FDA Review Document

Review of the
Essure System for Hysteroscopic Sterilization

Prepared for the
September 24, 2015 meeting of the
Obstetrics and Gynecology Devices Advisory Panel
Center for Devices and Radiological Health (CDRH)
United States Food and Drug Administration

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I. Introduction and Purpose of the Committee Meeting

Sterilization for permanent birth control may be accomplished in a variety of ways. One method, hysteroscopic sterilization, began to be widely used in the United States after the 2002 FDA approval of the Essure System (P020014; original applicant, Conceptus, Inc.). Since initial approval, FDA has continued to monitor the safety and effectiveness of the Essure System and the, safety concerns that have been raised within the patient and healthcare provider community. FDA believes that, in keeping with its public health mission, it is appropriate to do the following:

- have an open and transparent dialogue among FDA and its stakeholders, including the device manufacturer, health care providers, researchers, patients, and the public,
- review and discuss available data regarding the benefits and risks associated with the use of the Essure System, and
- obtain FDA Advisory Committee and public input on the safety and effectiveness of the Essure System.

As such, FDA's Obstetrics and Gynecology Devices Advisory Panel is being convened to review and discuss current information related to the effectiveness of the Essure System, adverse events associated with, or suggested to be associated with, the Essure device, and the overall benefit-risk profile of the device. The Committee will be asked to provide input regarding the need for product labeling changes, the collection of additional post-market safety data, or other mitigation steps, and the overall benefit-risk profile of the device based on current available information

The discussion at the Advisory Panel will focus on the Essure device, its approved use, effectiveness, and select reported complications. It will not focus on other cleared or approved medical devices (e.g., endometrial ablation devices) or, un-approved uses of Essure (e.g., treatment of hydrosalpinx).

This review memo will provide information for the Panel's consideration, including:

- Background on female sterilization
- Overview of the Essure System
- Summary of clinical data supporting the original PMA of the Essure System
- A description of the sources of data used to perform FDA's review of post-market information
- Information related to procedural and effectiveness outcomes
- Information related to post-procedural safety outcomes (including deaths)
- Information related to insert removal
- Outside the US (OUS) post-market information

II. Background on Female Sterilization

In 2015, elective (i.e. non-medically indicated) female sterilization is one of the most commonly performed surgical procedures in the United States. Approximately 650,000 elective procedures were performed in 2006 in the US.[1]

The first report in the medical literature describing surgical sterilization by tubal occlusion (at the time of repeat cesarean section) appeared in 1881.[2] In 1930, the Pomeroy method of tying off a loop of the Fallopian tube was first described as a method of elective surgical sterilization.[3] Also in the 1930s, the first report of a laparoscopic tubal occlusion procedure appeared in the literature.[4] However, elective sterilization remained uncommon until the 1960s, when many U.S. hospitals screened women requesting elective sterilization on the basis of age and parity.[5] In the 1970s, laparoscopic instrumentation was becoming increasingly available and, by 1978, approximately one third of all tubal occlusions were being performed laparoscopically, as compared to 1% in 1970.[6]

Evolution of Methods for Laparoscopic Tubal Occlusion

Prior to the widespread availability of laparoscopic instruments and electrosurgical accessories (e.g., electrocautery), elective tubal occlusion by partial salpingectomy (i.e., removal of a section of the Fallopian tube) was typically performed post-partum through a mini-laparotomy incision or in the setting of cesarean delivery. One of the earliest reports describing electrosurgical tubal coagulation using unipolar electrode during laparoscopy appeared in 1962.[7] Reports of serious burn injuries to both the patient as well as the surgeon appeared shortly after the unipolar procedure was adopted.[8] Bipolar electrodes were introduced in the early 1970s to mitigate the risk of thermal injury and began to replace unipolar electrodes for laparoscopic tubal occlusion.[9, 10]

Alternative laparoscopic sterilization methods that did not utilize electrocautery appeared in the literature in the mid-1970s with the introduction of the first implantable device, the Hulka Clip, which comprises two plastic jaws made of polycarbonate hinged by a stainless steel pin.[11] The Falope Ring, made from silicone rubber band became available in 1976.[12] The Filshie Clip, a titanium and silicone clip, was described in 1981.[13]

Regulation of Devices for Female Sterilization

FDA began to have premarket regulatory authority over medical devices with the enactment of the Medical Device Amendments to the Federal Food, Drug, and Cosmetics Act in 1976. Medical devices marketed prior to the 1976 Amendments, such as laparoscopes and accessories, the Falope Ring, and Hulka Clip, were permitted to remain on the market while FDA determined where the devices fit in FDA's three-tiered classification scheme (Class I devices were deemed low risk, Class II, moderate risk, and Class III high risk).

Laparoscopes and electrosurgical accessories were deemed moderate risk and assigned Class II status. The Hulka Clip and Falope Ring tubal occlusion devices, designed and manufactured specifically for laparoscopic tubal occlusion, were deemed high risk and classified into Class III with their own unique device regulation (21 CFR 884.5380 – Contraceptive Tubal Occlusion Device and Introducer). On October 1, 1987, FDA ordered manufacturers of devices under this classification to obtain approval through the premarket approval (PMA) process in order to continue marketing their devices. A "grace period" was granted to provide opportunity for preparation and FDA review of the submissions. The Filshie Clip, which was developed after the 1976 Amendments, was not marketed in the US until premarket approval was obtained in

1996. These three devices received premarket approval during 1993-1996 based on clinical trial data that showed the devices were effective (0.0 to 2.7% failure rate at 12 months) and had acceptable safety profiles.

Annual Incidence of Tubal Sterilization Prior to Approval of Essure System

The annual number of inpatient female sterilizations performed in the US rose sharply during the early 1970s from approximately 200,000 in 1970 to approximately 702,000 in 1977. Between 1975-1978, the proportion of sterilizations being performed laparoscopically was greater than 30%.[6] The US Collaborative Review of Sterilization (CREST) Study was a prospective, multicenter, longitudinal study that enrolled 12,138 women. This landmark study enrolled women from nine US cities who were scheduled for interval tubal sterilization (i.e., sterilization not performed during c-section or within the postpartum period) between 1978-1986. Peterson, et al. analyzed outcomes for 10,685 of these women for eight to fourteen years following sterilization. 41% of women underwent laparoscopic sterilization by electrocautery, 37% by Falope Ring, and 18% by Hulka Clip. Five percent had sterilization by partial salpingectomy (via laparotomy). Life-table cumulative probability of pregnancy at one year ranged from 0.7 to 18.2 per thousand women. At ten years, cumulative probability of pregnancy ranged from 7.5 to 36.5 per thousand. **[14]** Data on the distribution of laparoscopic sterilization by technique (e.g., electrosurgery, Hulka clip, Falope Ring) for more recent years prior to Essure approval are not readily available.

The number of female sterilizations performed annually in the US is estimated to have declined slightly from the mid-1970s to approximately 650,000 in 2002, the year that Essure System was approved. Approximately 30% of married couples in the US using a contraceptive method, use female sterilization as their method of family planning.[15] During 2002, slightly more than half of female sterilization procedures were performed in a hospital.[1] A large number of these inpatient procedures were likely post-partum sterilization (at cesarean delivery or by mini-laparotomy usually within 24 hours of a vaginal delivery), whereas many outpatient procedures were likely interval sterilizations that occur separate from pregnancy.[10]

Female Sterilization in the US Following Approval of Essure System for Permanent Birth Control

As discussed below, the Essure System for hysteroscopic sterilization received FDA approval in November 2002. From 2002 to 2007, uptake of the Essure procedure grew from 0% to 51% of all interval sterilization procedures at Detroit Medical Center hospitals.[16] A recent analysis of hysteroscopic sterilization in the US between 2005 and 2012 found that hysteroscopic sterilization represented 38% of interval sterilization procedures over this time.[17] While Essure is the only hysteroscopic sterilization method presently available in the US, the Adiana System was also legally marketed from July 2009 to May 2012, when it was withdrawn from the market (for reasons unrelated to safety and effectiveness). The Adiana method consisted of hysteroscopic delivery of RF energy to a small portion of the Fallopian tube lumen followed by placement of a cylindrical silicone matrix within the interstitial portion of the tube. Like Essure, the Adiana method required a three-month waiting period and confirmation of tubal occlusion prior to discontinuation of alternate contraception.

More than 750,000 Essure procedures have been performed worldwide since FDA approval in November 2002 through early 2013.[18] The number of Essure procedures worldwide has grown since that estimate was released, with approximately 80% of 2011 global revenue for this product coming from US sales. [19]

Complications Following Interval Laparoscopic Sterilization

The rates of intraoperative or postoperative complications following interval laparoscopic surgical sterilization also were evaluated by Jamieson, et al. using outcomes from the CREST study.[20] The analysis population was 9475; women undergoing concurrent surgeries other than diagnostic D&C or simple biopsies were excluded. Surgical sterilization was performed by one of the following methods: silicone band (3659), spring clip (1709), bipolar coagulation (2288) and unipolar coagulation (1485). This study collected outcomes data at one- and 12 months postoperatively. Six categories of complications were evaluated:

- Unintended major surgery
- Transfusion
- Febrile morbidity
- Life-threatening event
- Rehospitalization
- Death

The rate of women who experienced any of the above events was 153/9475 (1.6%). No deaths were reported; however, the risk of death following surgical sterilization has been estimated elsewhere at 3.4-4.0 per 100,000 procedures.[20]

Unintended major surgery (i.e., conversion to laparotomy) due to laparoscopic complications in this study occurred in 14 subjects and were due to bleeding from Fallopian tube or mesosalpinx (4), transection of the fallopian tube (3), bleeding from laparoscopic puncture site (2), stomach perforation (1), bowel perforation (1), bleeding from sacral promontory caused by Veress needle injury (1), bleeding not further described (1) and perforation of a structure believed to be an adhesion (1). There were 37 other conversions to laparotomy attributed to difficult Fallopian tube visualization or manipulation of which adhesions were cited as the cause in 27 cases. Fifty-six women (0.6%) were re-hospitalized. The most common reasons for re-hospitalization were pelvic infection, heavy vaginal bleeding, pregnancy complication, and abdominal or pelvic pain.

When the category of unintended major surgery was limited to true laparoscopic complications, the overall rate of complications in the above six categories was 0.9%. Independent predictors of any complication included diabetes mellitus (adjusted OR 4.5; 95%CI 2.3, 8.8), general anesthesia (OR 3.2; CI 1.6, 6.6), previous abdominal or pelvic surgery (OR 2.0; CI 1.4, 2.9), and obesity (OR 1.7; 1.2, 2.6).[21]

III. Overview of the Essure System

The Essure System for Permanent Birth Control is a medical device used for permanent sterilization by bilateral occlusion of the fallopian tubes. The Essure device includes an implantable insert and a delivery system for the placement of the insert. In contrast to other permanent sterilization procedures, Essure inserts are placed into each fallopian tube through the cervix, i.e. hysteroscopically. Once in place (Figure 1), fibers within the insert elicit a local, fibrotic reaction from the patient, which causes fibrous tissue to grow in and around the implant. Over a period of several months, this tissue ingrowth blocks the fallopian tubes, which prevents contact between oocytes (eggs) and sperm and fertilization. As part of the Essure procedure, patients undergo a radiologic confirmation test three months after insert placement in order to assure the proper placement and/or occlusion of the fallopian tubes.

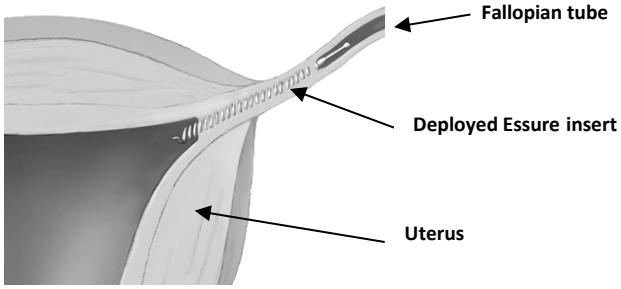


Figure 1: Essure System for permanent birth control

Description of the Use of the Essure System

The Essure System comprises a disposable delivery system, described below, and a wound-down insert. A disposable introducer is also provided to facilitate delivery system entry into the operating channel of a hysteroscope. The Essure insert consists of a super-elastic nickel-titanium (Nitinol) outer coil and a stainless steel inner coil wrapped in polyethylene terephthalate (PET) fibers. The wound-down insert is approximately 4 cm in length and 0.8 mm in diameter (Figure 2A). When released, the outer coil expands up to 2.0 mm in diameter, conforming to the varied diameters and shapes of the fallopian tube (Figure 2B). When expanded, the outer coil pushes against the fallopian tube wall, conforming itself to the diameter and shape of the fallopian tube, and acutely anchoring the insert in the utero-tubal junction. Once in place, the PET material surrounding the inner coil stimulates the fibrotic reaction and tissue ingrowth, leading to pregnancy prevention.

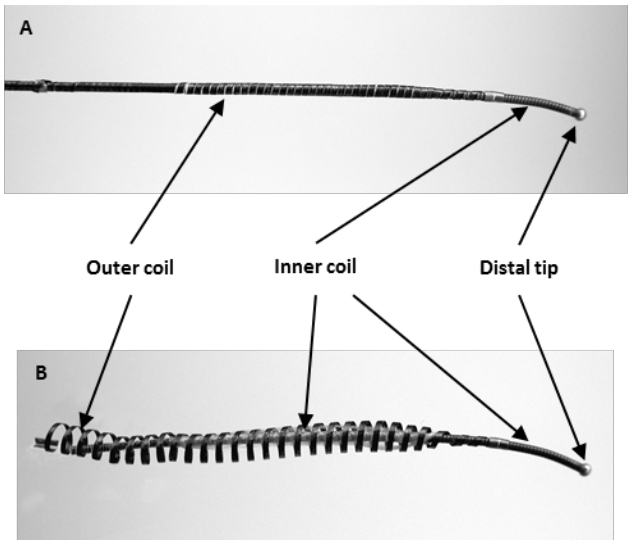


Figure 2: A) Essure insert in wound configuration. B) Essure insert with outer coil deployed.

The Essure insert is delivered into each fallopian tube via a disposable delivery system, which consists of a delivery catheter and handle (Figure 3). At the distal tip of the delivery catheter, the wound-down insert is attached to a delivery wire and sheathed by a flexible release catheter. The delivery handle controls the device delivery and release mechanism. During a placement procedure, the physician inserts the delivery catheter through a hysteroscope port with the aid of an introducer and guides the catheter to the fallopian tube under observation. Once the distal tip of the delivery catheter is in place, the physician uses the thumbwheel and button on the delivery handle to retract the delivery wire and deploy the insert. The physician must use two pre-loaded catheters to achieve bilateral placement.

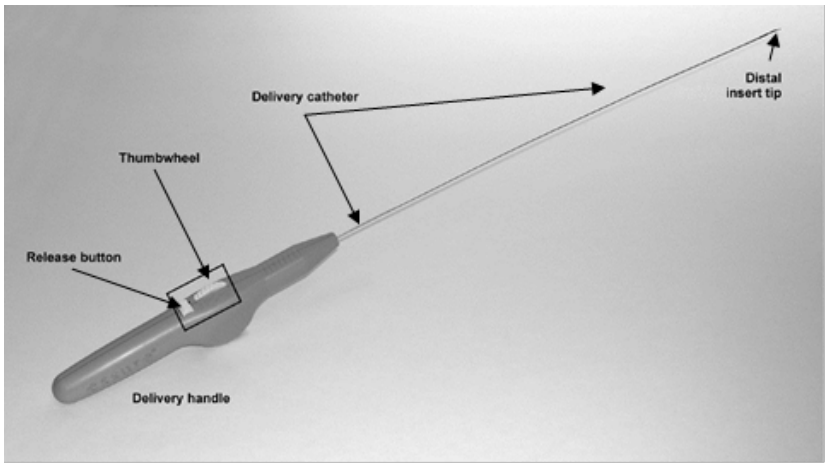


Figure 3: Essure System (delivery handle, catheter, and wound insert tip)

The insert placement does not require entry into the peritoneal cavity or general anesthesia, and can often be performed as an outpatient office procedure.

The Essure Confirmation Tests

The tissue ingrowth process into and around the inserts is gradual and may take several months to elicit full occlusion of the fallopian tubes. Therefore, patients who have the Essure procedure must continue to use alternate contraception, until occlusion has been confirmed by their physician, and the physician informs the patient that she may rely on the device. A patient must have a confirmation test performed three months after device placement to confirm proper insert location and/or occlusion of the fallopian tubes. Only after a satisfactory confirmation test can a patient rely on the Essure inserts alone for permanent contraception.

Until June 2015, the FDA-approved Essure confirmation test had been limited to a modified hysterosalpingogram (HSG) in which radiologic contrast dye is deposited in the uterus through the cervix. Fluoroscopy is utilized to visualize the Essure inserts and the dye within the uterus and fallopian tubes. If the tubes are fully occluded, the dye should not be able to pass into the distal portions of the fallopian tubes, and the dye will not be visualized on the radiograph distal to the Essure inserts. With this test, physicians determine if the inserts are appropriately located, and that tubal occlusion has occurred.

In June 2015, FDA approved an algorithm that allows transvaginal ultrasound (TVU) to serve as the confirmation test in lieu of the modified HSG when multiple criteria are satisfied (PMA Supplement 41). When these criteria are not met, or when the results of the TVU are unsatisfactory, the modified HSG must be performed before a patient can be advised to rely on Essure. The TVU method of confirmation utilizes a transvaginal ultrasound probe to generate images of the uterus, proximal fallopian tubes, and the Essure inserts. Physicians use these images to evaluate the suitability of the inserts' location; if the TVU demonstrates satisfactory insert location bilaterally, the patient may be advised to rely on Essure. The Essure TVU procedure, however, does not provide confirmation of occlusion. Individual physician training and assessment of comprehension is required before users may adopt the TVU/HSG protocol. TVU has been an accepted method for the Essure confirmation test in several countries in the EU and elsewhere since 2011.

Indications for Use and Contraindications to Use

Essure is indicated for women who desire permanent birth control (female sterilization) by bilateral occlusion of the fallopian tubes.

The Essure system is contraindicated for patients who:

- Are uncertain about ending fertility.
- Can have only one insert placed
- Have previously undergone a tubal ligation.
- Are pregnant or suspect pregnancy.

- Have delivered or terminated a pregnancy less than 6 weeks prior to the Essure procedure.
- Have an active or recent upper or lower pelvic infection.
- Have a known allergy to contrast media.

Regulatory History

The Premarket Application (PMA) for the Essure System for Permanent Birth Control was submitted to the FDA for review in April 2002. The PMA application was supported by clinical data from two studies including one with 2 years of follow-up (Phase II study) and 1 year of follow up in the other (Pivotal study). These studies will be described further in Section IV, Summary of Clinical Data Supporting the Original PMA of the Essure System.

When the PMA was submitted, the Essure System was commercially available in Australia, Austria, Belgium, Canada, Denmark, Finland, Germany, Holland, Indonesia, Italy, Norway, Portugal, Singapore, Spain, Sweden, Switzerland, Turkey, and the U.K. The Essure System was approved for marketing in Europe by the notified body TÜV in February 2001 and in Canada by Health Canada in November 2001. Information regarding outside of the US (OUS) post-market experience is described in Section XI, below.

As a first-of-a-kind device, the Essure System was presented to the CDRH Obstetrics and Gynecological Devices Advisory Panel on July 22, 2002. After deliberating on the information in the application and presentations at the panel meeting, the panel voted to recommend "approval with conditions" for the Essure PMA with 8 affirmative votes and 1 abstention. The panel recommended the following conditions for approval: 1) performance of mandatory HSG confirmation testing after placement of the device, 2) the training program to train physicians on the placement procedure be a prerequisite to performing the procedure, and 3) several modifications to the labeling be included, including addition of prominent information on failure/success rates, warnings about metal allergy, electrocautery, and pregnancy occurring while the device is in place, and training requirements.

In accordance with the recommendations of the advisory panel, the FDA approved the original PMA on November 4, 2002. As a condition of approval, FDA required that Conceptus continue gathering data from patients in the ongoing Phase II and Pivotal studies out to 5 years after discontinuation of alternative contraception, and conduct a new study to document the bilateral placement rates for newly-trained physicians.

Since approval of the original Essure System in 2002, there have been numerous modifications to the device. These changes did not change the basic design of the insert, the primary insert materials, or the device mechanism of action. Most of the changes were intended to improve device deployment and usability during the Essure placement procedure. The current model Essure (ESS305) was approved in 2007 (PMA Supplement 12) and was modified to include a new introducer design to prevent backsplash of distension fluid during hysteroscopy onto the surgeon and/or surgical field, a modification to the catheter/insert interface to improve insert detachment, and visual updates to ease device deployment and usability. As a condition of

approval for Supplement 12, Conceptus was required to perform a post-approval study (PAS) to evaluate the rate of successful bilateral insert placement on the first attempt.

