PS160001/R3

(b) (6)
(b) (6)
U.S. Food and Drug Administration
Center for Devices and Radiological Health
(b) (6)
10903 New Hampshire Ave.
Silver Spring. MD 20903
WO66-2252

February 28, 2018

(b) (6)
Global Regulatory Affairs
921 Parker Street
Berkeley, CA 94710
Phone: (b) (6)

RE: Postmarket Surveillance (PS) Study: PS160001/R003
18-Month Interim Postmarket Surveillance Report
Trade Name: Essure® System for Permanent Birth Control
Reference PMA: P020014

Dear (b) (6):

Reference is made to FDA's letter dated February 29, 2016 regarding order to conduct a postmarket surveillance study for Essure under Section 522 of the Federal Food, Drug and Cosmetic Act. Reference is also made to FDA's approval of the Essure 522 study plan on September 2, 2016.

Bayer is herewith submitting the 18-month Interim Postmarket Surveillance Report (see **Attachment 1**).

The information contained in this submission is considered confidential, and Bayer therefore requests protection of this information in accordance with 18 USC 1905, 21 USC 331 (1), 5 USC 522.

This submission is provided in accordance with the eCopy Program for Medical Device Submissions, Guidance for Industry and Food and Drug Administration Staff (October 10, 2013).

Bayer HealthCare Pharmaceuticals certifies that this submission has been scanned for viruses and is virus free using TREND MICRO™ Office Scan™ , Program Version Office Scan™, Program Version 11.0 or higher. For any questions regarding eCopy technical aspects of this electronic submission, please contact (b) (6) or by email at (b) (6).

Bayer looks forward to closely working with the FDA on this post market surveillance study. Should you require additional information, please feel free to contact (b) (6).

Respectfully,

(b) (6)

[redacted]

ATTACHMENT 1: 18-Month Interim Postmarket Surveillance Report

cc: (b) (6) [redacted]

18-Month Interim Postmarket Surveillance Report

An open-label, non-randomized, prospective observational cohort study to assess post-procedural outcomes in two cohorts of women who chose to undergo either hysteroscopic sterilization (Essure®) or laparoscopic tubal sterilization

Bayer Study (b)(4)

Postmarket Surveillance
Application #PS160001

Date of Report: 28 FEB 2018

Data Current to:

01 DEC 2017

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List of abbreviations

AE	Adverse event
DMC	Data monitoring committee
FAS	Full analysis set
IRB	Institutional review board
LTS	Laparoscopic tubal sterilization
MedDRA	Medical Dictionary for Medical Activities
(b)(4)	(b)(4)
PSV	Pre-selection visit
SAE	Serious adverse event
SOC	System organ class
TEAE	Treatment-emergent adverse event

1. General Information

Postmarket Surveillance Application Number: PS160001

1.1 Sponsor Information

Name: Bayer Healthcare LLC

Address: 100 Bayer Blvd.
P.O. Box 915
Whippany, NJ 07981 USA

Contact Person: (b) (6)
(b) (6)
Telephone: (b) (6)

Email Address: (b) (6)

1.2 Product Information

Device trade name and model number: Essure® System (ESS305)

Date of the 522 order: 29 FEB 2016

Date of postmarket surveillance plan approval: 02 SEP 2016

2. Report Information

Date of report: 28 FEB 2018

Data included in this report: clinical study

Type of submission: interim Postmarket Surveillance Report

3. Postmarket Surveillance Information

3.1 Study Purpose

3.1.1 Goals

Study (b)(4) is an open-label, non-randomized, continuous enrollment, prospective observational, postmarket surveillance study of two cohorts of subjects who chose to undergo:

- hysteroscopic sterilization (Essure System), or
- laparoscopic tubal sterilization.

3.1.2 Objectives

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3.1.3 Study Endpoints

(b)(4)

(b)(4)

3.2 Study Population

The planned study population includes subjects of reproductive age, between 21 and 45 years of age, who have not been pregnant within the past 6 weeks.

The Essure study population group will include subjects who chose to undergo hysteroscopic sterilization and who meet the criteria as outlined in the most current approved version of the Essure Instructions for Use.

(b) (4)

A sample size of 1400 subjects in each treatment group is planned.

Subjects will be followed for a total of 36 months post-procedure. Table 1 provides the subject follow-up visit schedule.

