3.0-8.1
Moderate or Severe Pain (%)*	10.1	7.0	10.8	8.9	9.4	7.0-10.8
Moderate or Severe Pain AND Continuous Pain (%)*	5.8	2.5	3.0	5.1	2.7	2.5-5.8
Moderate or Severe Pain AND Continuous Pain AND Abdominal or Pelvic Location (%)*	3.8	1.1	2.8	4.3	2.1	1.1-4.3

* Percentage of subjects reporting symptom since last scheduled contact among those rating satisfaction as very satisfied.

Notably, subjects reporting symptoms of pain since their last scheduled contact represent a heterogeneous group. The pain reported could include abdominal/pelvic pain or non-abdominal/pelvic pain, intermittent/infrequent episodes of pain or continuous pain, and pain associated with menses (either typical or atypical for the subject), dysuria (painful urination), and/or dyspareunia (painful sexual intercourse).

This analysis did not identify any "inappropriate discrepancies" in the data concerning the pain, comfort and satisfaction results. Rather, the analysis suggests that the presence or

absence of pain is not the sole determinant as to whether a woman rates her comfort wearing the device as excellent or very good, nor is it the sole determinant in whether a women is "very satisfied" with her implant.

Summary of Key Findings – Relationship of Pain With Comfort Wearing the Device and Subject Satisfaction

Overall, approximately 96-98% of women in the pivotal study rated their comfort wearing the device as excellent or very good, and 94-96% rated their satisfaction as "very satisfied". At each follow-up point, a small minority of these women reported pain since their last scheduled contact, sometimes moderate or severe in intensity. The presence or absence of pain does not appear to be the sole determinant of a women's comfort or satisfaction wearing the device.

5. Study Limitations

This analysis has several limitations. Most notably, it was conducted more than 13 years after the initial PMA approval for the product. As such, while FDA had access to the available CRFs, original source documentation and records were not available for review. It was not possible to determine whether all CRFs were present and whether the information contained on the CRFs was complete, or correctly transferred to the forms at the time of the original study. Nevertheless, the focus of this analysis was on the changes to CRFs after initial data documentation. Although it was not always possible to determine the identity of the person recording a change or the reason for a change, the FDA reviewed the available original and electronic CRFs and determined that the overall quality of the data auditing and change documentation within the reviewed documents appeared to be consistent with standard clinical trial procedures.

6. Summary and Conclusions

The FDA conducted a re-evaluation of the available case report forms (CRFs) from the original clinical trials supporting the initial approval of the Essure System for Permanent Birth Control. This re-evaluation was performed to assess allegations of study misconduct that: (1) items on the CRFs had been inappropriately modified (crossed out and/or changed) by study investigators and/or the manufacturer, and (2) the CRFs contain inappropriate discrepancies between the subject reported level of pain and the subject reported "comfort wearing the device."

CRFs from the Phase II and Pivotal Studies supporting initial device approval were reviewed. Less than 1% of CRF data items pertaining to key outcome measures (pain, bleeding, device placement/movement, pregnancy) were modified during the conduct of the Phase II or Pivotal Essure clinical trials. A pattern of CRF modifications favoring the device was not observed.

In addition, approximately 96-98% of women in the pivotal study rated their comfort wearing the device as excellent or very good, and 94-96% rated their satisfaction as "very satisfied". Among women rating the device highly, a small minority reported pain at follow-up, sometimes moderate or severe in intensity. The presence or absence of pain does not appear to be the sole determinant of a women's comfort or satisfaction wearing the device. Importantly, the reported comfort wearing the device and level of satisfaction observed in the clinical trial may not be representative of the comfort or satisfaction experienced by women receiving the implant outside of a clinical trial.

In summary, although occasional modifications to CRF data items pertaining to key outcome measures were identified, this analysis did not find evidence of systematic or intentional modification of study subject responses in an effort to falsify (provide a more favorable device profile) the data relied upon by FDA to make the original PMA approval decision in 2002.