Several labeling modifications have been made to the Essure System since approval of the original PMA. (See Appendices B and C for the current physician and patient labeling.) Principally, the labeling updates have added long-term efficacy and safety information from the Phase II and Pivotal clinical trials as they became available. The labeling was also updated to reflect information on pregnancies in commercial use of Essure. In 2011, the labeling was modified to remove the contraindication for nickel allergies, replacing it with a revised warning. In 2012, the physician's instructions for use and the patient brochure were updated to include information about device effectiveness and reasons for pregnancies based on commercial use of the device. In 2013, following an internal FDA review of post-market data, the patient brochure was amended to better reflect the adverse event information available in the physician labeling, including reports of chronic pelvic pain and device migrations. In the most recent labeling change (Supplement 41, approved in June 2015), transvaginal ultrasound (TVU) was added as a possible confirmation test in certain cases. One-year effectiveness data were added from the ongoing TVU clinical study and the discussion of device removal was expanded.

Beginning in late 2013, FDA has received a significant increase in the number of adverse event reports related to Essure; in particular, from patients who have received the device. The Agency has also been cognizant of complaints related to the device being conveyed in traditional and social media outlets. Accordingly, FDA has recently conducted an additional review of data related to the Essure system and determined that the information should be vetted and discussed in an open forum, i.e., this panel meeting.

IV. Summary of Clinical Data Supporting the Original PMA of the Essure System

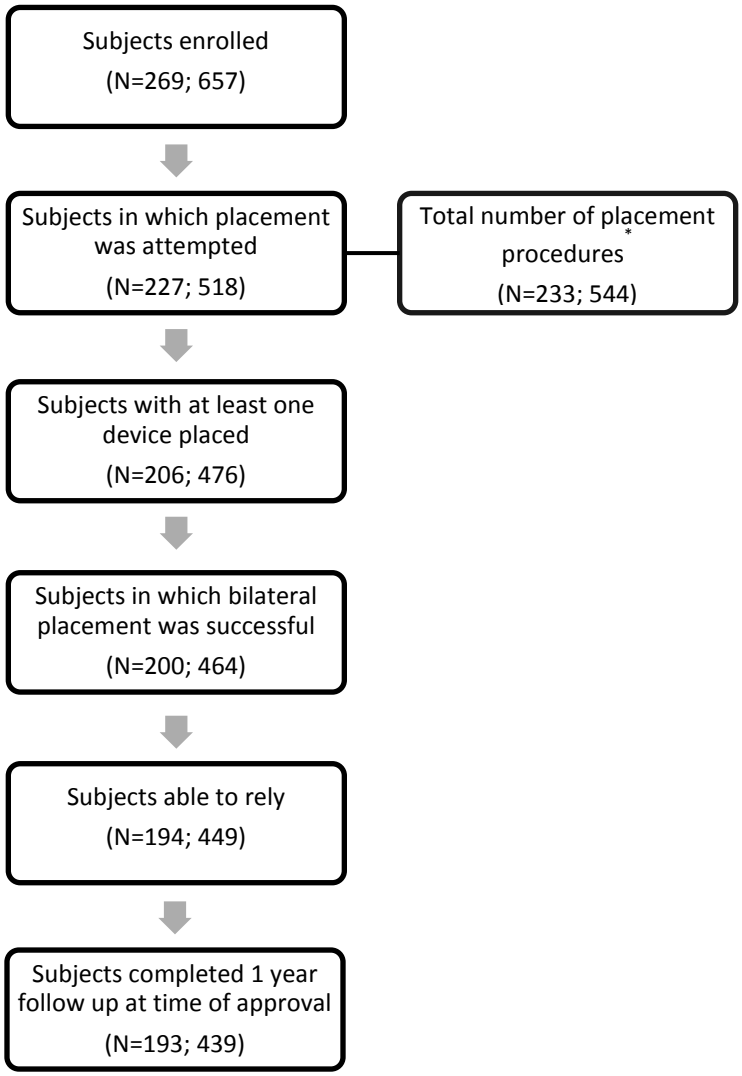
Prior to submitting the application for market approval ("original PMA"), the sponsoring firm, Conceptus, Inc., performed several clinical studies under the Investigational Device Exemption (IDE) program. As discussed in this section, at the time of original PMA approval, 2 year safety and effectiveness data were available from the Phase II study, and 1 year safety and effectiveness data were available from the Pivotal study. Additional data following the patients in these two studies for 5 years was collected postmarket as part of the conditions of approval.

Prior to the Phase II and Pivotal studies, beginning in 1996, preliminary investigations of different versions of the device were conducted with the devices placed either concurrently or in advance of hysterectomies. These studies, which included 99 and 63 patients for peri-hysterectomy and pre-hysterectomy studies, respectively, yielded data on device placement, patient comfort, as well as histological data to support the mechanism of action of the device.

In 1998, FDA approved Conceptus' IDE for a prospective, multi-center, non-randomized, single arm Phase II clinical study. In this study, the long-term safety and effectiveness of the device was to be evaluated for the first time in 227 women who were not undergoing hysterectomy. Devices were implanted bilaterally in women, who were then followed for up to 5 years post-placement for evaluation of adverse events and pregnancy rates. During the Phase II study,

Conceptus also began a larger, prospective, multi-center, non-randomized, single arm pivotal study of the device, also under an IDE. The placement procedure was attempted in 518 women in the Pivotal study, which investigated safety and effectiveness endpoints similar to the Phase II study, including evaluation of adverse events and pregnancies in subjects for a period up to 5 years. Figure 4 provides a patient accountability chart for the Phase II and Pivotal studies.

Figure 4. Phase II and Pivotal Study Patient Accountability Chart



Numbers of subjects in each category (N) are displayed as the number of subject in the Phase II and Pivotal study as (N=patients from Phase II; patients from Pivotal)

*Some subjects had more than one placement procedure, and so the total number of placement procedures is in excess of the number of subjects in which placement was attempted

All of the participants in the Phase II and Pivotal studies were between 21 and 45 years of age and were seeking permanent contraception prior to enrollment in the study. Additionally, all women had at least one live birth, had regular, cyclical menses and were able and willing to use alternative contraception for 3 months following Essure placement. Table 1 provides patient demographics for these studies.

Table 1. Demographics of Study Subjects in Phase II and Pivotal Clinical Trials of Essure

	Phase II N=227	**Pivotal Trial N=518**
Race	(not collected)	
White/Caucasian		428
Latin		31
Black		24
Other		9
Mean Age	35	32
Age < 28	7%	17%
Age 28-33	23%	47%
Age ≥ 34	70%	36%
Gravidity	Mean = 2.6 (0 – 10)	Mean = 3.03 (1 – 11)
Parity	Mean = 2.2 (0 – 5)	Mean = 2.26 (1 – 6)
BMI	Mean = 26 (17 – 57)	Mean = 27 (16 – 52)

The data from these IDE studies were used to support the PMA application, which was submitted to the FDA in 2002 as the "Essure System for Permanent Birth Control."

Adverse events

Adverse events in the original PMA application were reported from the Phase II and Pivotal IDE trials. When asked immediately after the procedure, the majority of women stated that they experienced mild to moderate pain during the procedure. As shown in Table 2, the most common adverse events reported during the recovery period the first day following device placement were cramping, pain, and nausea/vomiting. In addition, it was reported that the majority of women experienced spotting for an average of 3 days after the procedure.

Table 2: Adverse Events Reported During Recovery on Day of Placement

Phase II Study (N=233 procedures)		
Adverse Event	**Number**	**Percent**
Band detachment (device malfunction)	3	1.3%
Vaso-vagal response	2	0.9%
Pain	2	0.9%
Pivotal Study (N=544 procedures)		
Adverse Event/Side effect	**Number**	**Percent**
Cramping	161	29.6%
Pain	70	12.9%
Nausea/vomiting	59	10.8%
Dizziness/light headed	48	8.8%
Bleeding/spotting	37	6.8%
Vaso-vagal response/fainting	7	1.3%
Hypervolemia	2	0.4%
Band detachment	2	0.4%
Other*	16	2.9%

*Includes: ache (3), hot/hot flashes (2), shakiness (2), uncomfortable (1), weak (1), profuse perspiration (1), bowel pain (1), sleep (1), skin itching (1), loss of appetite (1), bloating (1), allergic reaction to saline used for distension (1).

Lower rates of adverse events were reported post-procedure. As seen in Table 3, the most commonly reported adverse events in the first year of reliance on Essure in the Pivotal trial were back pain (9.0%), abdominal pain/abdominal cramps (3.8%), and dyspareunia (3.6%). In addition to the reports from the Pivotal trial, 12/206 (5.8%) of women in the Phase II trial with at least one insert reported episodes of dysmenorrhea, ovulatory pain, or changes in menstrual function.

Table 3: Adverse Events by Body Systems, First Year of Reliance on Essure in Pivotal Trial*

Adverse Events by Body System	Number (N=476)	Percent
Abdominal:		
Abdominal pain/abdominal cramps	18	3.8%
Gas/Bloating	16	1.3%
Muscolo-skeletal:		
Back pain/low back pain	43	9.0%
Arm/leg pain	4	0.8%
Nervous/Psychiatric:		
Headache	12	2.5%
Premenstrual Syndrome	4	0.8%
Genitourinary:		
Dyspareunia	17	3.6%
Dysmenorrhea/menstrual cramps (severe)	14	2.9%
Pelvic/lower abdominal pain (severe)	12	2.5%
Persistent increase in menstrual flow	9**	1.9%
Vaginal discharge/vaginal infraction	7	1.5%
Abnormal bleeding – timing not specified	9	1.9%
(severe)	5	1.1%
Menorrhagia/prolonged menses (severe)		
Pain/discomfort – uncharacterized:	14	2.9%

* The patients in this table (N=476) were implanted with at least one device, and events occurred in the first year of reliance (up to 15 months post-procedure). Percentages presented reflect the number of events in the numerator and the number of women in the trial wearing at least one insert in the denominator. [2]Only events occurring in ≥ 0.5% are reported

** Eight women reported persistent decrease in menstrual flow

In addition to the events listed above, the adverse or other events listed in Table 4 delayed or prevented reliance on Essure for contraception.

Table 4: Events that delayed or prevented reliance on Essure for contraception

Phase II Study		
Event	**Number**	**Percent**
Perforation	6/206	2.9%*
Expulsion	1/206	0.5%
Other unsatisfactory micro-insert location	1/206	0.5%
Initial tubal patency	7/200	3.5%**
Pivotal Study		
Event	**Number**	**Percent**
Perforation	5/476	1.1%
Expulsion	14/476	2.9%***
Other unsatisfactory micro-insert location	3/476	0.6%
Initial tubal patency	16/456	3.5%**

*Four of the six perforations occurred with use of the since-discontinued Support Catheter

**Tubal patency was demonstrated in 7 women (Phase II) and 16 women (Pivotal) at the 3-month HSG, but all women were shown to have tubal occlusion at a repeat hysterosalpingogram (HSG) performed 6 months after Essure placement.

***Fourteen women experienced an expulsion, however nine of these 14 women chose to undergo a second micro - insert placement procedure, which was successful in all nine cases.

Effectiveness

The primary effectiveness endpoint of the Pivotal trial was the one-year contraceptive efficacy rate among relying subjects (e.g., those subjects who had a confirmation test that showed bilateral occlusion and location, and were told to rely on the device for contraception). Additional indicators of device performance included bilateral placement rate and reliance rate (i.e., the rate at which women with successful bilateral placement were confirmed to have tubal occlusion and location by HSG and told to rely).

In the Phase II and Pivotal trials, bilateral placement was achieved in approximately 90% of subjects who underwent hysteroscopy for device placement; some required a second procedure when bilateral placement was not achieved in the first. Of the women with bilateral placement, 97% were ultimately able to rely on Essure for contraception (Table 5).

Table 5: Essure Placement and Reliance Rates from Phase II and Pivotal Clinical Trials*

Outcome	Phase II N=227		Pivotal N=518	
	Number	**Percent**	**Number**	**Percent**
Bilateral Placement: After one procedure	196/227	86%	446/518	86%
Bilateral Placement: After two procedures**	200/227	88%	464/518	90%
Reliance rate: Among women with bilateral placement	194/200	97%	449/464	97%

* Note that the data above represents the rates based upon available information at the time of approval

** Four women in the Phase II study and 18 in the Pivotal study had successful additional placement procedures after failure to achieve bilateral placement on first attempt.

Since the original approval, the sponsor has made changes to the catheter to facilitate placement, although data on Essure placement rates have generally demonstrated a high rate of bilateral placement. In post-approval studies, higher bilateral placement rates were reported (>95%), and since approval of the Essure system, there has been consistently high bilateral placement rates (80-100%) reported in the literature. Appendix A provides post-market information on bilateral placement rates, the physician learning curve for device placement, and patient compliance with the confirmation testing requirement.

At the time of PMA submission, of the 745 subjects in whom placement was attempted in the Phase II or Pivotal trials, 643 subjects were told they could rely on Essure. In these women, there were no reported pregnancies. There were four luteal phase pregnancies reported in the Pivotal trial (pregnancies occurring prior to Essure placement but not detected on the day of placement). None of these women became pregnant while relying on Essure for contraception, and the luteal phase pregnancies were not reflected in the device failure rates. The cumulative failure rate for subjects relying on Essure for contraception in the Phase II trial at one and two years and for the Pivotal trial at one year was 0% (Table 6). As a comparison, a life-table 1-year cumulative probability of pregnancy among women undergoing tubal sterilization by six surgical methods of

0.55% was found in the large, prospective U.S. Collaborative Review of Sterilization (CREST) study, as reported by Peterson et al.[14]

Table 6: Essure Effectiveness Results of Phase II and Pivotal Clinical Trials at Time of Approval

Cumulative Failure Rates	Phase II N=193	Pivotal Trial N=439	Both Trials Combined N=632
One-year	0% (95% CI 0 – 1.53%) (Adj 95% CI 0-2.19%)*	0% (95% CI 0-0.68%) (Adj 95% CI 0-0.78%)*	0% (95% CI 0-0.47%) (Adj 95% CI 0-0.57%)*
	Phase II N=181	**Pivotal Trial N=16**	**Both Trials Combined N=197**
Two-Year	0% (95% CI 0-1.54%) (Adj 95% CI 0-2.36%)*	0% (95% CI 0-0.86%) (Adj 95% CI 0-0.93%)*	0% (95% CI 0-0.55%) (Adj 95% CI 0-0.67%)*

The data above represent the failure rates based upon available information at the time of approval. Although the failure rate established in the clinical trials of Essure ™ was 0%, no method of contraception is 100% effective, and pregnancies have occurred in the commercial setting.

*Adjustment using indirect method (CDC CREST study population) based on the age groups: <28 years, 28-33 years, and =34 years.

Five-Year Follow-Up of PMA Cohort

FDA has the authority to require sponsors to perform a Post-Approval Study (PAS) at the time of approval of a PMA to help assure continued safety and effectiveness of the approved device. As a Condition of Approval in 2002, FDA ordered two PAS's for the Essure original PMA, one of which required additional follow-up of the Phase II Study and Pivotal Study premarket cohorts for a total of five years of follow-up. This extended follow-up was completed in 2008, and the device label was updated to include 5-year performance data. The following information, from the complete 5-year reports of the Phase II and Pivotal studies, is arranged by the topics of interest outlined in Sections VI and VII of this executive summary.

Pregnancies

In the five-year follow up of the Phase II and Pivotal clinical trials, no pregnancies occurred in women relying on Essure. As described above, there were four luteal phase pregnancies reported in the Pivotal trial (pregnancies occurring prior to Essure placement but not detected on the day of placement).

Patient Comfort/Satisfaction

In the Phase II and Pivotal trials at follow up time points of 3, 6, 12, 18 24, 36, 48, and 60 months, at least 99% of women were reported to have rated comfort of wearing the Essure inserts as "good" or "excellent." In the Pivotal trial, at least 97% of women were reported to be "somewhat" to "very satisfied" at all visits through 5 years.

The FDA is aware of allegations from women who participated in the original Essure clinical trials that the feedback they provided about the comfort wearing the device was not recorded accurately by clinical staff. As part of the original PMA approval, FDA performed inspections at Conceptus and one clinical site. These inspections audited data provided in support of the PMA, as well as sponsor activities during the studies, and did not report findings concerning the case report forms or patient comfort/satisfaction data submitted in support of the PMA.

Post-market literature assessing patient comfort and satisfaction is discussed in Section VI.B of this document and also shows high patient satisfaction rates.

Post-procedural Pain (Chronic/Persistent Pain)

Patient pelvic and other pain was reported at follow-up visits up to 5 years for the Phase II and Pivotal trials. Follow up visits were recorded as either post-device placement (PDP) or post-alternative contraception (PAC; when alternative contraception was discontinued). Patients reported if they experienced pain in the previous follow up period. Unless noted, reports do not indicate duration, severity, or persistence. The pain reported at follow-up visits in the Phase II and Pivotal studies are summarized in Tables 7 and 8, respectively, below:

Table 7: Reports of pain at follow up visits of the Phase II study

Follow-up visit	Pelvic Pain			Other Pain
	Dysmenorrhea	Dyspareunia	Other Pelvic	
3 month N=203	29 (14%)	17 (8%)	5 (2%)	2 (<1%)
6 month N=199	11 (6%)	3 (2%)	3 (2%)	1 (<1%)
12 month N=196	5 (3%)	0	5 (3%)	0
18 month N=193	2 (1%)	0	10 (5%)	2 (1%)
24 month* N=194	8 (4%)	0	6 (3%)	6 (3%)
36 month* N=182	7 (4%)	1 (<1%)	2 (1%)	1 (<1%)
48 month* N=176	9 (5%)	2 (1%)	2 (1%)	2 (1%)
60 month* N=171	4 (2%)	1 (<1%)	3 (2%)	2 (1%)

Numbers are based upon the number of subjects reporting at that visit
* No data reported for some women that indicated unusual pain (N=2 at 24 months; N=1 at 36, 48, 60 months)

In the Pivotal study, additional analysis of recurrent and persistent pain was reported. Recurrent pain was defined as pain reported at more than one visit during the follow up period. Persistent pain was defined as pain reported at all visits during the follow up period.

Table 8: Reports of pelvic pain in the follow up visits of the Pivotal study

Follow-up visit	Pelvic Pain			
	Dysmenorrhea	**Dyspareunia**	**Ovulatory Pain**	**Other Pelvic**[†]
Baseline N=518	183 (35%)	22 (4.2%)	n/a	n/a
3 months PDP N=467	29 (6.2%)	29 (6.2%)	5 (1.1%)	32 (6.9%)
3 months PAC N=440	20 (4.5%)	10 (2.3%)	6 (1.4%)	26 (5.9%)
6 months PAC N=436	15 (3.4%)	8 (1.8%)	3 (0.7%)	16 (3.7%)
12 months PAC N=460	17 (3.7%)	15 (3.3%)	5 (1.1%)	27 (5.9%)
18 months PAC N=410	14 (3.4%)	9 (2.2%)	10 (2.4%)	11 (2.7%)
24 months PAC N=435	22 (5.1%)	9 (2.1%)	22 (5.1%)	13 (3.0%)
36 months PAC N=422[***]	14 (3.3%)	7 (1.7%)	12 (2.8%)	6 (1.4%)
48 months PAC N=402	3 (0.7%)	5 (1.2%)	6 (1.5%)	11 (2.7%)
60 months PAC N=386	14 (3.6%)	8 (2.1%)	10 (2.6%)	9 (2.3%)
Recurrent[*] N=473	29 (6.1%)	18 (3.8%)	14 (3.0%)	25 (5.3%)
Persistent year 1[**] N=460	0	0	0	1 (0.2%)
Persistent year 2[**] N=435	0	0	0	1 (0.2%)
Persistent year 3[**] N=422	0	0	0	0
Persistent year 4[**] N=402	0	0	0	0
Persistent year 5[**] N=386	0	0	0	0

[†]Other pelvic is defined as pain not reported to be dysmenorrhea, dyspareunia or ovulatory pain

[*] Recurrent: symptom reported at more than one visit during the follow-up period (i.e., symptoms do not have to be reported on consecutive visits).

[**]Persistent: symptoms reported at all visits during the follow up period

[***]Data missing on one patient

While reports of various types of pelvic pain ranged from < 1% to 7% throughout the follow up of the Pivotal study, persistent pelvic pain was reported in only 1 case at one and two year follow up appointments.

Changes in Vaginal Bleeding, Menstrual Patterns or Characteristics

Changes in menstrual patterns and bleeding were reported at various times during the Phase II trial. Rates of reports of irregular menses, spotting, and changes in flow ranged from 2-9% (Table 9).

Table 9: Reports of menstrual irregularities during the Phase II trial

Follow-up visit	Irregular menses	Spotting	Changes in flow	Other
3 month	Not asked	Not asked	Not asked	Not asked
6 month N=199	3 (2%)	6 (3%)	3 (2%)	0
12 month N=196	6 (3%)	5 (3%)	4 (2%)	0
18 month N=193	9 (5%)	4 (2%)	5 (3%)	0
24 month* N=194	4 (2%)	4 (2%)	10 (5%)	1 (<1%)
36 month* N=182	4 (2%)	3 (2%)	4 (2%)	2 (1%)
48 month* N=176	4 (2%)	3 (2%)	9 (5%)	2 (1%)
60 month* N=171	16 (9%)	3 (2%)	11 (6%)	2 (1%)

Numbers are based upon the number of subjects reporting at that visit

* No data reported for some women that indicated unusual bleeding (N=2 at 24 months; N=1 at 36, 48, 60 months)

In the Pivotal trial, changes in vaginal bleeding and menstrual patterns were recorded throughout the study over a period of 5 years (Table 10). Additionally, recurrent and persistent menstrual irregularities were reported.