Table 1 Subject Follow-up Visit Schedule

Time of Visit	Office Visit	Telephone Contact
(b)(4)		

3.3 Report Dates

The postmarket surveillance plan was approved by the Food and Drug Administration on 02 SEP 2016.

The data extract used for the tabulations provided in this report includes all data entered into the database as of 01 DEC 2017. Data are preliminary and will be updated with ongoing monitoring efforts.

The anticipated study/surveillance completion date is MAY 2023.

3.4 Summary of Study/Surveillance Progress Milestones/Timeline Elements

3.4.1 Site and Subject Recruitment Status

A total of 75 sites is planned. The targeted completion date for site enrollment is May 2018. A total enrollment of 2800 subjects (1400 subjects in each group) is planned. A subject is

considered to be enrolled after signing informed consent. The planned completion date for subject enrollment is May 2020. The site and subject enrollment progress as of 01 DEC 2017 is shown below.

- number of sites contacted: approximately 6839
- number completing Questionnaire #1 (Interest): 335 (267: Yes; 44: Maybe; 24: No)
- number completing Questionnaire #2 (Feasibility): 292
- number identified for pre-selection visit (PSV): 114
- number of PSVs completed: 96
- number of sites approved for participation: 84
- number of IRB approvals: 56
- number of clinical sites activated (approved to begin screening): 49
    - type of facilities (note: additional categories have been added to this section to reflect the verbatim response provided by sites for type of facility):
        - University Hospital: 6
        - Public/Private Hospital: 3
        - Research Center: 3
        - Private Practice: 23
        - Private Practice/Research Center: 8
        - Public/Private Hospital/Private Practice/Research Center: 2
        - Public/Private Hospital/University Hospital: 1
        - University Hospital/Research Center: 1
        - University Hospital/Private Practice: 1
        - Integrated Care System: 1
- number of sites with subjects enrolled: 34
- subject accrual start date: 03 MAY 2017
- subject accrual completion date: target = MAY 2020
- number of subjects enrolled (signed informed consent): 205 (Essure: 92; LTS: 113)

- percentage of subjects reaching each designated study phase: see Section 3.4.2.
- comparison of target versus actual enrollment and follow-up: Study planning predicted a faster rate of site activation and subject enrollment than was observed.

(b) (4)

3.4.2 Subject Disposition and Accounting

The disposition of subjects enrolled (signed informed consent) as of the 01 DEC 2017 data extract is shown in Table 2. Of the 92 subjects in the Essure group and 113 subjects in the LTS group who signed informed consent and entered the screening phase, (b) (4) and (b) (4) subjects, respectively, attended the procedure visit and of these, (b) (4) and (b) (4) subjects, respectively, had the procedure attempted. (b) (4)

(b) (4)

A full accounting of subjects by treatment group and study phase is in Table 3.

Table 2 Disposition – Overview (All Enrolled Subjects)

Disposition	Essure	Laparoscopic Tubal Sterilization	Total
Number (%) of subjects enrolled	92 (100.0%)	113 (100.0%)	205 (100.0%)
Screening Failures	(b) (4)		
Primary Reason			
Inclusion/exclusion criteria not met			
Withdrawal by Subject			
Other			
Entered Procedure Phase			
No Procedure Attempted			
Procedure Attempted			
Told to Rely			
Completed the End of Study visit			
Discontinued from the Study			
Primary Reason			
Physician Decision			
Withdrawal by Subject			
Other			

(b)(4)

Table 3 Subject Accountability by Treatment Group (Full Analysis Set)

Treatment Group: Essure

	(b) (4)
Eligible for visit	
Active	
Visit performed	
Missed visit	
Discontinued	
Lost to follow-up	

Treatment group: Laparoscopic Tubal Sterilization

	(b) (4)
Eligible for visit	
Active	
Visit performed	
Missed visit	
Discontinued	
Lost to follow-up	

(b) (4)

3.5 Subject Demographics, Baseline Characteristics, and Medical History

(b)(4)

Table 4 Demographics, Baseline Characteristics and Medical History (Full Analysis Set)

	Essure (b)(4)	Laparoscopic Tubal Sterilization (b)(4)	Total (b)(4)
(b)(4)			

Table 4 Demographics, Baseline Characteristics, and Medical History (Full Analysis Set) (continued; 2 of 3)

	Essure (b)(4)	Laparoscopic Tubal Sterilization (b)(4)	Total (b)(4)
(b)(4)			

Table 4 Demographics, Baseline Characteristics, and Medical History (Full Analysis Set) (continued 3 of 3)

	Essure (b)(4)	Laparoscopic Tubal Sterilization (b)(4)	Total (b)(4)
(b)(4)			

3.6 Procedure-Related Findings

(b)(4)

3.7 Interim Safety Results

(b)(4)

Table 5 Overall Summary of Adverse Events (Full Analysis Set)

	Essure (b)(4)		Laparoscopic Tubal Sterilization (b)(4)		Total (b)(4))	
	Number of AEs	Number of Subjects (%)	Number of AEs	Number of Subjects (%)	Number of AEs	Number of Subjects (%)
(b)(4)						

Table 5 Overall Summary of Adverse Events (Full Analysis Set) (continued; 2 of 2)

	Essure (b)(4)		Laparoscopic Tubal Sterilization (b)(4)		Total (b)(4)	
	Number of AEs	Number of Subjects (%)	Number of AEs	Number of Subjects (%)	Number of AEs	Number of Subjects (%)
(b)(4)						

Table 6 Subject Incidence of Treatment-emergent Adverse Events (TEAEs) by SOC and Preferred Term (Full Analysis Set)

	Essure (b)(4)		Laparoscopic Tubal Sterilization (b)(4)		Total (b)(4)	
	Number of AEs	Number of Subjects (%)	Number of AEs	Number of Subjects (%)	Number of AEs	Number of Subjects (%)
(b)(4)						

Table 6 Subject Incidence of Treatment-emergent Adverse Events (TEAEs) by SOC and Preferred Term (Full Analysis Set) (continued; 2 of 2)

	Essure (b)(4)		Laparoscopic Tubal Sterilization (b)(4)		Total (b)(4)	
	Number of AEs	Number of Subjects (%)	Number of AEs	Number of Subjects (%)	Number of AEs	Number of Subjects (%)
(b)(4)						

4. Summary

(b) (4)

The study team will actively monitor site and subject recruitment and move forward with continuing recruitment initiatives.

A (b)(4) meeting was conducted on 15 FEB 2018. (b) (4)
(b) (4)

5. Appendix

5.1 Adverse Events – Subject Listing (All Enrolled Subjects)

Treatment Group: (b) (4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After	Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)											

Footnotes please refer to the last page.

Adverse Events – Subject Listing (All Enrolled Subjects) (continued; 2 of 19)
Treatment Group: (b) (4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (All Enrolled Subjects) (continued; 3 of 19)
Treatment Group (b) (4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (All Enrolled Subjects) (continued; 4 of 19)
Treatment Group: (b) (4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (All Enrolled Subjects) (continued; 5 of 19)
Treatment Group: (b) (4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (All Enrolled Subjects) (continued; 6 of 19)
Treatment Group: (b) (4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (All Enrolled Subjects) (continued; 7 of 19)
Treatment Group: (b) (4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (All Enrolled Subjects) (continued; 8 of 19)
Treatment Group: (b) (4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (All Enrolled Subjects) (continued; 9 of 19)
Treatment Group: (b) (4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (All Enrolled Subjects) (continued; 10 of 19)

Treatment Group: (b)(4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (All Enrolled Subjects) (continued; 11 of 19)

Treatment Group: (b)(4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (Full Analysis Set) (continued; 12 of 19)

Treatment Group: (b)(4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (Full Analysis Set) (continued; 13 of 19)

Treatment Group: (b)(4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (Full Analysis Set) (continued; 14 of 19)

Treatment Group: (b)(4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (Full Analysis Set) (continued; 15 of 19)

Treatment Group: (b)(4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (Full Analysis Set) (continued; 16 of 19)

Treatment Group: (b)(4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (Full Analysis Set) (continued; 17 of 19)

Treatment Group: (b)(4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (Full Analysis Set) (continued; 18 of 19)

Treatment Group: (b)(4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Footnotes please refer to the last page.