Table 10: Reports of menstrual irregularities, rates of recurrence, and persistence during the Pivotal trial

Follow-up visit	Irregular menses	Bleeding between menses	Heavier than usual menstrual flow	Less than usual menstrual flow
Baseline N=518	9 (1.7%)	12 (2.3%)	n/a	n/a
3 months PDP	48 (10.3%) N=467	110 (23.6%) N=466	89 (19.2%) N=463	56 (12.1%) N=463
3 months PAC	36 (8.2%) N=440	40 (9.1%) N=440	96 (21.9%) N=439	55 (12.5%) N=439
6 months PAC	36 (8.2%) N=437	29 (6.6%) N=437	94 (21.6%) N=435	57 (13.1%) N=435
12 months PAC	35 (7.7%) N=455	31 (6.7%) N=460	77 (16.8%) N=458	67 (14.6%) N=458
18 months PAC	19 (4.6%) N=410	42 (10.2%) N=411	70 (17.0%) N=411	63 (15.3%) N=411
24 months PAC	20 (4.6%) N=435	32 (7.4%) N=435	89 (20.6%) N=432	53 (12.3%) N=432
36 months PAC	31 (7.4%) N=420	25 (6.0%) N=420	83 (20.2%) N=411	47 (11.4%) N=411
48 months PAC	33 (8.4%) N=393	33 (8.3%) N=396	69 (17.9%) N=386	52 (13.5%) N=386
60 months PAC	45 (11.7%) N=386	29 (7.5%) N=386	74 (19.6%) N=377	40 (10.6%) N=377
Recurrent*	70 (14.8%) N=473	89 (18.8%) N=473	177 (37.5%) N=472	110 (23.3%) N=472
Persistent year 1**	3 (0.7%) N=455	2 (0.4%) N=460	7 (1.5%) N=458	12 (2.6%) N=458
Persistent year 2**	0 (0%) N=435	1 (0.2%) N=435	4 (0.9%) N=432	3 (0.7%) N=432
Persistent year 3**	0 (0%) N=420	1 (0.2%) N=420	4 (1.0%) N=411	2 (0.5%) N=411
Persistent year 4**	0 (0%) N=393	0 (0%) N=396	3 (0.8%) N=386	1 (0.3%) N=386
Persistent year 5**	0 (0%) N=380	0 (0%) N=386	2 (0.5%) N=377	0 (0%) N=377

* Recurrent: symptom reported at more than one visit during the follow-up period (i.e., symptoms do not have to be reported on consecutive visits). The denominator (N) is the sum of all unique patients who responded over the course of their follow-up period. Not all women responded at all follow-up visits

** Persistent: symptoms reported at all visits during the follow up period

Irregular menses were reported at rates ranges from 4-12%. Heavier than usual menstrual flow was more commonly reported at 16-22% while less than usual menstrual flow was reported at rates ranging from 10-15%. Menstrual irregularities that were persistent occurred at rates ranging from 0-3% with the highest rate being changes reported as "less than usual flow."

Headache

Eleven cases of headaches were reported in 10/206 (4.9%) of subjects in the Phase II trial over the duration of the study. In the Pivotal trial, 226 cases of headaches were reported in 98/518 (18.9%) of subjects over the duration of the study.

Nickel Allergy/Hypersensitivity

There were no reported cases of nickel or metal allergy reaction identified in the Phase II and Pivotal clinical trials. Subjects were not tested for nickel or metal sensitivity at baseline or subsequent to Essure placement as part of the study.

Perforation and intraperitoneal migration

In the Phase II and Pivotal studies, perforations were discovered on the day of placement (on x-ray), at the Essure confirmation test, or during subsequent laparoscopic surgery. Details surrounding these perforations included surgical and histological findings when available.

In the 5-year follow-up of the Phase II trial, one perforation was identified in addition to the 6 identified premarket. Therefore, the rate of perforation at 5 years reported in the Phase II study was 7/227 (3.1%). In the Pivotal trial there were 5 perforations reported in the first year of reliance (Table 4). There were no additional perforations reported in the post-approval follow up. The rate of perforation at 5 years was therefore 5/476 (1.1%).

Of the 7 perforations reported in the Phase II study, 6 of the devices were reported as "intraperitoneal." Intraperitoneal devices were those either partially or completely within the peritoneal cavity. No other intraperitoneal devices were reported in this study.

Deaths

There were no deaths reported in the final 5-year report for the Phase II trial. A single death was reported secondary to leukemia during the post-market follow up of the Pivotal trial.

Essure insert removal

Information on device removal in the Phase II and Pivotal trials was not systematically reported and was compiled from various investigator reports. In the 5 year data from the Phase II and Pivotal trials, a total of 32 women were reported to have devices removed. Of these cases, 12 occurred in the Phase II trial (12/206, 5.8%) and 20 occurred in the Pivotal trial (20/476, 4.2%) (Table 11).

Table 11: Number of women in which device removal was performed during the Phase II and Pivotal Studies up to 5 years of follow up.

	Phase II	Pivotal
Total device removals	12	20
Laparoscopic removal	4	5*
Hysteroscopic removal	1**	-
Hysterectomy	5	15
Other removal	2***	-

*Inserts were removed laparoscopically prior to IVF in a woman who desired pregnancy, four others at time of sterilization

**In one woman, device removal was attempted hysteroscopically during the placement procedure

***Includes one woman in which devices were removed via cornual resection and one woman in which devices were removed via laparotomy.

Circumstances leading to the hysterectomies with device removal in Table 11 were:

- Abnormal bleeding (7)
- Heavy bleeding and pain (2)
- Pain (3)
- Prolapse (2)
- Asherman's Syndrome (1)
- Uterine myoma (1)
- Unknown (4)

Circumstances surrounding the laparoscopic, hysteroscopic, and other device removals in Table 11 were:

- Tubal ligation following unsatisfactory placement (8)
- Pain (2)
- Desire for fertility (1)
- Unsatisfactory location during placement procedure (1)

In addition to the above, there was one case in the Phase II study and four cases in the Pivotal study in which salpingectomies for sterilization were performed, but information regarding device removal was not available

V. Post-Market Data: Sources

As described in Section IV, FDA ordered post-approval studies for the Essure original PMA, including but not limited to follow-up of the Phase II Study and Pivotal Study premarket cohorts for a total of five years.

The remainder of FDA's memo will summarize safety and effectiveness data for the Essure device which has been developed since the original PMA approval in 2002 and outside of the original corresponding post approval studies which were discussed above and which collected

data out to 5 years on the IDE cohorts. A particular emphasis will be placed on specific events or outcomes of interest which have become a significant concern to the patient community.

This section of the memo describes the sources of the data which FDA reviewed – the results will be presented in Sections VI and VII below. These sources of data, which will be described in more detail, include the ongoing ESSTVU prospective clinical trial used to support approval of TVU as an alternate confirmation tool (PMA Supplement 41), clinical studies cited in the recent peer-reviewed medical literature, published or presented case reports/series, Medical Device Reports (MDRs) submitted to the FDA's Manufacturer and User Facility Device Experience (MAUDE) database since approval, current product labeling, and information from social media listening tools and outside-the-US regulatory bodies.

ESSTVU Study Safety Data ("TVU Study")

As noted previously, FDA recently approved a change to the Essure confirmation test protocol to allow TVU as a possible test in certain cases. This change was approved in Supplement 41 to the PMA and was supported by the ongoing ESSTVU Study 16974 prospective, multi-center, international study, which includes 597 women ages 21-44. Enrollment took place from May 2011 – October 2012; data for subjects with 1 year follow-up supported the approval of the PMA Supplement. The subjects in this study continue to be followed; the results are reported to FDA annually. Pertinent safety information from the ESSTVU study current to the most recent annual report (data up to June 2015) will be presented for the outcomes of interest in Section VII.

Literature: Peer-Reviewed Studies

A PubMed search was conducted on June 26, 2015, using the strategy "Essure OR (hysteroscop* AND sterili*)" in order to identify articles pertaining to the following topics:

1) Pregnancy-related outcomes including unintended pregnancies after Essure placement;
2) Safety issues and adverse events after Essure placement;
3) Patient satisfaction with the Essure procedure and device;
4) Confirmation testing, including patient compliance;
5) Placement rates and problems, including migration and expulsion, and physician learning curve.

The literature studies reviewed and summarized in Sections VI and VII had a number of limitations. Many studies were retrospective reviews which may be more susceptible to study bias than prospective studies, and which can lead to biased estimates of incidence rates. Very few articles reported data for a comparison group receiving an alternate sterilization procedure, such as tubal ligation. Therefore, it was difficult to assess incidence rates and device-relatedness of events such as menstrual irregularities as compared to the general population or women who receive other sterilization procedures. Publications were often single-site studies which reported results obtained by physicians with extensive device experience and some publications may have been reporting on the same study or patient population from a given center at different time points. Study enrollment varied considerably in numbers of patients included. In addition, some studies provided limited follow-up in terms of duration and/or percentage of patients completing follow-up. Details (such as timing after procedure and intervention) about events such as device

migration and perforation were lacking in many articles. Multiple studies and authors listed affiliation with the manufacturer of Essure (Conceptus or Bayer), which may introduce a publication bias toward publishing positive results. Multiple (10) articles were translated to the best of our ability from French, Spanish, or Finnish to English, in order to better assess the effectiveness and safety profile of Essure (especially in light of differing confirmation test protocols in Europe), but there was a possibility for translation error. Finally, one article presented combined data for Essure and Adiana sterilization devices, and results were not stratified by device.[17]

Literature: Case Reports/Series

Using the criteria above, PubMed, Embase, and Google Scholar were also searched for case reports and series, as well as abstracts, posters, and presentations which cited safety-related outcomes following Essure placement. Information from these sources will be summarized separately from peer-reviewed clinical studies within each safety outcome section below although similar limitations (e.g., retrospective reviews, single-site reports, limited follow-up, etc.) apply.

Medical Device Reports (MDRs)

Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries, and malfunctions. The MAUDE database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters, such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a “real world” setting/ environment, including:

    - rare, serious, or unexpected adverse events
    - adverse events that occur during long-term device use
    - adverse events associated with vulnerable populations
    - off-label use
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important post-market surveillance data sources. Other limitations of MDRs include, but are not limited to:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MAUDE data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MAUDE data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

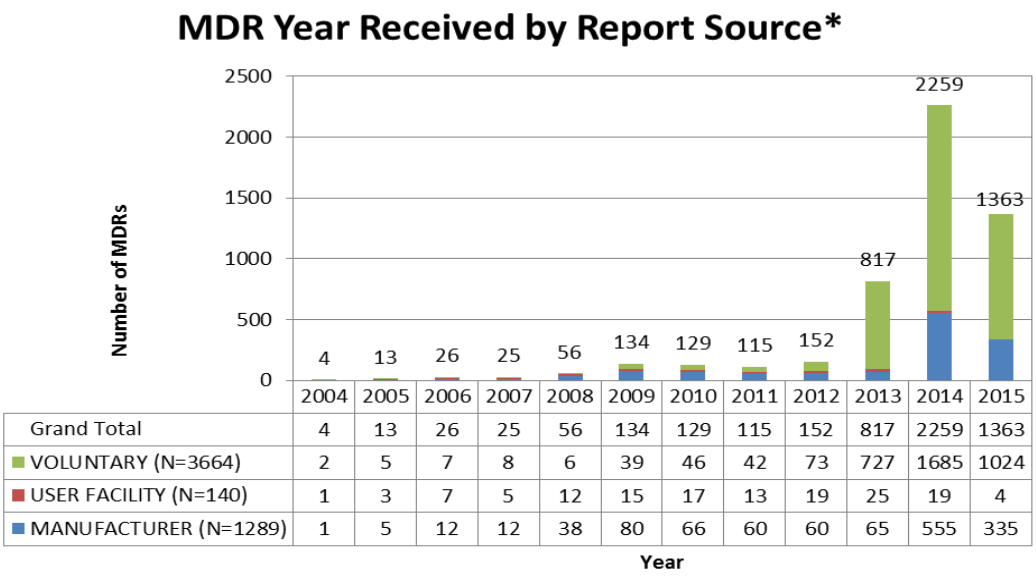
As such, MDR numbers and data should be taken in context and along with other scientific information.

Within the MDR sections of this memo, reference will occasionally be made to "patient problem codes or PPCs." A given PPC is intended to indicate the effects that an event may have had on the patient, including signs, symptoms, syndromes, or diagnosis. It should be noted that a given report may contain more than one PPC (no maximum) and that a report may not have every event captured as a coded PPC.

For the purpose of this review memo, the MAUDE database was queried for all reports related to Essure entered into FDA's database prior to June 1, 2015. This resulted in a total of 5,093 reports since approval. Figure 5 below provides an overview of the number of reports received per year broken down by the report source. As can be seen, there was a sharp increase in the number of MDRs received starting in 2013, largely due to a large number of voluntary reports being submitted. However, it should be noted that many of the MDRs received in/after 2013 described events from earlier years.

Note: FDA sends copies of voluntary reports to the device manufacturer, who evaluates the data and submits MDRs for those it considers to meet the mandatory reporting criteria. Because of this, there are many instances in which multiple MDR reports have been submitted for the same event. It is not usually possible to accurately match voluntary reports to manufacturer reports. Due to the potential duplicative reporting of adverse events, as well as the known limitation of underreporting, it is not possible to use MDR data to determine the actual number of incidents that have occurred in clinical practice.

Figure 5 – Number of MDRs Received per Year, Prior to June 1, 2015, by Report Source



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Grand Total	4	13	26	25	56	134	129	115	152	817	2259	1363
VOLUNTARY (N=3664)	2	5	7	8	6	39	46	42	73	727	1685	1024
USER FACILITY (N=140)	1	3	7	5	12	15	17	13	19	25	19	4
MANUFACTURER (N=1289)	1	5	12	12	38	80	66	60	60	65	555	335

Of the reports received, 4608 were coded as patient injury reports, 474 as device malfunctions, and 11 as deaths (discussed in Section VIII)

Essure Product Labeling

In Sections VI and VII, parts of the currently approved physician labeling and patient labeling relevant or pertinent to the topic being discussed are provided within each section. The exact content from the labeling is provided in *italics*, and all tables are "cut-and-pasted" from the labeling brochure to provide relevant information in one place. (Table numbers from the labeling may be removed so as not to cause confusion with numbering within this memo). Complete physician and patient labeling can be found in Appendices B and C, respectively.

VI. Post-Market Effectiveness Outcomes (Non-PAS)

The risks associated with a given therapeutic product or modality cannot be viewed in isolation. An assessment of a device's overall performance and benefit-risk profile must include consideration of the effectiveness of the device. As such, Section VI provides a review of literature and MDRs related to pregnancy outcomes and patient satisfaction for the Essure System.

A. Unintended Pregnancy

For the Essure System, effectiveness depends on procedural outcomes, including the rates at which devices can be placed (i.e., bilateral placement rate) and the rates at which patients who had devices placed successfully can rely on the device (i.e., reliance rate). As with any surgical or interventional procedure, outcomes may be dependent on the training or experience of the physician or device user. FDA also sought to assess information related to the "learning curve"

associated with the use of the Essure System, published since the original PMA and its PAS. Appendix A addresses the post-market literature regarding device placement rates, physician learning curve, and patient compliance with confirmation testing requirements.

The effectiveness of a permanent birth control procedure is determined by its ability to prevent unintended pregnancies while the woman or partner is not using any other methods of contraception. As discussed previously, surgical tubal ligation is considered an effective permanent sterilization procedure, but it is not 100% effective. It is important to note that, unlike surgical tubal ligation, which is effective immediately, the Essure System relies on the following:

- patient compliance with utilizing alternative birth control until a satisfactory confirmation test
- performance of the alternative birth control
- patient compliance with undergoing a confirmation test
- correct interpretation of the confirmation test.

The premarket studies used to support original PMA approval of the Essure System had zero pregnancies among 632 patients who relied on the Essure device for one year following confirmation testing (and out to 5 years of follow up). However, pregnancies may occur in the commercial setting because of device failure or because of patient compliance or other issues related to confirmation testing.

Literature on Unintended Pregnancy

When assessing rates of unintended pregnancies after Essure placement, it is important to differentiate among:

- luteal phase pregnancies that are already present but unrecognized at the time of the Essure procedure,
- pregnancies that occur between Essure placement and the three month confirmation test, and
- pregnancies that occur after the three month confirmation test.

Previous systematic reviews have concluded that unintended pregnancy is rare in women with successful confirmation tests[22] with rates comparable to other methods such as tubal ligation.[23] Retrospective analysis of worldwide data from FDA's MAUDE database, literature, and manufacturer reports has suggested that many unintended pregnancies are associated with patient or physician noncompliance and misinterpreted or misleading confirmation tests[24,25] and that failure rates of Essure are likely to vary by "perfect use" versus "typical use".[26] For example, FDA's literature review showed that compliance rates with confirmation testing ranged from 28.8% to 100% (see Appendix A for additional information regarding patient compliance with confirmation testing).

Tables 12 and 13 present data on occurrences of unintended pregnancy after Essure placement from published articles that were identified by the current review in addition to select articles identified by the FDA's 2009 literature review. Table 12 focuses on unintended pregnancies

occurring in the first 3 months following device placement, usually before confirmation testing. Most studies were retrospective reviews, so follow-up time may vary. Table 13 provides unintended pregnancies occurring in studies with follow-up of more than one year; some of the pregnancies in these studies may also be in the first 3 months.

Most articles reported low rates of unintended pregnancy, including zero pregnancies in the post-approval five year follow-up study (excluding luteal phase pregnancies).[27] However, this study suffered from high rates of loss to follow-up of the original intent-to-treat population (~30%). Several authors reported unintended pregnancies after patient noncompliance with confirmation testing or using alternative contraception in the three month period before confirmation testing.[28,29,30,31,32,33] There were also a number of unintended pregnancies that occurred after an apparent successful confirmation test.[34,35,36,37] Of note, Povedano, et al., reported one pregnancy that occurred 32 months after Essure placement and successful x-ray and ultrasound confirmation testing; after delivery, HSG showed apparent bilateral occlusion, but a tubal perforation of the insert, rather than occlusion was found upon laparoscopy. [36] Sakinci, et al., reported one pregnancy nine months after abandoning alternative contraception; after termination of the pregnancy, subsequent repeat HSG again showed bilateral occlusion. The patient chose to undergo laparoscopic tubal sterilization; no perforation was noted.[37]

An analysis of French hospital discharge data reported that 39,169 Essure procedures were performed between 2006-2010, and Essure patients became pregnant at a statistically significantly lower rate (143 unintended pregnancies, or 0.36%) than laparoscopic ligation patients (0.46%; hazard ratio 0.62, 95% CI: 0.40-0.96).[38] Information regarding confirmation test results or time interval between sterilization and pregnancy was not presented.

Table 12. Unintended pregnancies occurring before or near the time of confirmation testing (Studies with three months of follow-up).

Author	Country	n	Unintended Pregnancy
Anderson, 2013[39]	U.S.	638	Multiple pregnancies before confirmation
Aparicio-Rodriguez-Minon, 2015[34]	Spain	517	6/467 (1.3%) with successful confirmation test** 1/41 (2.4%) without confirmation test**
Connor, 2011[40]	U.S.	118	0/40 in women with additional follow-up
Duffy, 2005[29]	U.K.	55	1/55 (1.8%): noncompliant with confirmation test, possibly due to immediate expulsion of 1 device
Grosdemouge, 2009[41]	France	1061	2 pregnancies: 1 luteal phase, and 1 after unsatisfactory confirmation test
Lazarus, 2012[35]	U.S.	235	1 after successful confirmation test**
Legendre, 2011[30]	France	311	2/293 (0.7%): both noncompliant with confirmation
Levie, 2006[31]	U.S.	96	1/96 (1.0%): noncompliant with using alternative contraception
Panel, 2011[42]	France	382	0/382
Rajecki, 2014[43]	Finland	120	0/120
Rodriguez, 2013[44]	U.S.	229	0/229
Savage, 2009[32]	U.S.	884	8 pregnancies: 4 unsuccessful HSG, 3 misread HSG, 1 noncompliant HSG
Shah, 2011[45]	U.K.	18	0/17
Veersema, 2010[46]	Netherlands	47	0/47

* NR=Not reported.

**Timing of pregnancy not reported.

Table 13. Long term data for unintended pregnancy (Studies with > 1 year of follow-up).

Article	Country	n	Length of F/U	Unintended Pregnancy
Andersson, 2009[47]	Sweden	57	Mean 23 months	0/57
Arjona, 2008[28]	Spain	1615	Up to 42 months	3/1615 (0.2%): at least 1 due to patient noncompliance (did not use alternative contraception)
Chern, 2005[48]	Singapore	77	1218 woman-months total	0/77
Chudnoff, 2015[27] Cooper, 2003[49]	Europe, U.S., Australia	518	5 years	0/453 for women with follow-up data at 5 yrs 4 luteal phase pregnancies
Donnadieu, 2007[50]	France	20	Mean 14 months	0/20
Franchini, 2011[51]	Italy	45	5 years	0/45
Kerin, 2003[52]	Europe, U.S., Australia	198	21-45 months	0/198
Lopes, 2008[53]	France	140	18-58 months	0/140
Povedano, 2012[36]	Spain	4306	1 year	7/4242 (0.2%): 3 before confirmation test, 4 after confirmation test
Rios-Castillo, 2013[54]	Spain	1321	5 years	3/1200 (0.3%): 2 luteal phase, and 1 before confirmation test due to device migration
Sakinci, 2015[37]	Turkey	32	8 years	1/30 (3.3%): 9 months after successful confirmation test
Shavell, 2008[33]	U.S.	79	Up to 4 years	1/79 (1.3%): noncompliant with confirmation test
Syed, 2007[55]	U.S.	20	2 years	0/20
Thiel, 2011[56]	Canada	610	6 years	2 pregnancies: both diagnosed before confirmation test
Veersema, 2011[57]	Nether-lands	1145	2 years	4/1037 (0.4%): 2 due to device expulsions, 1 due to placement failure, 1 due to perforation
Wittmer, 2006[58]	U.S.	52	10-26 months	0/52

*NR=Not reported.

MDR Reports on Unintended Pregnancy

Since the Essure System was approved in 2002 through June 1, 2015, FDA has received 337 MDR reports related to unintended patient pregnancy associated with Essure use. This includes 21 reports which cite more than one pregnancy in a given patient post-Essure placement and 69 involving ectopic pregnancy.

Of the 127 MDRs which cited a pregnancy and provided a fetal outcome, 76 reported a live birth, 32 reported a miscarriage, and 19 reported electively terminating the pregnancy.

Essure Physician Labeling Related to Pregnancy

The following information regarding pregnancy is provided in the Essure Physician Labeling (Appendix B).

Warnings

- *Pregnancies (including ectopic pregnancies) have been reported among women with inserts in place. Some of these pregnancies were due to patient non-compliance, which included failure to:*

    - *Use alternate contraception during the 3-month "waiting period" prior to Essure Confirmation Test (modified HSG);*
    - *Return for the Essure Confirmation Test (modified HSG) to determine if the inserts are in the correct location and tubal occlusion is present; and*
    - *Use alternate contraception or undergo sterilization by another method if the Essure Confirmation Test (modified HSG) reveals tubal patency. In this case, the clinician should inform the patient of the Essure Confirmation Test (modified HSG) finding and counsel her not to rely on the Essure System for contraception.*

  Therefore, it is critical that clinicians properly counsel patients regarding the risk of pregnancy (including ectopic pregnancy) attributable to non-compliance during all stages of the Essure procedure.

Clinical Trial Results

Effectiveness Results as of December 2007

CUMULATIVE FAILURE RATES Phase II and Pivotal Trials Combined				
One-Year[C]	**Two-Year**[C]	**Three-Year**[C]	**Four-Year**[C]	**Five-Year**[C]
0% **N=635** (95% CI 0 – 0.10%)[A, B]	**0%** **N=605** (95% CI 0 – 0.20%)[A, B]	**0%** **N=586** (95% CI 0 – 0.30%)[A, B]	**0%** **N=567** (95% CI 0 – 0.40%)[A, B]	**0%** **N=567** (95% CI 0 – 0.50%)[A, B]

[A] 95% confidence intervals are based on a "constant-hazard" exponential failure-time model, whose parameter is determined by the total number of woman-months accumulated during the trial.

[B] Combined effectiveness data obtained using Bayesian statistics.

[C] The number of women "N" were considered to have completed follow-up at 1 year if patient contact occurred at ≥11 months, 2 years if contact occurred at ≥23 months, 3 years if contact occurred at ≥ 35 months, 4 years if contact occurred ≥ 47 months and 5 years if contact occurred at ≥ 59 months.

No pregnancies were reported in the clinical trials. However, no method of contraception is 100% effective and pregnancies have occurred in the commercial setting.

Commercial Setting Data

In the commercial setting, unintended pregnancies have been reported in women who have worn the inserts.

[The table below] summarizes the reasons for pregnancy from reports received by Bayer HealthCare LLC and additional reports from the published scientific literature.

Potential Contributing Factor	United States		Outside the United States**		Total	
	n	% of US causes	n	% of OUS causes	n	%
Patient Non-compliance (e.g., failure to use alternate contraception or return for **Essure** Confirmation Test)	213	32%	16	18%	229	31%
Perforation*** / #	91	14%	4	5%	95	13%
Unsatisfactory Placement***	32	5%	13	15%	45	6%
Physician Non-compliance	22	3%	13	15%	35	5%
Pregnant at time of Placement (Luteal)	26	4%	6	7%	32	4%
Inadequate Confirmation Test***	28	4%	0	0%	28	4%
Expulsion***	20	3%	4	5%	24	3%
Tubal Patency***	19	3%	1	1%	20	3%
Insufficient Information to determine	209	32%	31	35%	240	32%
Total	660		88		748****	

*Table includes pregnancy reports received directly by Bayer HealthCare LLC, recorded in the FDA MAUDE database and reported in the scientific literature; data reported to FDA in PMA Annual Reports. Pregnancies in **Essure** patients may be underreported.

Outside of the United States, the **Essure Confirmation Test may be an x-ray or transvaginal ultrasound; device location alone, not occlusion, is primarily used to determine whether the patient may rely on **Essure**. Use of an x-ray or transvaginal ultrasound in the United States is not in accordance with approved labeling.

*** Most of these pregnancies are due to misinterpreted **Essure** Confirmation Tests. Please note that many misinterpretations are due to the fact that occlusion is seen on the HSG films even though the insert is not properly located.

****Number of pregnancies reported from worldwide commercial launch in 2001 through end of 2010. 497,306 **Essure** kits sold during this time. Note that an accurate pregnancy rate is difficult to obtain as the number of devices actually implanted is not known.

#The causal association cannot be established between the perforation and the pregnancy. However, perforations have been identified in pregnant women who were relying on **Essure** for contraception.

The majority of unintended pregnancies are preventable. Most unintended pregnancies are related to patient non-compliance and physician misinterpretation of the Essure Confirmation

Test. In order to ensure maximum contraceptive effectiveness by Essure, the physician should ensure that the patient is properly counseled in accordance with Section XI. It is also important to evaluate both insert location and occlusion carefully before telling the patient that she may rely on Essure for contraception.

Essure Patient Labeling Related to Pregnancy

The following information regarding pregnancy rates is provided in the Essure Patient Labeling (Appendix C).

- *The Essure procedure is 99.83% effective, based on five-year clinical study data.*
- *No birth control method is 100% effective. There is a chance that you can become pregnant after completing the Essure procedure. In the original premarketing studies for Essure, no pregnancies were reported for women who had Essure inserts for up to 5 years. Although successful pregnancies have been reported with Essure devices, if you do become pregnant after Essure, the risks to you, the fetus, the pregnancy and childbirth are unknown.*
- *The risks to you and your fetus if you get pregnant after the Essure procedure are not known*

B. Patient Satisfaction

In the Pivotal study, at all study visits after the 1-week phone visit, 99% of women rated their comfort with wearing Essure as "good" to "excellent" and > 97% rated their overall satisfaction as somewhat to very satisfied (including women not able to rely on Essure).

Literature

In FDA's review of the current published literature, 8 articles reported rates of patient satisfaction after the procedure by asking patients to rate their level of satisfaction with Essure, or state whether they would recommend Essure to a friend or relative (see Table 14).[27,30,37,41,43,59,60,61] All articles reported satisfaction rates of 93% or higher. Five articles measured satisfaction at the time of the three month confirmation test.[30,41,43,60,61] The other three articles measured satisfaction at up to one year,[59] five years,[27] and eight years[37] of follow-up.

Table 14. Patient satisfaction

Article	N	Time of F/U	Satisfaction Rating Scale	Satisfaction Rate
Grosdemouge, 2009[41]	1061	3 mos	Scale: 1 (dissatisfied) to 5 (very satisfied)	93% satisfied or very satisfied
Legendre, 2011[30]	311	3 mos	Very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied, or very dissatisfied	95% very satisfied
Ploteau, 2009[60]	168	3 mos	Very satisfied, satisfied, somewhat satisfied, or not satisfied	93% (145/156) satisfied or very satisfied
Rajecki, 2014[43]	120	3 mos	Scale: 1 (very dissatisfied) to 5 (very satisfied)	96% satisfied
Rufenacht, 2015[61]	143	3-16 mos	• Satisfied (yes/no) • Whether they would recommend the procedure to a friend	• 89.2% (107/120) satisfied • 95.8% (115/119) would recommend to friend
Sakinci, 2015[37]	32	3 mos 8 yrs	• To what extent they were satisfied • If they recommend the method to anybody else	• At 3 months: 100% (30/30) happy with procedure, would recommend to friend • At 8 years: 100% (26/26) happy with result of procedure, would recommend to friend*
Levie, 2010[59]	209	1-12 mos	• Rate satisfaction on a scale from 1-5, with 1 being “not satisfied” and 5 being “very satisfied” • Whether they would have the procedure done again • Whether they would recommend the procedure to a friend	• Average satisfaction score: 4.7 (SD 0.71) • 93% (164/176) would do procedure again • 98% (173/176) would recommend to friend
Chudnoff, 2015[27]	518	5 yrs	Very satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied, or very dissatisfied	98% (376/384) somewhat or very satisfied

*One patient who became pregnant after the three month confirmation test was excluded from eight year follow-up.

VII. Post-Market Safety Outcomes (Non-PAS)

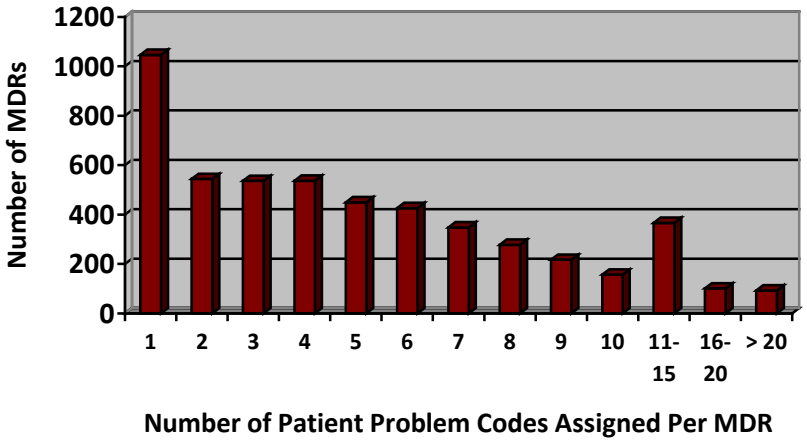
As indicated previously, FDA has noted a significant rise in the number of adverse event reports submitted in the past 1-2 years, in particular from women who had been implanted with the device. There have been different types of events or symptoms reported in those MDRs and Table 15 below provides a summary of many of those, listed by body system or symptom complex.

Table 15. Symptoms Reported in Essure MDRs

GYNECOLOGICAL			
• Menorrhagia • Menstrual irregularities • Amenorrhea • Constant spotting • Metorrhagia • Polymenorrhea • Dysmenorrhea • Hot flashes • Premenstrual Dysphoric Disorder • Loss of libido	• Pelvic pain • Cramping • Abdominal spasms • Dyspareunia • Breast tenderness • Breast engorgement	• Pregnancy • Miscarriage • Early menopause • Endometriosis • Adenomyosis • PCOS • PID • Adhesions	• Ovarian cysts • Uterine cysts • Uterine fibroids • Fallopian tube cysts • Uterine infection • Bacterial vaginosis • Yeast infections • Vaginal discharge • Urinary tract infections • Cervical dysplasia
GENERAL	**PAIN**	**NEUROLOGICAL**	**GASTROINTESTINAL**
• Fatigue • Weight gain or loss • Edema/swelling • Excessive sweating • Fevers • Night sweats • Insomnia • General aches/pains • Vitamin D deficiency • B12 deficiency • Dental caries, chipping • Changes in vision • Changes in hearing	• Abdominal pain • Pelvic pain • Low back pain* • Leg pain • Joint pain	• Headache/Migraine • Dizziness • Vertigo • Paresthesia • Weakness • Tremors • Cognitive (“fog”) • Memory loss • Seizures • Stroke symptoms • Syncope • Myasthenia gravis • Multiple sclerosis	• Nausea • Vomiting • Diarrhea • Constipation • Metallic taste in mouth • Heartburn • Metallic taste • Abdominal pain • Abdominal cramping • Gallstones • Pancreatitis
RENAL/URINAY	**DERMATOLOGICAL**	**MUSCULOSKELETAL**	**PSYCHIATRIC**
• Polyuria • Incontinence • Hematuria • Kidney stones • UTIs	• Rash, hives • Alopecia • Pruritis • Easy bruising • Dry skin • Acne	• Back pain • Joint pain • Tendonitis • Muscle spasms • Rheumatoid arthritis	• Mood changes • Depression • Anxiety • Panic attacks • Mood swings • Irritability
HEMATOLOGICAL	**IMMUNOLOGICAL**	**CARDIOVASCULR**	**RESPIRATORY**
• Anemia (IDA) • Blood clots, emboli • ITP	• Food, chemical, metal sensitivities • Difficulty fighting infections • Frequent infections	• Palpitations • Chest pain	• Sleep apnea • Pulmonary embolism
ENDOCRINE	**AUTOIMMUNE**		
• Hypoglycemia • Thyroid disease • Adrenal problems • Degenerative bone disease	• SLE • Rheumatoid arthritis • Fibromyalgia • Raynaud’s • Myasthenia gravis		

The majority of MDRs received by FDA (particularly since late 2013) each contain multiple, concurrent symptoms believed to be associated with, or a consequence of, having the Essure device implanted. Figure 6 below depicts the number of Patent Problem Codes (PPC) contained within a given MDR. As can be seen, many listed more than 10, and some, more than 20.

Figure 6. Number of Patient Problem Codes per MDR Report



FDA sought to focus our review on available data related to specific adverse events which have been more commonly discussed or reported in the patient community and in our MDR database including

- Pain and cramping (abdominal, pelvic) – with a focus on chronic/persistent pain
- Abnormal bleeding or menstrual irregularities
- Headache
- Metal allergy/sensitivity.

A. Post- Procedural Pain (Chronic/Persistent Pain)

Pain is a well-known and commonly reported complaint *during* the Essure insertion procedure and recovery period. In the Pivotal study, almost 30% of women reported cramping during the recovery period, and 13% reported pain. However, the pain/discomfort experienced during the procedure typically resolves within hours or days. Kerin, reporting data from the Phase II trial[52], noted that of those patients who did experience procedural or peri-procedural pain, 59% had the pain resolve within 1 day, 88% within 3 days, and 99% within 1 week. Two patients had pain last longer than 1 week – but both resolved within 2 weeks. In Arjona's prospective study of over 1600 women at one Spanish site, 7% of patients needed oral analgesics for 1-2 days after the procedure.[28] Mino, reporting on a population of 857 patients from the same institution, noted that of the fewer than 10% of patients who took oral analgesics following the procedure, 43% took the drugs on the day of the procedure alone, 30% for 2 days, 13% for 3 days, and 12% for 4 or more days. This latter group accounted for only 1% of the overall population. [62]

Abdominal and pelvic pain are common symptoms, and both acute and chronic pain may arise from multiple sources, including organs of the digestive, genitourinary reproductive, musculoskeletal, and nervous systems. As such, in many cases, it may be challenging to definitively link persistent or new abdominal or pelvic pain to the Essure System. However, several potential Essure device-related causes of post-procedural pain have been suggested, including, but not limited to:

- Malpositioned device within the fallopian tube, including subserosal placement or a kinked insert
- Uterine or fallopian tube perforation (discussed below)
- Migration with intra-abdominal or pelvic organ damage (see below)
- Infection
- Tubal pressure from > 1 insert within a tube (not consistent with device labeling)
- Nickel allergy with or without local inflammation
- Concurrent procedure (e.g., endometrial ablation, not consistent with device labeling).

It should be emphasized that the presence of any of the above does not necessarily mean the device recipient will have/develop pain, and likewise, pain may develop in the absence of any of these.

ESSTVU Study Safety Data Related to Pain

In the most recent annual report for the ESSTVU study (including data current to June 2015), pelvic pain was recorded in 4.7% of subjects and abdominal pain in 2.7%. In addition, dysmenorrhea was noted in 2.5% of subjects, and dyspareunia in 0.7%. These rates do not include procedural pain, but do include events that occurred any time during the first year after the procedure.

Literature Related to Persistent Pain

In 2013, Al-Safi, et al., reported that there were 217 reports of Essure-related pain within the MDR database from 2002-2012. The onset of the pain ranged from immediately after placement to years after the procedure, and in 54 cases, perforation was discovered during subsequent imaging or surgery.[63] However, post-procedural pain has not been a common outcome reported in the literature. In the current review, there were several articles that specifically looked at the occurrence of Essure-related chronic pain after the three month confirmation test (i.e., not intraoperative or postoperative pain). Conover, et al., used claims data from a large cohort of U.S. women with employer-provided health insurance plans who received hysteroscopic sterilization with either Essure or Adiana devices (no longer available in the U.S. market), and reported that 236 of 26,927 women (0.88%) experienced opioid-managed pelvic pain at a mean follow-up time of 275 days. This rate was comparable to a similar cohort of women who underwent laparoscopic sterilization, of which, 420/44,948, or 0.93% experienced pelvic pain with a mean of 283 days of follow-up (between-group differences were not statistically significant, OR= 0.97 (0.83;1.14)). The authors defined the pelvic pain outcome with the following criteria: (1) at least two diagnoses relating to pelvic pain, including dysmenorrhea, abdominal pain, or symptoms associated with female genital organs, and (2) at least two opioid

prescriptions filled on separate days. This study excluded women who experienced childbirth within six months of sterilization, underwent concurrent endometrial ablation, or had a history of opioid use or pelvic pain.[17] Results were not stratified by type of device (Essure vs. Adiana).

A retrospective cohort study using data on 458 subjects with successful bilateral Essure placement at a U.S. university medical center recently reported a higher rate of chronic pain (4.2%), defined as pain lasting >3 months after insertion. Of those with chronic pain, 75% reported pain within 130 days of the procedure, and 91% had appropriate tubal occlusion confirmed with HSG. The authors reported that those with a previous diagnosis of any chronic pain before the Essure procedure (chronic pelvic pain, chronic low back pain, chronic headache, and fibromyalgia) were six times more likely to report chronic pain after Essure (OR=6.15, 95% CI: 2.09-18.05). The authors did not identify causes of pain (such as perforation) for each individual, but suggested that a causal relationship between Essure and chronic pain was likely in these patients due to the temporal relationship of procedure and pain onset, and suggested that HSG may not enable discernment of small perforations or malpositioning that may cause pain.[64]

Arjona-Berral reviewed the medical records of 4,274 women who received Essure in a hospital in Spain and published findings in 2014. Seven women (0.16%) returned to the hospital seeking device removal for "chronic pelvic pain" which started either immediately or one week post-op, increased with time, and was not responsive to standard analgesic drugs. At the time of the procedure, the surgeon reported satisfactory placement in six patients and unsatisfactory placement in one. The procedure was rated as difficult by the surgeon in three cases although subsequent HSG demonstrated correct placement. The other four patients received an x-ray confirmation test (results not given). The Essure devices were removed either hysteroscopically or laparoscopically in all seven patients, with time between procedure and removal between 4-57 months. All seven patients reported immediate resolution of pelvic pain after removal.[65] This publication did not specifically comment on whether additional patients experienced chronic pain but were responsive to pain medications and/or did not seek device removal. In addition, the rate of women experiencing pelvic pain in this study may have been an underestimate as it relied on the patient's self-report of pain to the hospital and its peripheral centers. Another publication from this same Spanish facility two years earlier noted one patient out of 4,306 implanted over a 7-year period who experienced "persistent abdominal pain" (0.02%). However, this patient's symptoms did not resolve with administration of NSAIDs or after device removal.[36]

Additionally, Sakinci, et al., recently reported that at five years follow-up of 30 patients, no patients reported persistent pelvic pain, and 2 patients reported a slight groin pain from time to time that they were unsure was related to the device.[37]

Earlier, in 2007, Sinha published on a prospective cohort of 122 women who received the Essure device at a single site in the UK.[66] Postal questionnaires were sent to 84 women who had completed 3 months of follow-up. Of the 76 patients who responded, 5 (6%) reported "new pain or discomfort since the procedure" and two (3%) described "new pain or discomfort with sexual intercourse." In 2005, Duffy reported a cohort controlled comparative study which included 48 women with successful bilateral Essure placement and 24 women undergoing laparoscopic sterilization.[29] Of the 35 women in the Essure group providing data at 3 months follow-up, 4 (11.4%) reported abdominal or pelvic pain. However, information regarding the timing of the events and whether any represented persistent/chronic pain was not specified.

Case Reports/Series Related to Persistent Pain

Several published case reports describe patients with persistent pain following Essure placement – even if it was not the primary reason for publishing the report. In many of these reports, the onset of pain was at the time of the procedure, but some reports noted a period where the patient was asymptomatic for weeks or even months before it started[67,68,69,70] Duration of symptoms was variable although some note pain that persisted for months and even years before either presenting for evaluation or having symptomatic relief. [69,71,72,73,74,75,76] The abdominal or pelvic pain may have been unilateral or bilateral, constant or intermittent, and, in cases, unresponsive to traditional analgesics.[36, 65, 67, 73, 75,77]

Difficult or improper placement and perforation were noted in some cases[78,79, 70, 75,76, 81] while in others, the authors specifically noted correct insert placement with no procedural difficulties and no evidence of malpositioning or perforation.[65 67, 77, 80, 72 73, 79, 74 75,81]

Multiple case reports note that the patients underwent removal of their inserts as a treatment for pain presumed to be secondary to the device. Several describe hysteroscopic removal as far out as 55 months from placement.[65, 67, 79, 74] Others describe laparoscopic removal via salpingectomy or salpingotomy[65, 77, 71, 82, 72, 73, 83, 84] or hysterectomy/oophorectomy[71, 75] – up to 4 or more years after insert or start of pain. Many of the case reports which described insert removal for pain noted resolution of symptoms following the procedure.[36,67,77,71,72,73,74,76,85,83,84] When time to resolution was provided it ranged from "immediately" to several weeks. However, other cases noted only partial resolution of pain symptoms[84], unchanged symptoms[36,65,71] or even worsening of pain following removal.[71]

MDR Reports Related to Pain

The majority of MDRs received by FDA note the presence of abdominal or pelvic pain and/or cramping. The numbers of reports coded with each of these pain-related Patient Problem Codes (PPC) are shown below in Table 16. Some reports were coded with multiple pain-related PPCs. There were a total of 3,516 reports which were coded with at least one of these PPCs indicative of pain. Over 69% (3516/5093) of the reports mention pain or cramping of some sort.

Table 16. MDRs Coded with Pain/Cramps*

PPC	Number of MDRs
Pain	2907
Pain, abdominal	1012
Cramps	529
Abdominal cramps	491

*Each MDR report may contain more than 1 patient problem code.

There was variability in the type and amount of information provided in the MDR reports regarding the symptom of pain including specific information related to the timing of the onset of pain relative to the placement procedure, location of the pain within the abdominal/pelvic region, the intensity and quality of pain, the consistency of the pain (continuous versus cyclical/intermittent), and the duration of pain (including some beyond 8 years). Although it is not possible to determine which were primarily or solely done for persistent pain, 452 total MDRs for Essure described women having their devices removed. As will be discussed in a later section (Section IX), women who underwent device removal *and* provided information related to symptom outcome generally reported improvement or resolution to their symptoms (176/196, or 90%).

Essure Physician Labeling Related to Pain

Warnings

- *Some Essure patients have reported pelvic pain that may be device related. If device removal is indicated, this will require surgery.*

Precautions

- *Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort. Terminate the procedure and work-up patient for possible perforation.*

Other Statements/Study Results

- *Table (Pivotal Trial Adverse Events by Body Systems, First Year of Reliance (N=476 patients implanted with at least one insert))* – NOTE: Table modified to include only pain events

Adverse Events by Body System	Number	Percent
Abdominal:		
Abdominal pain/abdominal cramps	18	3.8%
Musculo-skeletal:		
Back pain/low back pain	43	9.0%
Arm/leg pain	4	0.8%
Genitourinary:		
Dysmenorrhea/menstrual cramps (severe)	14	2.9%
Pelvic/lower abdominal pain (severe)	12	2.5%
Dyspareunia	17	3.6%
Pain/discomfort - uncharacterized:	14	2.9%

Essure Patient Labeling Related to Pain

- *You may experience mild to moderate pain and/or cramping, vaginal bleeding, and pelvic or back discomfort for a few days after the procedure.*
- *There are reports of chronic pelvic pain in women, possibly related to Essure*

Summary for Persistent/Chronic Pain

Reports of various types of pelvic pain ranged from < 1% to 7% throughout the follow up of the Pivotal study. However, persistent pelvic pain was reported in only 1 case at one and two year

follow up appointments. When reviewing data from these studies, it is important to recognize that patients with chronic pain syndromes were excluded from enrollment, and a recent retrospective study suggested that patients with such conditions are at significantly higher risk for post-procedural chronic pain.[64] In addition, lack of a control group may make the assessment of causality or association difficult for such a common symptom. There is a paucity of clinical studies within the peer reviewed literature regarding persistent or chronic abdominal/pelvic pain following Essure placement. Several of these have reported rates of < 1%, although these were largely based on retrospective data collection/review. One recent retrospective single-site study, however did report a rate of chronic pain of 4.2%.[64] Limited data were often available in these studies regarding the onset of pain, pain characteristics, and associated findings or causes (e.g., presence of perforation). Interpreting chronic or persistent pain in the literature is made more difficult by the lack of consistent terminology and what is included in the case definition of pain. Multiple case reports in the literature and MDRs submitted to FDA cite pain – and when the information was provided, the pain often resolved with device removal. However, information from case reports and MDRs cannot be used to calculate rates of the event, and considering the large volume of device use, it is not possible to assess whether the number of individual reports noted fall within the range which might be expected based on data from the prospective IDE studies.

B. Changes in Vaginal Bleeding, Menstrual Patterns or Characteristics

Many of the voluntary MDRs which have been received by FDA for the Essure System note changes related to vaginal/uterine bleeding and/or menstrual symptoms. In the Pivotal study, irregular menses were reported at rates ranging from 4-12% throughout the 5 year follow up period after subjects had discontinued alternative contraception. However, persistent menstrual irregularity rates were significantly lower, ranging from 0-3%, with the higher rates of persistent changes reported as "less than usual flow."

ESSTVU Study Safety Data Related to Bleeding and Menstrual Changes

Table 17 below lists the rates of various vaginal bleeding and/or menstrual symptoms (per MedDRA coding) reported in the most recent annual report from the ESSTVU study (including data current to June 2015).

Table 17. Menstrual Symptoms from ESSTVU Study

Event	Rate
Menorrhagia	3.9%
Dysmenorrhea	2.5%
Vaginal hemorrhage	2.3%
Uterine hemorrhage	1.5%
Metrorrhagia	0.8%
Dyspareunia	0.7%
Menstrual irregularity	0.5%
Amenorrhea	0.5%
Dysfunctional uterine bleeding	0.3%

The most commonly reported of these events has been menorrhagia with heavy and/or prolonged menstrual bleeding. A total of 23 women (3.9%) reported this in the study report.

Literature Related to Bleeding and Menstrual Changes

Two recent articles reported information about menstrual irregularities. In one clinical trial published in 2015 (published results of the 5-year Pivotal IDE cohort), one subject reported lower abdominal pain and very heavy periods at her 18- and 24-month follow-up visits; she ultimately underwent hysterectomy at 34 months. Another subject in that trial experienced irregular menstrual bleeding, which resolved following dilation and curettage. Overall, 29/473 patients (6.1%) reported dysmenorrhea at one or more follow-up visits. At the five year follow-up visit, 12% of subjects reported irregular menses, 8% reported intermenstrual bleeding between menses, 20% reported heavier than usual menstrual flow, and 11% reported lighter than usual menstrual flow.[27] Fifteen women underwent hysterectomy as of the five-year visit – with bleeding being a reason in seven of those cases, and dysmenorrhea in two. As noted previously, this study suffered from a high rate of loss to follow-up, which could result in biased rates. In a Turkish study, also reported in 2015, 4/30 (13.3%) patients reported an increase in menstrual bleeding, while 5/30 (16.7%) patients reported a decrease at eight year follow-up.[37]

In 2009, Andersson reported a retrospective review of 61 women implanted with Essure at one Swedish site, 58 of whom had successful bilateral insert placement.[47] Fifty (50) women responded to an outcomes questionnaire with a mean follow-up of 23 months (range, 7-67). Heavier periods were reported in 9 women although none sought medical attention. Eight patients reported lighter periods. In 2007, Kerin published a multi-center retrospective review of a subset of women undergoing repeat hysteroscopy 4-43 months following Essure placement. Of 545 women who had undergone the procedure at the facilities, 20 required a diagnostic second-look due to abnormal and/or heavy bleeding. However, it is unknown how many other women experienced abnormal bleeding but did not undergo a second look.[86] Also in 2007, Sinha reported on outcomes for 76 of 84 Essure patients who responded to a 3-month questionnaire, noting that 26% had persistent changes in menstrual pattern including heavier-than-normal menses in 18%, amenorrhea in 4%, irregular bleeding in 3% and intermenstrual bleeding in 1%.[66]

Mino, however, reported no changes in volume or pattern of menstruation in a survey of 857 women after 3 months.[62]

Case Report/Series Related to Bleeding and Menstrual Changes

In 2013, Levie presented an abstract report describing 193 women who had undergone Essure placement and 139 who had surgical BTL between 2004 and 2011 at a single U.S. center.[87] Irregular cycles were experienced by 30% of Essure patients and 28% of BTL patients, and menorrhagia was reported in 36% and 46% respectively.

MDR Reports Related to Bleeding and Menstrual Changes

Irregularities in vaginal bleeding, menstrual patterns or symptoms were noted in the MDR reports. Many reports were coded with multiple menstrual-related PPCs which resulted in a total of 1,580 reports which were coded with at least one of these PPCs. Table 18 lists the more commonly reported PPCs related to this topic.

Table 18 MDRs Coded with Menstrual Signs/Symptoms*

PPC	Number of MDRs
Heavier menses	867
Menstrual irregularities	807
Hot flashes	187
Intermenstrual bleeding	182

*Each MDR report may contain more than 1 patient problem code.

When described in the MDRs, changes in vaginal bleeding patterns after Essure placement included prolonged, frequent, and/or heavy menstrual bleeding when compared to prior experiences, irregular bleeding, intermenstrual bleeding or spotting, bleeding that was less frequent and/or less severe than in the past, as well as amenorrhea. However, as seen in Table 18 above, over half of the reports noted heavier menses.

Essure Physician Labeling Related to Bleeding and Menstrual Changes

Observed Adverse Events from Pivotal Trial

Pivotal Trial
Adverse Events by Body Systems, First Year of Reliance*
(N=476 patients implanted with at least one insert)

Adverse Events by Body System	Number	Percent
Abdominal:		
Abdominal pain/abdominal cramps	18	3.8%
Gas/bloating	6	1.3%
Musculo-skeletal:		
Back pain/low back pain	43	9.0%
Arm/leg pain	4	0.8%
Nervous/Psychiatric:		
Headache	12	2.5%
Premenstrual Syndrome	4	0.8%
Genitourinary:		
Dysmenorrhea/menstrual cramps (severe)	14	2.9%
Pelvic/lower abdominal pain (severe)	12	2.5%
Persistent increase in menstrual flow	9**	1.9%
Vaginal discharge/vaginal infection	7	1.5%
Abnormal bleeding - timing not specified (severe)	9	1.9%
Menorrhagia/prolonged menses (severe)	5	1.1%
Dyspareunia	17	3.6%
Pain/discomfort - uncharacterized:	14	2.9%

* Only events occurring in ≥ 0.5% are reported
** Eight women reported persistent *decrease* in menstrual flow
In the Phase II trial, 12/206 (5.8%) women with at least one insert reported episodes of period pain, ovulatory pain, or changes in menstrual function.

Essure Patient Labeling Related to Bleeding and Menstrual Changes

- *Will I still get my period after the Essure procedure? Yes, you will still have a period. Some women find that their period may become slightly lighter or heavier after the procedure. These changes are often temporary. They may also be due to you stopping your previous hormonal birth control, rather than the Essure procedure.*

Summary for Vaginal Bleeding and Changes in Menstrual Patterns

General menstrual irregularities were reported at rates ranging from 4-12% throughout the 5 year follow up period of the Phase II and Pivotal trials after subjects had discontinued alternative contraception. Heavier than usual menstrual flow was more commonly reported at 16-22%; however, less than usual menstrual flow was reported at rates ranging from 10-15%. Irregularities that were *persistent* occurred at rates ranging from 0-3%. Few peer-reviewed publications have addressed the issue of changes in bleeding patterns following Essure placement although longer term follow-up from the Pivotal study reported higher rates for several pattern changes (e.g., up to 20% reporting heavier menses).[27] Several case reports and abstracts – largely single center experiences – have also reported these higher rates. However, these have included higher rates of both increased/heavier menses (some over 30%) as well as *lighter* menses or even amenorrhea (close to 20%). Numerous MDRs describe bleeding irregularities, ranging from heavy, prolonged, frequent bleeding to amenorrhea. Again, rates of these events cannot be determined by the numbers of case reports and MDRs. In addition, much of the data related to Essure and menstrual changes do not provide information related to prior menstrual history and do not take oral contraceptive use, or its discontinuation, in to account. Furthermore, most studies lacked a control group to account for natural progression of symptoms as the woman ages. These limitations may make it more challenging to ascribe the changes to the device.

C. Headache

FDA evaluated current data related to post-procedural headaches as this symptom was one of the more commonly reported events in MDRs. In the initial pre-market data, headaches which were deemed at least possibly related to the device or procedure were reported in up to 2.5% of subjects whereas those that were rated as unlikely or not related were reported in up to 19% Headaches were reported in 4.9% of women in the 5-year follow up of the Phase II study and 18.9% of patients through 5 year of follow-up in the Pivotal trial. However, it is not clear whether the latter rate represents all headaches, or only those which were deemed by the investigator to be possibly related to the device or procedure.

ESSTVU Study Related to Headaches

In the most recent annual report for the ESSTVU study, the rate of reported headache was consistent with that seen in the original PMA cohort; traditional headache was reported in 0.7% of subjects, migraine headache in 0.5% and premenstrual headache in 0.3%.

Literature Related to Headaches

FDA has been unable to locate any significant scientific literature which specifically evaluated headaches following Essure treatment. Yunker's 2014 publication evaluating risk factors for chronic pain in Essure patients found that women with previous diagnoses of chronic pain syndromes, including headaches, were at increased risk for chronic pain post-Essure.[64] However, this study did not report on the occurrence or rates of headaches or migraines post-operatively. In Duffy's 2005 publication, one subject out of 48 who had bilateral Essure placement reported a headache.[28] This was documented at the 1-week follow-up visit.

Case Reports/Series Related to Headaches

In 2010, Hurskainen submitted an abstract describing a retrospective cohort from one Finnish hospital which evaluated 103 patients who had undergone Essure placement, and 104 who had undergone surgical BTL with Filshie Clips.[88] Patients were assessed via questionnaires and review of medical records. The patients receiving Essure had a lower rate of post-operative headaches ($p=0.05$) through the first week, although exact values were not provided.

MDRs Related to Headaches

Approximately 1400 MDRs received list the presence of headache (including migraine headaches) as a symptom following Essure placement. However, as headaches were often one of several symptoms noted in a given report, additional details regarding the headache were limited. The frequency of headaches varied considerably – from constant/every day to monthly or just occasionally. Reports did not usually provide significant information related to prior headache history, or information regarding evaluation and treatment specific to the headache, although a handful of reports did note improvement in headache symptoms after device removal.

Summary for Headaches

Headache has been noted in a significant proportion of voluntary MDR reports submitted to FDA, although limited details were available. No significant data are available from the published literature regarding the rates of post-procedure headaches, and data from the prospective IDE studies have shown rates that varied considerably. Because these prospective studies did not have a control group, and because headaches are common, it is difficult to assess causality.

D. Nickel Allergy/Hypersensitivity

Although allergic reactions were not specifically identified in the Pivotal and Phase II studies, many of the MDRs which have been received by FDA related to the Essure product claim an allergy to the nickel in the device and/or a general allergic-type of reaction following placement.

It is estimated that about 10 to 25% of all women in the United States have a general nickel allergy.[89] The most common manifestation is a contact dermatitis which appears in a previously sensitized patient after future cutaneous contact as a result of a Type IV delayed hypersensitivity process. However, symptoms are also possible in a sensitized individual following exposure

through other routes, including intravenous and oral ("systemic contact dermatitis").[90,91] In addition, some authors have suggested that non-dermatological allergic symptoms may be associated with nickel hypersensitivity, including chest pain, migraine headache, palpitations, edema, respiratory issues, and digestive symptoms.[92,93]

Nitinol, a combination of nickel and titanium, is present in the Essure System and is a common alloy used in medical implants, including intravascular cardiac devices (IVC filters, septal occluders, etc). Nitinol tends to have low levels of nickel leaching - approximately 0.14 µg/day in Essure – possibly because of the formation of a titanium oxide coating.[89]

The results of *in vitro* nickel release testing conducted on Essure devices can be compared with nickel release information of other nitinol devices. Nickel release is expected to be highest initially, and then to taper off over time. Data presented at a 2012 FDA Public Workshop entitled "Cardiovascular Metallic Implants: Corrosion, Surface Characterization, and Nickel Leaching" [94,95] are summarized in Table 19. The peak rates in the table reflect release rates on the first day; the chronic rates reflect rates measured up to 60 days; the totals reflect the total amount released in 60 days. These data demonstrate that the release of nickel from two Essure inserts is comparable to or lower than the release from selected cardiovascular nitinol devices.

Table 19. Nickel release from Essure compared to other selected implant devices.

	Peak rate (µg/day)	Chronic rate (µg/day)[a]	Total (µg)[a]
Selected cardiovascular implant devices	0.043-4.8	<0.015 – 1.31	0.11-110
Essure (2 inserts)	< 0.77[b]	< 0.007[c]	< 1.4

[a] Most of the testing reported at the workshop was conducted at 60 days.
[b] Based on seven day *in vitro* measurements; as a worst case, the 0.77 µg/day is based on all of the nickel in the seven day test being released in a single day.
[c] Based on longer-term *in vitro* testing, in which nickel release was not detected (for days 30-60); the worst case estimate of 0.007 µg/day in the table is based on the detection limit.

The mechanism of hypersensitivity reaction to implanted metal devices has yet to be fully elucidated. Although presumed to be the mechanism, there is insufficient evidence to confirm a delayed Type IV reaction.[93] As such, there is currently no proven method to prospectively identify individuals who will develop adverse events to their implant.[96] A correlation between serum nickel levels and allergy has not been demonstrated and self-reporting of nickel allergy is unreliable.[93,89] Although patch testing is standard for identifying Type IV delayed hypersensitivity in the skin to external allergens, it is unknown whether it can reliably identify sensitivity to *internal* materials, or can predict/identify peri-implant or systemic reaction to nickel.[89, 96,97] Because of the relatively high prevalence of nickel allergy (in women particularly), as well as nickel's common presence in consumer products, the results of a positive patch test can not necessarily attribute causation to the presence of an implanted device and do not necessarily correlate with a clinically significant reaction.[90,98] Likewise, a negative result does not preclude the development of a complication.[98] An alternative to patch testing is the

lymphocyte transformation test (LTT) which measures the proliferation of peripheral blood lymphocytes in the presence and absence of given allergens. However it is rather expensive, complex, and has limited availability. Several authors have instead proposed a clinical set of "criteria" for assessing a potential allergic reaction to a metal implant.[97,98] These have focused on dermatological symptoms or findings and include a dermatologic eruption on the skin overlying the metal implant (weeks to months after placement) with the absence of other contact allergens or systemic cause, a positive skin patch test, and recovery following removal of the implant.

ESSTVU Study Safety Data Related to Allergic/Hypersensitivity Reactions

In the most recent annual report from the ESSTVU study, only 1 subject (0.2%) was reported to have an "allergy to metal." This was rated as a mild event, and no treatment was rendered. In addition, one patient (0.2%) was diagnosed with dermatitis and two (0.3%) with a rash – all of which were rated as mild and resolved with medical therapy.

Literature Related to Allergic/Hypersensitivity Reactions

Zurawin & Zurawin performed an analysis of the MAUDE database for the years 2001-2010 as well as data published from the Phase II and Pivotal clinical trials. During this period, 436,927 Essure kits were sold, and sixty-three reports of nickel hypersensitivity were identified. The authors used these numbers to suggest a rate of 0.014%. Thirteen of twenty patients who underwent patch testing tested positive for nickel allergy; these patients reported symptoms including rash, hives, pain, nausea, swelling, increased symptoms of asthma, and arthritis. Device removal performed in 9/13 positive patch test patients resulted in resolution of symptoms for four patients, no resolution of symptoms for two patients (one case of pelvic pain two years post-procedure that was judged to be unrelated to Essure and one case of rash and hives four years post-procedure that was judged to be unrelated to Essure), symptom resolution that occurred before device removal for one patient, and unknown resolution for two patients lost to follow-up. In 3/13 positive patch test patients who did not undergo device removal, symptom resolution was achieved by oral medication in two patients with rash and skin reaction, and the third patient had confirmed nickel allergy but no symptoms. Of the seven negative patch test patients, two with post-procedure total body itching underwent device removal and reported symptom resolution. Overall, in this sample of twenty women with potential nickel-related reactions, not all symptomatic women were patch-test positive, not all patch-test positive women were symptomatic, and most adverse events were not judged by the physician to be device-related. The authors concluded that despite the likelihood of underreporting, the incidence of nickel-related reactions is very low, lower than the proportion of women with contact nickel allergy in the population, and suggested that the relationship between Essure devices and nickel-related reactions is not a clinically relevant consideration for placement of nitinol-containing micro-inserts.[89]

Al-Safi's review of the MDR database alone, published in 2013[63] found 20 reports of what was considered an allergic or hypersensitivity reaction (including such symptoms as itching, nausea and abdominal pain). The disparity in numbers compared to Zurawin's review may be the result of the use of different sources to identify the cases, but also may be reflective of a difference in the definition of an allergic or hypersensitivity reaction.

During our review of the literature, cases of nickel allergy were noted in two large cohort studies conducted in Spain. The first article reported two cases of nickel allergy out of 4,306 patients. The first case was a woman with history of atopy who presented shortly after the procedure with papular urticarial and erythema; symptoms disappeared after device removal. The second case was a woman with history of persistent general pruritis, who was referred one year post-procedure; she underwent device removal as well (information about symptom resolution not reported).[36] The second article reported one case of nickel allergy out of 517 patients. The patient experienced eczematous skin lesions and underwent hysterectomy with salpingectomy; this patient was then lost to follow-up.[34]

A systematic review by Adelman, et al., reviewed these articles among others and concluded that severe nickel allergy requiring Essure removal is rare, and universal patch testing before placement is not cost-effective and not recommended, except possibly in women in whom nickel allergy is suspected preoperatively.**Error! Bookmark not defined.**

Case Reports/Series Related to Allergic/Hypersensitivity Reactions

In addition to the studies and cases noted above, several individual case reports have cited suspected nickel reaction in patients implanted with the Essure device. In 2010, Al-Safi published a report on a 27 year-old who developed generalized pruritus and intermittent nausea 3 days following insertion. Skin patch testing was positive to nickel and symptoms resolved following hysteroscopic removal of both inserts at day 8.[99] In 2013, Bibas reported a woman who presented 3 months post-placement with a generalized rash unresponsive to steroids.[91] A patch test was positive and, within 3 days of being removed, the rash began improving. By 3 months, it had resolved. In 2014, Goldwaite reported on a patient with a prior history of metal sensitivities who developed an abdominal rash 3 days after Essure placement.[100] After an unsuccessful trial of steroids, she underwent hysteroscopic removal of the implants and her rash resolved within 36 hours. More recently, Lane reported a case involving a woman experiencing recurring rash (pelvis, neck, axilla) for 10 weeks post-placement in addition to facial edema and pruritis.[101] The patient was patch-test positive for nickel but had only a partial response to steroids. The patient underwent laparoscopic removal of the device and had resolution between 2 and 6 weeks after surgery.

Published abstracts have attempted to address the question as to whether pre-placement patch-test *negative* patients convert their patch-test status after device insertion. In one Dutch study, patch testing was done pre-operatively and 3 months after Essure placement.[102] Only 1 woman (of 97) who was negative at baseline tested positive at 3 months. In another report describing 50 women, there were no conversions from negative at baseline to positive at 3 months and no allergic symptoms were reported.[103]

For Essure recipients who were known to be patch test-*positive* prior to the procedure, one abstract reported a retrospective cohort review of patients at one Spanish site implanted 2003-2010 and noted no documented side effects among 25 such patients.[104]

MDR Reports Related to Allergic/Hypersensitivity Reactions

As noted above, the signs and symptoms which constitute an allergic reaction to an implanted medical device is ill-defined and may vary by author/reporter. This makes the determination of which MDRs reflect a real or potential allergic or hypersensitivity reaction extremely difficult. For this review of MDRs, all reports containing reference to a metal or nickel allergy or hypersensitivity (e.g., patient stating they had an allergic reaction or hypersensitivity reaction), or skin manifestations were included for evaluation – regardless of the specific symptoms the patient noted. For example, many reports described pain, headache, and/or menstrual changes as the symptoms associated with the presumed allergic reaction. With these considerations, a total of 878 MDR reports were coded as allergies/hypersensitivities.

When cited, there was variability in time to onset of symptoms (hours to weeks after insertion), duration of symptoms (weeks, months, years), and whether dermatological manifestations such as rash or pruritis were present. Limited information was provided regarding formal evaluations for the suspected nickel hypersensitivity or how the events were managed clinically and whether they responded to medical therapy. However, 212 of these MDRs describe device removal at least in part due to the presumed allergic reaction. The status of symptoms following removal was provided in 117 of these reports – and all of these noted symptom improvement or resolution. The remaining reports provided no follow-up information related to post-removal symptoms.

Of the 878 MDRs which were coded as allergy/hypersensitivity, 407 (46%) stated that the patient had a history of nickel allergy prior to device placement.

Essure Physician Labeling Related to Allergic Reactions

Warnings

- *The Essure micro-insert includes nickel-titanium alloy, which is generally considered safe. However, in vitro testing has demonstrated that nickel is released from this device. Patients who are allergic to nickel may have an allergic reaction to this device, especially those with a history of metal allergies. In addition, some patients may develop an allergy to nickel if this device is implanted. Typical allergy symptoms reported for this device include rash, pruritus, and hives.*

Essure Patient Labeling Related to Allergic Reactions

- *The Essure insert is made of materials that include a nickel-titanium alloy. Once placed inside the body, small amounts of nickel are released from the inserts. Patients who are allergic to nickel may have an allergic reaction to the inserts. Symptoms include rash, itching, and hives.*

Summary for Allergic/Hypersensitivity Reactions

Although cutaneous nickel allergy is known to be present in a substantial percentage of women, what constitutes an allergic or hypersensitivity reaction to a metallic medical implant and the role of patch testing in predicting or diagnosing such a reaction is not well-defined. The prospective IDE studies supporting approval of the original PMA or PMA Supplement have reported very few specific metal allergy reactions or dermatological events. Few studies in the peer-reviewed literature have addressed this symptom complex, and although they typically cited rates of < 1%, the data was obtained from retrospective reviews at single sites, or was based on MDR numbers divided by kits sold (which has significant limitations as a method to calculate or estimate event rates). A handful of case reports in the medical literature have noted individuals who developed a rash following placement (as early as 3 days), subsequent positive patch test results, and timely resolution of the rash following device removal, all of which are suggestive of a traditional hypersensitivity reaction. Little information is available in the literature related to "conversion" of patch-test status after placement, or the development of symptoms in patients known to be patch-test positive prior to placement. The MDRs received by FDA citing allergic reactions to the device, are numerous, including some noting resolution of symptoms with device removal. However, the limited information provided, and the variety of symptoms reported to represent the reaction make interpretation more difficult.

E. Perforation

Due to the technique and location of placement of the device, it is possible that the Essure insert may penetrate either partially or wholly through the wall of the uterus or fallopian tube during or after insertion. In the latter case, the device may migrate into the intraperitoneal cavity (see "Intra-Peritoneal Migration" below). Multiple factors have been suggested to increase the risk for a difficult or incorrect insert placement, which may in turn lead to perforation. These factors include the following: [78, 79,66, 105,106,107,108,109,110]

- Poor visualization or obscuring of tubal ostia by endometrium, adenomyosis, fibromas
- Tubal spasm
- Anatomic abnormalities including tubal obstruction, stenosis, tortuosity, retroverted uterus
- Uterine or abdomino-pelvic adhesions
- Prior history of STD
- Larger uterine size
- Patient procedural pain/discomfort

Perforation due to the hysteroscope itself is also possible. Furthermore, Essure kits distributed soon after approval included a "support catheter" which may have contributed to early cases of perforation.

It is important to note that perforations may not always be detected or diagnosed. In the Phase II and Pivotal clinical trials, perforations were suspected due to abnormal device position observed on the day of placement procedure via x-ray or during the Essure confirmation test (modified HSG). Perforations were also detected as a result of adverse events, such as pain or abnormal

bleeding, or upon observation in later surgical procedures. Perforations may not be diagnosed if they are not found during placement or confirmation tests and if there are no associated symptoms. Additionally, perforations may not be explicitly reported as adverse events and may only be reported by the symptoms or outcomes resulting from the perforation (e.g., pain or a failed confirmation test).

Perforation is a known risk with use of the device, and, in the complete 5 year report from the Phase II and Pivotal studies, uterine or fallopian tube perforation was reported at rates of 3.1% and 1.1%, respectively.

ESSTVU Study Safety Data Related to Insert Perforation

In the most recent annual report for the ESSTVU study (including data current to June 2015), three events of perforation were described in 2 unique subjects. One subject presented 16 months after device placement with a positive pregnancy test and, upon laparoscopic evaluation, was noted to have bilateral perforation – one uterine, one fallopian. Both devices were left in place during laparoscopic bilateral tubal ligation. The second patient also presented with pregnancy – approximately one year after placement. This patient was diagnosed with a unilateral fallopian tube perforation. The insert was removed at the time of laparoscopic bilateral tubal ligation.

Literature Related to Insert Perforation

A rate of perforation was reported in several articles as presented in Table 20.

Table 20. Rates of Perforation (Literature)

Author	Country	N	Perforations (%)
Aparicio-Rodriguez-Minon[34]	Spain	517	1 uterine (0.2%)
Grosdemouge[41]	France	1061	2 (0.2%)
Gerritse[78]	Netherlands	100	1 (1%)
Langenveld[79]	Netherlands	149	3 (2%)
Legendre[30]	France	311	1 uterine (0.3%)
Levie[31]	U.S.	578	2 uterine* (0.3%)
Panel [42]	France	382	1 (0.3%)**
Povedano[36]	Spain	4306	1 (0.02%)
Sakinci[37]	Turkey	30	1 uterine*** (3.3%)
Sinha[66]	U.K.	112	1 (1%)
Thiel [56]	Canada	610	22 (3.6%)
Veersema[57]	Netherlands	1145	7 (0.6%)

* one during insertion of hysteroscope
**underwent concomitant endometrial ablation
***asymptomatic, identified at HSG

The highest rate, 22/610 (3.6%), was seen in a retrospective medical chart review performed in the Saskatchewan province of Canada. The authors reported that 2/7 proximal, 1/3 distal, and 12/12 uterine perforations were associated with tubal patency on HSG.[56] These rates may be underestimates due to the varying study designs and method of follow-up data collection; in addition, not all perforations may have been discovered or documented (especially in asymptomatic cases).

The systematic review by Adelman, et al., identified 166 cases of perforation, and reported that many cases of perforation were associated with a difficult placement.**Error! Bookmark not defined.** Al-Safi's review of the MDR database through February 2012 noted 90 cases of suspected or confirmed perforation.[63]

Case Reports/Series Related to Insert Perforation

Since Thoma's report in 2006[111], multiple case reports or series describing uterine or tubal perforation during or following Essure placement have appeared in the literature. The timing of the perforation relative to the insertion is often difficult to determine as the reports often describe the time at which the event was *diagnosed* – and this may have been after prolonged periods of time (with or without symptoms). Some note a diagnosis of perforation within days of placement, and others, out to several years afterwards.[36,104,76] Although a difficult insertion procedure is often cited in these cases, multiple reports note perforation in the setting of an uncomplicated procedure.[67,68,112, 69, 75,113] In addition, several reports note that a perforation was diagnosed sometime after a confirmation imaging exam demonstrating proper placement and successful bilateral tubal occlusion.[36,69,75,113] In other words, proper placement at the 3-month confirmation did not preclude subsequent perforation diagnosis.

Patient presentation at diagnosis of perforation varied in the case reports, and in general can be categorized into three types:

- *Abdominal/pelvic pain*
  Several case reports note the presence of abdominal or pelvic pain preceding the diagnosis of uterine or fallopian tube perforation. For some, the pain was persistent following placement and may have lasted months or years before the diagnosis was made.[67,78,79,75,76,81] In others, the pain started after a period where the patient was asymptomatic following placement – sometimes out to one year.[69,70] Although abdominal or pelvic pain was the only (or major) symptom in most of these reports, a few noted patients also presenting with nausea and vomiting.[68,114,85] All of these latter cases involved perforation complicated by insert migration to, or entanglement of, the small bowel with subsequent small bowel obstruction. In one of these cases, the insert perforated through the fundus of the uterus, into and through the wall of the small bowel to the mesenteric aspect, causing small bowel (terminal ileum) perforation.[85] This patient required an ileocecectomy as part of the treatment.

- *Asymptomatic perforation found at confirmatory HSG*

Multiple reports note asymptomatic patients presenting for their confirmatory HSG who were found to have a patent fallopian tube and then, upon further evaluation, diagnosed with perforation[69,72,79,70,110,81,115,116]

- *Pregnancy*
  A handful of reports noted a woman eventually being diagnosed with a perforation after presenting to their physician with an ongoing pregnancy[36,79,113,117] or after a spontaneous miscarriage[118] but without pain.

Most reports were unilateral events, but a few noted bilateral perforation.[67,118,81] Although most described penetration through the organ wall, some noted perforation which remained "subserosal."[79,70] Multiple reports of insert perforation note migration of the insert (or fragments) to the abdominal or pelvic cavity (See below under "Intra-Peritoneal Migration").

MDR Reports Related to Insert Perforation

FDA has received reports related to Essure which describe perforation events including but not limited to reproductive organs. Table 21 below describes the number of reports for each location.

Table 21 – Perforation MDR Reports

Perforation	Voluntary Reports	Manufacturer/User Facility Reports	Total
INTRA-PROCEDURAL PERFORATION			
Uterus	4	12	16
Fallopian Tube	2	10	12
Uterine Horn	0	1	1
Cervix	1	0	1
Unknown	0	3	3
INTRA-PROCEDURAL Totals:	7	26	33
POST-PROCEDURAL PERFORATION			
Fallopian Tube	46	92	138
Uterus	24	40	64
Uterine Horn	0	18	18
Bowel	1	11	12
Amniotic Sac	1	4	5
Other**	1	2	3
Unknown	2	24	26
POST-PROCEDURAL Totals:	75	190	266*

PERFORATION Grand Total:	**82**	**216**	**299***

* 14 reports included two different perforation locations.
** Other included: abdominal cavity, small intestine, ostium, terminal ileum and ovary

As was the case for the reports in the literature, patient presentation varied and subjects may have been diagnosed upon evaluation of abdominal/pelvic pain or a patent tube on HSG – either at the scheduled confirmation test time, or following a pregnancy.

In addition to perforations of the uterus and fallopian tubes, several reports have been received which describe insert perforation involving other organs or structures. FDA has received 5 MDRs in which the reporter alleges that an Essure implant may have been involved in the perforation of the amniotic sac or uterus of a pregnant woman. No additional information supporting the events was provided. Although 5 reports were submitted, it is difficult to determine to what degree the reports overlap. However, all 5 note the preterm death of the fetus.

In addition, 12 MDRs have been received which describe bowel perforation. These include cases where the insert was free within the abdomen (e.g., migrated) or was still within, but perforating through the uterus or fallopian tube. One of these reports notes a "full thickness perforation" through the small bowel wall, requiring an ileo-cecectomy. Two other reports describe the insert ensnaring a loop of small bowel, causing small bowel obstruction in addition to perforation, and the need for an ileo-cecectomy. It is possible that these two latter reports represent the same event reported from 2 sources, and may overlap with the case reports described..

<u>Essure Physician Labeling Related to Insert Perforation</u>

Warnings

- *Do not attempt hysteroscopic Essure insert removal once placed unless 18 or more trailing coils are seen inside the uterine cavity. Attempted removal with less than 18 trailing coils may result in fractured insert, fallopian tube perforation or other injury.*
- *To reduce risk of uterine perforation, terminate procedure if excessive force is required to achieve cervical dilation.*
- *Never attempt to advance Essure insert(s) against excessive resistance. If tubal or uterine perforation occurs or is suspected, discontinue procedure and work-up patient for possible complications related to perforation, including hypervolemia. A false positive HSG and pregnancy have been associated with tubal perforation by insert in the literature; evaluate Essure Confirmation Test for perforation if excessive resistance is experienced during procedure. Only 1.8% (12/682) of clinical trial patients had device related perforations. If necessary, retrieval of perforating inserts requires surgery.*

Precautions

- *Do not advance the Essure system if the patient is experiencing extraordinary pain or discomfort. Terminate the procedure and work-up patient for possible perforation.*

Clinical Trial Description

- *Phase II trial, the following adverse events prevented reliance: Perforation (7/206; 3.4%),*
- *Pivotal trial, the following adverse events prevented reliance: Perforation (5/476; 1.1%);*

Section on Potential Adverse Events Not Observed in Phase II/Pivotal Clinical Studies
The following adverse events were not experienced by Phase II/Pivotal clinical trial participants prior to marketing but are still possible and/or have occurred in the commercial setting:

- *Perforation of internal bodily structures other than the uterus and fallopian tube.*

Essure Patient Labeling Related to Insert Perforation

- *In rare cases, part of an Essure insert may break off. Your doctor may remove the piece or let it leave your body during your period.*
- *In rare cases, part of an Essure insert may puncture the fallopian tube. Surgery may be necessary to repair the puncture.*
- *Your doctor may be unable to place one or both Essure inserts correctly.*

Summary for Device Perforation

The Phase II study of the Essure device noted a uterine/fallopian perforation rate of 3.1% in the full 5 year report. Subsequent prospective IDE studies (Pivotal Trial, ESSTVU) have reported rates of ≤ 1.1%. Most of the peer-reviewed literature which was assessed also cite rates of 1% or less. However, many of those studies were retrospective, single-site experiences, and/or of short-term follow-up (e.g., 3 months). Other, but fewer studies have reported rates of perforation up to 3.6%. Case reports and MDRs have appeared describing perforations of the uterus and/or fallopian tube – some diagnosed at the time of placement, but many others in the post-procedural window, including some beyond confirmation testing with positive bilateral occlusion.. Perforations were typically diagnosed during evaluation of abdominal pain or evaluation in asymptomatic women following an HSG which revealed patent tubes. Because pain is not always indicative of a perforation and because perforations may be asymptomatic, it may be difficult to detect or confirm such an event on clinical grounds alone, and this may in turn impact reporting of the event and calculations of event rates.

F. Intra-Peritoneal Migration

Proximal insert migration or expulsion into the uterine cavity is a well-known event following the Essure procedure – in particular during the first months following placement. However, reports of insert (or insert fragment) migration into the *intra-peritoneal* space (thought to largely occur as a result of perforation) is also possible. In 7 cases of perforation in the Phase II study, 6 devices were reported as "intraperitoneal," meaning that at least a portion of the device was identified to be in the peritoneal cavity.

ESSTVU Study Safety Data Related to Insert Migration

In the ESSTVU study, locations of devices in the two reported perforations were described by investigators during follow up procedures. In one of the two cases, per the investigator, the

insert had "migrated" from the fallopian tube to the pelvis. In the second reported case of perforation, the investigator observed the perforated devices during a laparoscopic sterilization procedure. The investigator described one insert as sticking through the utero-tubal junction, and the other as sitting "in the left ovary." No other instances described as "migration" were reported.

Literature Related to Insert Migration

In our evaluation of published studies or reviews in the medical literature, the occurrence of device migration into the intra-peritoneal space has been described as rare.**Error! Bookmark not defined.** Cases of migration in such are listed in Table 22. Information regarding timing of device migration was not commonly available; however, in many cases, device migration was noted upon confirmation testing and was associated with unintended pregnancy in at least one case.[54]

Table22. Insert Migration – Literature

Article	Country	n	Migrations
Arjona[27]	Spain	1630	3 migrations to the abdominal cavity
Aparicio-Rodriguez-Minon[34]	Spain	517	1 case: migration of both devices into abdomen
Grosdemouge[41]	France	1061	8 migrations (location not specified)*
Panel[42]	France	382	5 migrations: 1 peritoneal cavity, others unspecified
Povedano[36]	Spain	4306	2 asymptomatic migrations into abdomen
Rios-Castillo[54]	Spain	1321	1 (location not specified)*
Thiel[56]	Canada	610	14 proximal or distal migrations noted on HSG*
Gerritse[78]	Netherlands	100	1 migration to the abdominal cavity

*May have included migration within the fallopian tube, or expulsion into the uterine cavity

Case Reports/Series Related to Insert Migration

In addition to cases described as part of clinical studies, several individual case reports describing intra-peritoneal migration have been presented. Like perforations, the timing to the diagnosis has been presented in some of the cases, but the time of the actual migration event cannot be easily assessed. Several migrations were noted in the days/weeks following placement.[112,114,81] These were often noted after evaluation of symptomatic patients (e.g., abdominal pain, nausea, vomiting). Many insert migrations, however, were noted in asymptomatic women during confirmation test imaging which showed patent fallopian tube(s).[115,69,72,116,110]

Although uterine or fallopian tube perforation was documented or presumed to be associated with the device migration, in some cases authors specifically noted that no perforation was present at the time of laparoscopic evaluation and retrieval of the device.[68,116,110] At least one

author suggests the possibility the device may have migrated distally through the fallopian tube into the peritoneal space.[110]

In the case reports, the device or device fragments migrated to the:

- Abdominal cavity[104,63,69]
- Omentum[78,76,110,81]
- Small bowel serosa or mesentery[68,112,115,114,116]
- Large bowel mesentery[112]
- Cul-de-Sac[72]

Several complications or intra-operative observations were reported in association with the migrated device (fragments) including:

- Small bowel obstruction due to insert entanglement or inflammation[68,114]
- Small bowel perforation[114]
- Adhesions[68,112,69,72]
- Local inflammation[68]

In the majority of the reports, the inserts were removed laparoscopically without complications. However, in several, intra-operative fluoroscopy was required to locate the insert or insert fragments.[112,69,76] Some patients required more than one laparoscopy because fluoroscopy was not used in the initial retrieval procedure and unsuspected fragments were unintentionally left behind.[72,76] In addition to insert removal, patients may have undergone concurrent BTL or lysis of adhesions[68,112,72] and, as previously described, one patient required an ileocolectomy for small bowel obstruction and perforation.[114] Some surgeons, however, elected to leave the inserts/fragments in place if the patient was asymptomatic.[115,116]

MDR Reports Related to Insert Migration

FDA has received a total of 227 reports which discuss migration outside the uterus. Table 23 shows the location of migration as noted in those reports.

Table 23 – Migration MDR Reports

Location of Migration	Voluntary Reports	Manufacturer/User Facility Reports	Total
Abdominal cavity/ Peritoneal cavity/Pelvic cavity	21	51	72
Bowel (Colon/Small Intestine)	9	26	35
Fallopian tubes	16	6	22
Omentum	0	10	10
Other	3	1	4

Unknown	57	27	84
Total	**106**	**121**	**227**

Although FDA attempted to delineate reports which involved intra-peritoneal migration from proximal or vaginal expulsion, it is possible that some of the reports noted above, in particular the "unknown" reports represent the latter. In cases where the device migrated to, or around, the small bowel, the patient may have presented with signs or symptoms of bowel perforation and/or bowel obstruction (e.g., abdominal pain, nausea, vomiting, and/or fevers). At least one report noted that a patient required surgical ileocecectomy because of a full thickness perforation of the terminal ileum secondary to the migrated insert. This case may overlap with one of the literature case reports.

In May-June 2013, FDA conducted an inspection that included an evaluation of Conceptus/Bayer's complaint handling and adverse event reporting practices. When any firm receives complaints, the firm is required to investigate each event and make a determination whether the complaint represents an event that is required to be reported to FDA under the medical device reporting regulations (21 CFR Part 803). The firm is then responsible for submitting such reportable events to FDA as medical device reports (MDRs). As part of the inspection process, part of FDA's review focused on 16,047 complaints the firm received on the Essure device between January 2011 and the date of the inspection. From these complaints, the firm identified 183 reportable MDRs and submitted them to FDA. Of these, 22 reports were associated with insert perforations and/or insert expulsions involving the Essure device. In several of these cases, it was reported that the insert was located in the peritoneal cavity. During the inspection, FDA assessed whether the firm's general investigation and MDR reporting practices were compliant with FDA regulations and concluded that, based on available information, the firm's reporting practices were consistent with the FDA's mandatory reporting requirements.

<u>Essure Physician Labeling Related to Insert Migration</u>

Section on Insert Removal

- *The technique for removal of an insert that has perforated the uterus or tube or is within the peritoneal cavity will depend on the location of the insert. Localization should be assessed with imaging prior to the surgical procedure and confirmed intraoperatively. Availability of intraoperative fluoroscopy and/or intraoperative x-ray is recommended to identify the location of the insert or fragments of the insert during surgery.*

<u>Essure Patient Labeling Related to Insert Migration</u>

- *There are reports of the Essure insert migrating into the lower abdomen and pelvis. If this happens, it may be necessary to surgically remove the migrated device.*

<u>Summary for Device Migration</u>

Prospective studies conducted under IDE for the Essure PMA reported 6 cases of perforations that resulted in at least a portion of a device being in the peritoneal cavity. Limited reports of intra-peritoneal device migration have been published – either as part of prospective or retrospective studies, or as individual case reports/series. Although it is presumed that a perforation had occurred prior to migration, not all authors noted evidence of perforation at time of laparoscopic evaluation. Insert migrations were often asymptomatic and detected at follow-up confirmation test imaging, or in some cases, earlier when associated with symptoms related to entanglement or perforation of the small bowel. Most authors elected to remove the migrated components via laparoscopy, although the potential for device fragmentation led some to suggest the importance of intra-operative fluoroscopy to ascertain that all components had been retrieved. Other clinicians elected to not retrieve the device if the patient was asymptomatic. Information within MDR reports received is consistent with the reports noted in the literature.

G. Pregnancy-Related Safety Outcomes

Ectopic Pregnancy

An ectopic pregnancy occurs when a fertilized egg implants outside the uterine cavity. Women with a history of damage to fallopian tubes from PID, previous tubal surgery, and/or previous ectopic pregnancy are at increased risk for ectopic pregnancy.[119] Without treatment, an ectopic pregnancy can lead to a ruptured fallopian tube, which can result in life-threatening bleeding for the mother. No pregnancies, including ectopic pregnancies, were reported in the original PMA studies.

ESSTVU StudySafety Data Related to Ectopic Pregnancy
In the ESSTVU study, no ectopic pregnancies have been reported.

Literature Related to Ectopic Pregnancy

Our review of the medical literature revealed little in the way of clinical studies reporting on rates of ectopic pregnancy following Essure. Of 61 pregnancy-related adverse events noted in Al-Safi's review of the MDR database through 2012, 29 ectopic pregnancies were noted.[63]

Malacova, et al., recently published a population-based retrospective cohort based on extraction of data related to all women aged 18-44 undergoing tubal sterilization between 1990 and 2010 from hospital records in Western Australia.[120] The set of 44,829 women included 278 who had undergone hysteroscopic sterilization with Essure. No ectopic pregnancies were reported in this group.

Case Reports/Series Related to Ectopic Pregnancy

In 2011, Bjornsson reported a patient who presented with acute abdominal pain, nausea, and dizziness – approximately 2-3 years after Essure placement (with documented bilateral occlusion on 3-month HSG).[121] The patient was found to be in hypovolemic shock, with a positive urine pregnancy test, and free fluid in the abdomen by ultrasound. She underwent an emergency

laparotomy, and an ectopic pregnancy in the left fallopian tube was identified – even though both Essure inserts appeared to be in proper location.

In 2013, Huguelet reported on a woman who presented with acute pelvic pain and positive pregnancy test 4 years after her Essure procedure despite having bilateral tubal occlusion documented at 3 month HSG.[122] An ultrasound showed a questionable 3.3-cm left adnexal mass and the patient underwent laparoscopy where no adnexal/tubal pathology was found, but the left insert was seen perforating the uterus. Post-laparoscopy, the patient continued to have rising hCG levels and was treated with methotrexate for a presumed ectopic pregnancy of unknown location.

MDR Reports Related to Ectopic Pregnancy

Of the 337 MDR reports FDA has received for Essure related to pregnancy, 69 involved ectopic pregnancy (including one MDR reporting a woman who experienced two ectopic pregnancies).

Product Physician Labeling Related to Ectopic Pregnancy

- *Pregnancies (including ectopic pregnancies) have been reported among women with inserts in place.*
- *Section on Potential Adverse Events Not Observed in Phase II/Pivotal Clinical Studies The following adverse events were not experienced by Phase II/Pivotal clinical trial participants prior to marketing but are still possible and/or have occurred in the commercial setting:*
- *Pregnancy and ectopic pregnancy in women relying on Essure inserts.*

Product Patient Labeling Related to Ectopic Pregnancy

- *Women who have the Essure procedure are more likely to have an ectopic pregnancy if they get pregnant. Ectopic pregnancy is when the pregnancy occurs outside of the uterus. The pregnancy usually happens in one of the fallopian tubes. Ectopic pregnancies can be very serious or life- threatening.*

Premature Rupture of Fetal Membranes (PROM) /Fetal Death

When premature rupture of membranes (PROM) occurs prior to the 37th week of pregnancy, it is referred to as preterm premature rupture of membranes (PPROM). PPROM may lead to significant perinatal morbidity, including respiratory distress syndrome, infections/sepsis, placental abruption, and fetal death. Although not seen in the premarket PMA trials or the ESSTVU Study, one potential concern for women who become pregnant following Essure placement is the possibility for the trailing coils within the uterus to interfere with the pregnancy.

Literature Related to PROM

The potential risk of a trailing coil of the Essure insert leading to preterm premature membrane rupture has been discussed in the literature.[123] Live full term birth outcomes have been reported

in women seeking pregnancy via assisted reproductive technology who underwent the Essure procedure in order to isolate the uterine cavity from hydrosalpinx fluid prior to embryo transfer.[124]

Veerseema reported on 50 intended and unintended pregnancies which occurred after unilateral or bilateral Essure insertion.[125] This included 2 reports of stillbirth in one IVF patient: one singleton pregnancy at 19 weeks of gestation due to premature rupture of membranes, and then later, one twin pregnancy at 18 weeks of gestation due to premature rupture of membranes with evidence of chorioamnionitis. The second pregnancy and stillbirth occurred after the hysteroscopic removal of the Essure inserts. The authors stated that "the cause of both fetal losses was not likely related to the presence of micro-inserts." There was one additional case of premature rupture of membranes at 37 weeks gestation, resulting in vaginal delivery of a healthy infant. Two additional studies which reported on IVF results noted cases of PROM.[124,126] Both cases resulted in a healthy infant.

MDR Reports Related to PROM

As noted above ("Perforations") FDA has received 5 MDR reports describing pre-term death of a fetus for which the reporter felt that the presence of the Essure insert may have contributed to the perforation of the amniotic sac or uterus.

Summary for Adverse Outcomes of Pregnancy

No cases of ectopic pregnancy or premature rupture of membranes were reported in the IDE studies used to support PMA or PMA Supplement approval. Within the literature, limited reports exist describing ectopic pregnancy or PROM in women with unintended or intended pregnancies following Essure placement. However, FDA has received 69 MDRs describing cases of ectopic pregnancy. In addition, 5 reports related to PROM (all resulting in fetal death) have been submitted in which the reporter suggests the Essure device may have contributed to the event. The limited data for these latter reports make it difficult to assess causality.

VIII. Reports of Death

During the IDE studies that supported approval of the original PMA or PMA Supplement, no deaths were reported. In the post-approval follow up in these studies, two deaths were noted. One death, secondary to leukemia, occurred in a woman from the Pivotal study during the 5 year follow up. The other death was a woman in the ESSTVU study that occurred during the post approval follow up period. This second patient died of a myocardial infarction following coronary artery bypass surgery. Both events were classified as unrelated to the device.

Prior to June 1, 2015, FDA has received 11 MDRs which were coded as involving a patient "death" and which note such an event. The 11 reports represent 9 unique events, as duplicate reporting occurred. It is crucial to remember that the coding of a report as a death does not necessarily prove the causality between the device and the event. In many cases it is difficult to come to that conclusion based on the information available. Of the 11 reports, 5 describe fetal

death (discussed above, Perforation). The remaining 6 reports describe 4 unique events including the following:

- A 30 year old woman with Group A Streptococcal infection 2 days following placement.
- A 31 year old woman experiencing cardiopulmonary arrest during insertion. Autopsy revealed probable paradoxical air embolism with a patent foramen ovale. (Two reports received for one event)
- A woman who died 13 days after undergoing a hysterectomy to remove the Essure implants. This was suspected to have resulted from a pulmonary embolism. (Two reports received for one event)
- One woman who committed suicide (No additional information provided)

IX. Essure Insert Removal

Essure is intended to be a permanently implanted device. However, removal of devices did occur in the follow-up of the original clinical trials. Twelve of 206 (5.8%) women had devices removed in the Phase II trial and 20/476 (4.2%) of women had devices removed in the Pivotal trial. As noted in previous sections, several publications, case reports/series, and numerous MDRs describe patients seeking and having surgery for implant removal. Reasons for seeking removal have included:

- Identification of an incorrectly placed or perforated insert
- Displaced/migrated implant
- Persistent pain
- Persistent menstrual symptoms
- Presumed allergic reaction

<u>ESSTVU Study Safety Data Related to Insert Removal</u>

In the ESSTVU study, information on device removals was obtained based upon the association with adverse events. To date, with 2-3 years of follow-up, 11 of the subjects enrolled in the ESSTVU Study (1.8%) have undergone device removal associated with adverse events. Reasons for removal included:

- Abdominal or pelvic pain or cramping (8)
- Intermenstrual bleeding (1)
- Fibroids (1)
- Worsening endometriosis (1)

The majority of device removals (64%, 7/11) was performed via laparoscopic salpingectomy and was performed for symptoms related to pain. Five involved bilateral insert removal, and 2, unilateral. Four other removals (36%) were accomplished via hysterectomy with bilateral salpingectomy.

In terms of symptom status following device removal, 8 of the 11 subjects reported resolution of the symptoms. The one patient with fibroids continued to have symptoms despite hysterectomy and the status of two patients who reported pain as the indication for removal are unknown as the patients both exited the study.

Literature on Insert Removal

Chudnoff's publication of the 5-year follow-up for the Pivotal IDE cohort (described above) noted 15 hysterectomies (of 397 evaluable patients) to remove the devices, including two which the investigators felt were possibly due to the Essure implants. Arjona-Berral reported that 7/4274 (0.16%) patients presented with chronic pelvic pain requiring device removal by hysteroscopy in two cases and by laparoscopy in five cases.[65] Zurawin & Zurawin reported eleven cases of device removal noted in adverse event reports submitted to FDA.[89] Two additional articles describing cohort studies, noted a few cases of device removal before confirmation testing due to post-procedural pain: 1 removal (laparoscopically) out of 638 patients in one study, and no rate given for the second study of 458 patients (did not report how devices were removed).[64,39]

Case Reports/Series on Insert Removal

Several case reports have been published noting successful and uncomplicated hysteroscopic insert removal out to 55 months.[28,118,74,127,128] More case reports and series describe laparoscopic surgical removal via salpingotomy or salpingectomy and in some cases, hysterectomy years following placement.[72,73,128,84,129] At least one author found that the ease of removal was not influenced by the duration implants were in place.[84]

In the case of removal of inserts that had migrated into the intra-abdominal space, several authors have suggested the use of intra-operative fluoroscopy to assist in the location of the implant, particularly in cases in which the coil is suspected to have fragmented and be in multiple pieces.[112,76]

As noted in sections above, the removal of the implants may or may not have completely resolved the symptoms which were suspected to be associated with the presence of the device.[67,71,74,84]

MDR Reports on Insert Removal

As noted previously, multiple MDRs describe women who sought removal of their devices for one or more symptoms or events. FDA reviewed 1202 Essure reports which included any of the following terms: "hysterect", "salpingec", "laparo", or "remov". Of these, 452 describe device removal including 265 being performed by hysterectomy. The majority of the hysterectomy removals were related to device removal due to perforation and migration issues. The device removals related to allergy/hypersensitivity symptoms were nearly evenly split between hysterectomy and non-hysterectomy removal.

Less than half of the 452 device removal reports provide further information related to symptom outcomes following surgery. Of those that do provide that information, 176 reports state that the symptoms originally attributed to the Essure device either resolved or significantly improved following device removal. Many noted improvements soon after surgery. A given report describing such resolution may have mentioned several improved signs/symptoms including: abdominal/pelvic pain, back pain, joint pain, headaches, rash, hair loss, fatigue, weight gain/loss,

dyspareunia, irregular menstrual bleeding, nausea, mood swings/ irritability, edema, visual changes, and more. Conversely, 20 of the 452 reports specifically noted that the woman's symptoms did not improve or resolve following the hysterectomy. All of these women still reported pain after the device removal with a few reporting the continuation of other symptoms such as fatigue, weight gain/loss, and headaches.

In addition to the 452 reports describing device removal, many additional reports cited women who were already scheduled for, or actively seeking, removal surgery.

Essure Physician Labeling on Removal*

Warnings

- *Do not attempt hysteroscopic Essure insert removal once placed unless 18 or more trailing coils are seen inside the uterine cavity. Attempted removal with less than 18 trailing coils may result in fractured insert, fallopian tube perforation or other injury.*
- *Effects, including risks, of Essure inserts on in vitro fertilization (IVF) have not been evaluated. Risks to the patient, fetus and continuation of pregnancy are unknown.*
- *The Essure procedure should be considered irreversible. Safety or effectiveness of reversal surgery is unknown.*

Section on Insert Removal

- *WARNING: Essure inserts are intended to be left in place permanently. Do not remove insert(s) unless patient is experiencing an adverse event(s) associated with its presence, or if removal is demanded. If insert removal is indicated, patient should be counseled on unknown risks as techniques for insert removal post-placement have not been evaluated in clinical studies.*

  For all surgical device removal procedures, care should be taken to avoid transecting the insert during removal. Avoid use of any instrument that is likely to result in fragmentation of the insert. Application of electrocautery to the outer coil should be avoided. During removal, grasping both the inner and outer coils together may help prevent excessive stretching of the outer coil, which could result in fragmentation.

  Location of Essure inserts should be confirmed through imaging prior to any attempted surgical removal.

  Limited case reports describe hysteroscopic insert removal up to seven weeks following placement. In these cases the proximal coils were visible within the uterine cavity and were easily removed with gentle traction. When hysteroscopic removal is not feasible, linear salpingotomy or salpingectomy via laparoscopy or laparotomy can be used to remove an insert within the tube. In some cases, a cornual resection of the proximal fallopian tube may be required for insert removal. In these cases, patients should be counseled about the risk of hysterectomy in order to achieve hemostasis.

1. *To perform a linear salpingotomy, make a small incision (approximately 2 cm in length) along the antimesenteric border of the fallopian tube overlying the insert. Use of vasoconstrictive agents is at the discretion of the operating surgeon. The insert needs to be exposed and may need to be freed from the surrounding tissue prior to grasping the coils. Once the insert is exposed, a grasping instrument may be used to extract the insert using gentle traction. Removal may be along with, or independent of, an incisional sterilization procedure.*

2. *When removing insert via salpingectomy, the location of the proximal and distal portions of the insert within the fallopian tube should be reconfirmed intraoperatively by palpation and/or imaging prior to transecting the tube. The insert may be exposed and visualized via salpingotomy prior to transection or removal of the fallopian tube.*

3. *The technique for removal of an insert that has perforated the uterus or tube or is within the peritoneal cavity will depend on the location of the insert. Localization should be assessed with imaging prior to the surgical procedure and confirmed intraoperatively. Availability of intraoperative fluoroscopy and/or intraoperative x-ray is recommended to identify the location of the insert or fragments of the insert during surgery.*

*Note: Labeling provided here reflects major changes to the labeling that were approved in June 2015, via Supplement 41.

<u>Essure Patient Labeling on Removal</u>

- *Is Essure reversible? No, the Essure procedure is not reversible. Like having your tubes tied or a vasectomy for men, Essure is permanent birth control. You need to be sure you are done having children before you decide to have the Essure procedure.*
- *The safety and effectiveness of reversing the Essure procedure are not known*
- *The safety and effectiveness of in vitro fertilization after the Essure procedure are not known*
- *The risks to you and your fetus if you get pregnant after the Essure procedure are not known*

<u>Summary for Insert Removal</u>

Complete 5-year follow-up of patients in the Phase II and Pivotal study has reported that 5.8% of women had devices removed in the Phase II trial and 4.2% of women had devices removed in the Pivotal trial. In addition, recent data on the ESSTVU study demonstrate device removal in approximately 2% of subjects. In this study, the most common reasons for undergoing device removal were abdominal/pelvic pain or abnormal bleeding. Limited data are available from peer-reviewed studies, although several case reports have been published citing hysteroscopic or laparoscopic removal or hysterectomy out to several years past insertion to remove the device for a variety of symptoms, and/or for a migrated device. Many MDRs received by FDA describe

women who were seeking or scheduling a hysterectomy to remove the device, or women who had already had the devices removed – many by hysterectomy. For those women who underwent device removal, and for whom symptom status was provided, the majority noted improvement or resolution of their symptoms after the hysterectomy. Several case reports and data from the ESSTVU study also note improvement in symptoms following removal.

X. Social Media

The Food and Drug Administration has been exploring various tools for "social listening" as a means to expand our ability to identify and refine new safety signals. Among those efforts was a pilot program with Epidemico, Inc's MedWatcher Social program which is intended to review public posts on several popular patient and consumer web sites including Twitter, Facebook, and select patient forums. The program uses a Bayesian classifier which identifies "posts with resemblance to adverse events" or "Proto-AEs" based on a probability score. The internal classifier has been trained with over 350,000 manually coded posts and an internal dictionary is able to translate vernacular to MedDRA terms.

The Agency recognizes that these types of social listening tools are still evolving, and the data they provide has important limitations that may significantly impact the ability to interpret the inforation. These limitations include but are not limited to the potential for patients to incorrectly assign symptom causality to the device and the potential for large volumes of posts which may be duplicative or include "false positives." Despite these known limitations, within the pilot evaluation, early data on Essure was collected from postings between September 2013 and July 2015. Of the approximately 350,000 mentions of Essure, the software identified 20,000+ posts which it classified as containing Proto-AEs. The vast majority of these Proto-AEs were from Twitter posts. Keeping in mind that this is preliminary data (e.g., false positives not yet removed, reports not unduplicated, retweets not consolidated), the top Proto-AEs for Essure posts were as follows:

- Pain
- Hysterectomy
- Malaise
- Pregnancy
- Medical device removal
- Device dislocation
- Pelvic pain
- Surgery
- Abdominal distension
- Hemorrhage
- Allergy to metals

Although raw information, these are consistent with the types of events or complaints received by FDA through the MDR reporting process.

XI. Outside-the-US (OUS) Post-market Experience

During its review of post-market information related to Essure, FDA contacted several of its larger global regulatory counterparts where the Essure device has been approved/marketed for more than 10 years. The types of adverse events and safety outcomes reported to those bodies have also been reported within the United States. No new issues were being reported abroad that were not included in the information provided above. However, the number of reports received yearly by our foreign colleagues through their adverse event reporting processes has been significantly less. On average, the OUS regulatory organizations were receiving fewer than 20-30 reports per year regarding Essure.

XII. Summary

The Essure device has been approved for marketing within the United States (and many other nations) for over 10 years. Two prospective clinical trials were performed by the sponsor, and reviewed by FDA and its Obstetrics and Gynecology Devices Advisory Panel in support of the approval decision in 2002.

Over the past 2 years, FDA has seen a dramatic increase in the number of adverse events submitted in relation to the Essure device. The majority of these reports have come from women implanted with the device.

FDA has recently conducted a review of effectiveness and safety performance data from several sources as related to the Essure device. As part of the preparation for this panel meeting, FDA has summarized that post-market data and information – focusing largely on specific commonly reported safety issues and concerns raised by portions of the patient community.

FDA has provided information in this memo related to Essure safety and effectiveness from several different sources, including studies done under IDE as well as studies within the peer-reviewed literature. The IDE studies were prospective, multi-center studies, each conducted with several hundred subjects and performed in line with FDA regulations. Two of those studies followed patients out to 5 years, and the third has provided data out to 2-3 years and is still ongoing. These studies did/do not have a control arm which limits interpretation of some of the outcomes of interest, and data was not available on all subjects at the 5-year point for two of the studies. Peer-reviewed literature was reviewed and numerous publications related to the effectiveness of the device were included. Fewer publications specifically addressed many of the adverse outcomes selected for discussion. Although relatively low rates were reported in many of these publications, significant limitations must be taken into account when reviewing the data, including a large amount of data being generated from retrospective studies (chart reviews, physician or patient surveys or phone interviews, etc.), single-arm cohort studies, studies from single institutions, separate studies from the same institutions reporting on patient populations with significant overlap, studies with limited follow-up (e.g., 3 months), studies with notable loss to follow-up, and/or reviews using MDR data to estimate rates.

FDA also attempted to summarize information from case reports – both from the medical literature (including abstracts and posters) as well as MDRs received into our MAUDE database. Limitations to the literature case reports and abstracts are similar to those described for the peer-reviewed literature. As noted, most of the MDRs received by FDA have been voluntary reports from patients themselves, and many of the reports describe numerous symptoms or side effects following device placment. A number of these events have not previously been presumed to be associated with the device and which, if true, may call in to question a "systemic" process. MDRs are a valuable source of information to FDA, but in general, can also have limitations including under-reporting, and biased or incomplete/unverified reporting. In addition, MDR data alone cannot be used to establish rates of events, or confirm whether a device actually caused (or worsened) a specific event. Because rates of events cannot be determined by MDR data, it is not possible to determine whether the numbers of reports represent a true increase in rates of particular known or expected events, or rather represents an increase in the reporting of adverse events or increase in the number of devices in clinical use.

The Committee will be asked to review this data, along with other information provided by the device manufacturer and members of the clinical and patient communities at the day of the panel meeting. The Committee will be asked to provide input and recommendations regarding the benefit-risk profile of the device, specific safety issues, and potential mitigating actions, if any, which should be considered by the FDA and public.

Appendix A. Device placement, physician learning curve, and patient compliance; post-market information

The effectiveness of the Essure system depends on successful bilateral insert placement and patient compliance with the confirmation testing requirement. If the devices are not correctly placed, a woman may not rely on the device for contraception. Successful placement is dependent on a variety of factors, including but not limited to device design (e.g., catheter), physician training and experience, and patient anatomy. In the Phase II and Pivotal Trials, which supported the original approval of the Essure System, rates of bilateral placement, and the reliance rates were measured. In the post-market, there have been numerous additional studies of bilateral placement rates, physician learning curve for successful placement, and patient compliance with confirmation testing requirements.

Successful Device Placement

Since the original approval, the sponsor has made changes to the catheter to facilitate placement, although data on Essure placement rates have generally demonstrated a high rate of bilateral placement. In the initial premarket study, successful bilateral placement rates were reported to be ~86-90%. In subsequent post-approval studies, higher bilateral placement rates were reported (>95%), and since approval of the Essure system, there has been consistently high bilateral placement rates (80-100%) reported in the literature. Subsequent post-approval studies showed higher rates.

The second PAS, ordered at the time of original PMA approval, evaluated the bilateral placement rate at first attempt for *newly* trained physicians in the U.S., and evaluated factors predictive of bilateral placement failure. The target sample size was 40 physicians and 800 women, per protocol. In 2005, after reviewing data in a PAS report, FDA considered this condition of approval to be satisfied, with 514 women enrolled in the study. The sponsor used Bayesian statistics to demonstrate that enrolling additional women would not change the observed results for the main study endpoint. There were 476 women in whom bilateral placement was possible and bilateral placement was achieved in 458 women, for 96.2% success rate. Placement rates did not change by calendar time, place where procedure was performed, device configuration, hysteroscope shape, or patient characteristics (age, body mass index, education level, income, and race). There were 13 adverse events that included perforation (2 cases, one secondary to hysteroscope), pelvic pain, bleeding, light headed, increased blood pressure and temporary decreased pulse. The device labeling was updated based on the results of this PAS.

In addition, FDA approved a PMA supplement for the model ESS305 design in 2007. A PAS was ordered at that time to evaluate if design changes and material modifications affected the bilateral placement rate. This PAS was an observational cohort study with 76 sites in the US that enrolled 584 women. The new model had a bilateral placement rate of 97.2%, excluding placement non-attempts.

Literature

Essure placement rates from studies included in our literature review are summarized in Tables 24 and 25. Placement was generally assessed at the time of the procedure by the number of coils trailing into the uterine cavity. It was commonly reported that more than one attempt was sometimes needed to successfully place the inserts. The most common reasons reported for unsuccessful Essure placement were poor visualization of the tubal ostia, tubal stenosis, tubal spasm, previous tubal occlusion, anatomical irregularities, and patient discomfort during the procedure.

A number of studies investigated potential factors that could be associated with Essure placement success or failure, such as patient age, body mass index, parity, history of sexually transmitted infection, or procedure setting;[39,130,32,131] however, no patient characteristic emerged as a definitive risk factor for placement failure. One group of authors from Spain reported that use of the oral contraceptive desogestrel before Essure placement was associated with decreased endometrial thickness and subsequently, better visualization of the ostia and higher placement rates; however, the sample size was not large enough (16 women in each group), and the physician was not blinded to treatment group.[134] Methods to improve success rates included placement during the follicular phase of the menstrual cycle (i.e., before ovulation) to improve visualization of the tubal ostia,**Error! Bookmark not defined.** and premedication with nonsteroidal anti-inflammatory drugs (NSAIDs).[106]

Table 24. Successful placement rates in articles with no three month follow-up data.

Article	Country	Successful bilateral placement		Reasons for unsuccessful placement
		First Attempt	Second Attempt	
Chapa, 2015[132]	U.S.	43/45 (95.6%)	3/4 (75%)	Suspected tubal spasm
Chudnoff, 2010[133]	U.S.	74/80 (92.5%)	n/a	Not Reported
Haimovich, 2013[134]	Spain	28/34 (82.4%)	n/a	Visualization of ostia (n=4) Menstruation (n=2)
Isley, 2012[135]	U.S.	54/58 (93.1%)	n/a	Visualization of ostia (n=2) Coil could not advance into one tube (n=1) Patient unable to tolerate (n=1)
Leyser-Whalen, 2012[131]	U.S.	292/324 (90.1%)	n/a	Tubal stenosis or spasm (n=18) Visualization of ostia (n=9) Cervical stenosis (n=3) Severe uterine prolapse (n=1)
Panel, 2010[106]	France	440/492 (89.4%)	13/15 (86.7%)	Visualization, tubal stenosis, or spasm (n=23) Salpingectomy or tubal occlusion (n=23) Previous tubal occlusion (n=2) No additional information given (n=4)
Thiel, 2011[136]	Canada	84/85 (98.8%)	n/a	Not Reported

Table 25. Successful placement rates in studies with ≥ 3 months of follow-up.

Article	Country	Successful placement[a]
Anderson, 2013[39]	U.S.	95.5%
Aparicio-Rodriguez-Minon, 2015[34]	Spain	517/534 (96.8%)
Garcia-Lavandeira, 2014[137]	Spain	55/61 (90.2%)
Gauchotte, 2011[138]	France	88/94 (94%)
Grosdemouge, 2009[41]	France	992/1051 (94.4%) first attempt
Howard, 2013[139]	U.S.	131/136 (96.3%)
Legendre, 2010[140]	France	73/78 devices (93.6%)
Legendre, 2011[30]	France	293/311 (94.2%)
Pachy, 2009[141]	France	22/25 (88%)
Paladini, 2015[142]	Italy	27/27 (100%)
Panel, 2011[42]	France	321/341 (94.1%)
Povedano, 2012[36]	Spain	4075/4306 (94.6%)
Rajecki, 2014[43]	Finland	103/120 (85.8%)
Rios-Castillo, 2013[54]	Spain	1166/1200 (97.2%)
Sakinci, 2015[37]	Turkey	24/32 (75%)
Savage, 2009[32]	U.S.	850/884 (96.2%)
Tatalovich, 2010[143]	U.S.	48/48 (100%)
Thiel, 2014[144]	Canada	30/30 (100%)
Veersema, 2011[57]	Netherlands	1034/1145 (90.3%)

* NR=Not reported.
[a] Overall placement rates including placements that required multiple attempts

Essure Physician Labeling Regarding Insert Placement

Clinical Trial Results Section

Insert Placement Rate at first attempt in the Commercial Setting Using the Essure System ESS305

Placement Status	ESS305 Post Approval Study	
	Number	Percent
Bilateral Placement*:	593/612	96.9%
Intent-to-Treat Bilateral Placement**:	593/619	95.8%
Unilateral Placement or No devices placed***:	26/619	4.2%

*Bilateral placement rate excludes seven patients in whom insert placement was not attempted.

** Intent-to-treat bilateral placement rate includes all participants who underwent hysteroscopy regardless of whether insert placement was attempted.

*** Unilateral placement occurred in 10 participants; 6 participants had no placement in either fallopian tube; insert placement was not attempted in 7 participants. Tubal obstruction and visualization problems due to uterine anatomy were the most common reasons for placement failure.

Physician Learning Curve

Literature Regarding Physician Learning Curve

In our current literature review, 3 articles reported on the physician learning curve for the placement of Essure.[130,145,146] A Dutch study that collected data from 631 procedures performed by 15 gynecologists inexperienced with the Essure procedure found that increasing experience was significantly associated with decreasing procedure time through the physician's 15th procedure; however, experience was not associated with placement success, pain scores, or complication rates. Successful bilateral placement (confirmed by TVU or x-ray) was achieved in 480/631 (76.1%) patients at first attempt, and the overall rate of sterilization success was 537/631 (89.5%). The authors reported 40 complications such as vasovagal collapse and nausea/vomiting, but no cases of perforation, migration, or expulsion.[145]

A French study classified 498 surgeons into four groups according to experience with hysteroscopy. At the surgeons' first Essure placement, failure rates ranged from 4.7% for the most experienced group to 16.3% for the least experienced group of surgeons. The presence of an instructor from Conceptus (previous manufacturer of Essure) during the procedure was associated with faster improvement during the surgeons' second and third placements. Overall the placement success rate (bilateral and unilateral) was 1054/1144 (92.1%). Complication rates were not reported.[146]

Levie & Chudnoff published the results of the "Newly Trained Physicians" post-approval study. The group of 39 experienced physicians had each performed ≥25 Essure placements, while 37 newly trained physicians had each performed 3-5 proctored placements. The successful placement rate (bilateral and unilateral) was 339/346 (98%) vs. 223/232 (96.1%) for experienced versus newly trained physicians ($p>.05$); procedural time was 7.9 minutes versus 10.7 minutes, respectively ($p<.01$). Six subjects experienced adverse events, including two cases of uterine perforation (one at the time of cervical dilation, and one during hysteroscope insertion); it was not reported whether these procedures were performed by newly trained or experienced physicians.[130]

Patient Compliance with Confirmation Test

As described previously, although surgical tubal ligation may be considered effective immediately, due to the mechanism of action of the Essure device, a period of time is required to ensure that the fallopian tubes are occluded. A woman must have a successful "confirmation test" before she can stop alternative birth control and rely on the Essure device. As noted above, failure to comply with this confirmation testing has been cited as a factor in a significant percentage of reported unintended pregnancies. As such, adherence to this step is crucial to the device's effectiveness.

Literature on Confirmation Test Compliance

FDA's literature review showed that patient compliance rates with the confirmation testing ranged from 28.8% to 100% (Table 26). Health insurance coverage was an important factor in

patient compliance; in multiple studies, privately insured women were more likely to be compliant with HSG confirmation testing than women with public insurance or no insurance. Only 53% of women were compliant with HSG testing in one study of mostly publicly insured women from Kansas City, Missouri.[139] Another study with a very low compliance rate (28.8%) reported that insurance issues were the most frequently reported reason for noncompliance in their urban-based clinic population in Detroit, Michigan.[147] Comparatively, a sample of 884 women in the Kaiser Permanente Northern California healthcare system had a compliance rate of 86.5%, and more than a third of those lost to follow-up were no longer Kaiser Permanent Northern California members at the end of the study period.[32] In a study conducted at Vanderbilt University Medical Center, patients were 2.05 times more likely (95% CI: 1.22, 3.43) to undergo HSG testing if they had private insurance compared with Medicaid insurance.[39]

Two articles reported on methods implemented in order to increase patient compliance. Mahmud, et al., reported an increase in compliance from 68.6% to 78.4% using an electronic reminder for staff.[148] Guiahi, et al., reported an increase in compliance from 71.1% to 87.3% after hiring a dedicated staff nurse to schedule HSG appointments and track compliance.[149]

Outside the U.S., it is general practice to use pelvic x-ray or TVU to assess device placement, rather than tubal occlusion. Multiple authors recommend ultrasound as the first line of confirmation testing, followed by the modified HSG, when indicated by an inconclusive result.[56,137,142] In a large Dutch prospective cohort, three-month TVU results were satisfactory for 892/944 women (94.5%); of the 52 unsatisfactory results, subsequent HSG confirmed bilateral occlusion in 50 cases. However, the authors noted that two of four observed pregnancies were possibly due to misinterpreted TVU results that appeared satisfactory (no HSG performed).[57] Similarly, a retrospective Canadian study reported that 524/610 (85.9%) women had satisfactory TVU results and 86/610 women underwent HSG due to inconclusive or abnormal TVU results. There were two pregnancies during six years of follow-up, both due to non-compliance.[56] In two articles, there was a case where TVU or x-ray showed correct placement of the devices, but HSG showed that one or both tubes remain patent.[45,46]

Table 26. Confirmation test compliance data

Author	Country	n	Confirmation Compliance	Successful Completion of Confirmation Test[b]
Anderson, 2013[39]	U.S.	638	58.7%	88%
Aparicio-Rodriguez-Minon, 2015[34]	Spain	517	476/517 (92.1%)	X-ray/US: 467/476 (98.1%) HSG: 67/76 (88.2%)
Connor, 2011[40]	U.S.	118	101/118 (86%)	Contrast infusion sonography: 53/57 (93%)
Franchini, 2011[51]	Italy	45	NR	45/45
Garcia-Lavandeira, 2014[137]	Spain	61	55/55 (100%)	Ultrasound: 43/55
Gauchotte, 2011[138]	France	94	58/94 (62%)	X-ray/US: 53/58 (91%)
Grosdemouge, 2009[41]	France	1061	1014/1015 (99.9%)	X-ray: 982/1014 (97%)
Guiahi, 2010[149]	U.S.	228	78% before intervention (hiring staff to schedule) 90.9% after intervention	123/173 (71.1%) before and 48/55 (87.3%) after
Howard, 2013[139]	U.S.	132	70/132 (53.0%)	61/70 (87.1%)
Lazarus, 2012[35]	U.S.	235	NR	218/240 (90.8%)
Legendre, 2010[140]	France	40	39/40	61/64 devices
Legendre, 2011[30]	France	311	257/305 (84.3%)	US: 195/227 (85.9%)
Leyser-Whalen, 2013[150]	U.S.	286	243/286 (85.0%)	NR
Mahmud, 2015[148]	U.S.	211	68.6% before eReminder 78.4% after	NR
Pachy, 2009[141]	France	25	24/25 (96%)	US: 21/21
Paladini, 2015[142]	Italy	27	27/27 (100%)	US: 35/51 devices HSG: 50/51 devices
Panel, 2011[42]	France	382	317/341 (93.0%)	NR
Povedano, 2012[36]	Spain	4306	4108/4242 (96.8%)	X-ray (plus [137,142]TVU or HSG when indicated): 4095/4108 (99.7%)
Rajecki, 2014[43]	Finland	120	NR	X-ray or US: 85.8%
Rodriguez, 2013[44]	U.S.	229	229/281 (81.4%)	221/229 (96.5%)
Sakinci, 2015[37]	Turkey	32	30/30 (100%)	30/30 (100%)

Author	Country	n	Confirmation Compliance	Successful Completion of Confirmation Test[b]
Savage, 2009[32]	U.S.	884	739/854 (86.5%)	687/739 (93.0%)
Shah, 2011[45]	U.K.	18	18/18 (100%)	17/18 (94.4%)
Shavell, 2010[147]	U.S.	14	21/73 (28.8%)	NR
Tatalovich, 2010[143]	U.S.	48	38/48	37/38
Thiel, 2011[56]	Canada	610	NR	US: 524/610 (85.9%) HSG: 85/86
Thiel, 2014[144]	Canada	30	30/30 (100%)	30/30 (100%)
Veersema, 2010[46]	Netherlands	47		X-ray: 44/47
Veersema, 2011[57]	Netherlands	1145	1051/1072 (98%)	TVU: 892/944 (64.5%) HSG: 150/164 (91.5%)

*NR=Not reported

.[a]Confirmation test used was HSG unless otherwise noted. US=Ultrasound.

MDR Reports Related to Confirmation Testing

As noted previously, FDA has received 337 MDRs which cite unintended pregnancy following Essure placement. A large number of those MDRs (175) did not provide any information related to whether the confirmation test was performed, when, and/or what the results were. Of the remaining reports, 131 specified that the HSG test had been completed, 4 noted that a TVU was done, and 27 specifically stated that no confirmation testing had been completed.

Essure Physician Labeling Regarding Patient Non-Compliance

Warnings

- *Physicians performing the Essure procedure must adhere to the Essure Confirmation Test (modified HSG) protocol in these Instructions for Use. The protocol for interpretation of the Essure Confirmation Test (modified HSG) is different from a standard HSG for infertility. In addition to patient noncompliance, incorrect interpretation of the Essure Confirmation Test (modified HSG) has led to pregnancy.*

- *Pregnancies (including ectopic pregnancies) have been reported among women with inserts in place. Some of these pregnancies were due to patient non-compliance, which included failure to:*

    - *use alternate contraception during the 3-month "waiting period" prior to Essure Confirmation Test;*
    - *return for the Essure Confirmation Test (modified HSG) to determine if the inserts are in the correct location and tubal occlusion is present; and*
    - *use alternate contraception or undergo sterilization by another method if the Essure Confirmation Test is (modified HSG) reveals tubal patency. In this case, the clinician*

should inform the patient of the Essure Confirmation Test (modified HSG) finding and counsel her not to rely on the Essure System for contraception.

Therefore, it is critical that clinicians properly counsel patients regarding the risk of pregnancy (including ectopic pregnancy) attributable to non-compliance during all stages of the Essure procedure.

Essure Patient Labeling Regarding Patient Non-Compliance

- *You can rely on Essure for birth control only after your doctor has reviewed your Essure Confirmation Test results and told that you may rely. If you rely on Essure for birth control before having your Essure Confirmation Test, you are at risk of getting pregnant*
- *Talk to your doctor about which method of birth control you should use for the 3 months after the procedure. Some women can remain on their current birth control. Other women, such as those using an intrauterine device or contraceptive, will need to switch to another method.*
- *It can take longer than three months for the Essure procedure to be effective. In rare cases, it has taken up to 6 months. Make sure to continue using an alternate form of birth control up until your doctor has reviewed your Essure Confirmation Test results and confirmed that you can rely on Essure for birth control*
- *After 3 months, a doctor administers the Essure Confirmation Test using contrast dye and a special type of x-ray. The test confirms that the inserts are placed correctly, your fallopian tubes are blocked, and pregnancy will be permanently prevented. Until you receive confirmation from your doctor, you must continue to use another form of birth control to prevent pregnancy. Essure inserts do not contain hormones, so you'll continue to have your normal period and your ovaries will continue to release eggs. Since the eggs cannot be fertilized, they are simply absorbed back into your body.*

Appendix B: Physician Labeling for the Essure System

Appendix C: Patient Labeling for the Essure System

Appendix D: Mandatory Medical Device Reporting

Appendix E: Summary of Safety and Effectiveness Data, Original Approval (P020014)

Appendices B, C, D, and E are provided in separate pdf files.

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