Adverse Events – Subject Listing (Full Analysis Set) (continued; 19 of 19)

Treatment Group: (b)(4)

Unique Subject Identifier/ Age/Race	Attended Sterilization Procedure/ Attempted Sterilization/ Rely on Sterilization	SOC/ Preferred Term/ Reported Term	Start Prior to Index Event/ After Censor/ AEOSI	Serious/ Reason	Adverse Event Start Date (Day)/ End Date (Day)/ Duration (days)	Intensity	Relation to Procedure / Type of Procedure	Treatment of AE	Outcome	Comment
(b)(4)										

Race is identified as: A = Asian, B = Black, W = White, AI = American Indian or Alaska Native, NH = Native Hawaiian or Other Pacific Islander, NR = Not Reported, MUL = Multiple.
The unit of 'Age' is years.
'(Day)' is the day relative to the index event date.
Y=Yes, N=No
AEOSI = adverse event of special interest

(b) (6)

From: (b) (6)
Sent: Thursday, March 01, 2018 3:12 PM
To: (b) (6)
Cc: (b) (6)
Subject: PS160001/R3 - Bayer Healthcare, LLC - email receipt

Trade Name: Essure System for Permanent Birth Control
Document Number: PS160001/R3
Dated: February 28, 2018
Received: March 1, 2018

Dear (b) (6) :

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has received your section 522 postmarket surveillance (PS) 18 month report. Within 60 days of the receipt date, FDA will notify you in writing of the decision.

Please be sure that future correspondence regarding your 522 PS study is sent to the attention of (b) (6) (b) (6) . If you have any procedural or policy questions concerning postmarket surveillance requirements, please contact (b) (6)

Thank you,

(b) (6)

Excellent Customer Service is important to us. Please take a moment to provide feedback regarding the customer service you have received.
(b)(4)

(b) (6)

From: (b) (6)
Sent: Friday, April 27, 2018 10:02 AM
To: (b) (6)
Cc:

Subject: FDA Decision - Bayer Healthcare, LLC - PS160001/R3

Dear (b) (6) :

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your section 522 postmarket surveillance (PS) study report PS160001/R3. This report is for the Postmarket Surveillance Study.

We have determined that you have sufficiently met the reporting expectations for the above report.

Advisories

1. Please be advised that your study status will be marked as "Progress Adequate" on the Section 522 Postmarket Surveillance Studies webpage (www.fda.gov/522studies).

(b)(4)

(b)(4)

Your next scheduled report is due September 2, 2018.

Thank you,

(b) (6)

Excellent Customer Service is important to us. Please take a moment to provide feedback regarding the customer service you have received.

(b)(4)

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

MEMORANDUM

Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Date: April 27, 2018

From: (b) (6)

Subject: PS160001/R003
Essure System for Permanent Birth Control, Bayer Pharma AG
522 Study Requirement Name: Postmarket Surveillance Study
Epidemiologic Review of Postmarket Surveillance (PS) Study Interim Report

PS Order: Date of PS Order: February 29, 2016
ODE/OIR Document(s) on which the PS order was issued: P020014

To: (b) (6)

Through: (b) (6)

Conclusion/Recommendation:
The interim report (PS160001/R003) can be accepted.
522 Requirement Progress Status: Progress Adequate

Purpose:

The purpose of this memorandum is to present the epidemiologic review for the 12-month 522 Postmarket Surveillance (PS) Study Interim Report for the Essure System for Permanent Birth Control submitted by Bayer Pharma AG.

This memo includes:

- background information
- PS study protocol overview
- the review and assessment of the interim study results
- PS study tracking information
- overall conclusions and recommendations

- any applicable deficiencies.

Background:

Device Description

A. Essure System Components

The Essure System is comprised of the Essure micro-insert, a disposable delivery system, and a disposable split introducer.

Essure Micro-Insert

The Essure micro-insert is a spring-like device that consists of a stainless steel inner coil, a nickel titanium (Nitinol) expanding outer coil, and polyethelene terephthalate (PET) fibers. The PET fibers are wound in and around the inner coil. The micro-insert is 4 cm in length and 0.8mm in diameter in its wound down configuration. When released from the delivery system, the outer coil expands to 1.5 to 2.0 mm in diameter to anchor the micro-insert in the varied diameters and shapes of the fallopian tube. The spring-like device is intended to provide the necessary anchoring forces during the acute phase of device implantation (3 months post-micro-insert placement), during which time the PET fibers are eliciting tissue in-growth into the coils of the Essure micro-insert and around the PET fibers.

The Essure Micro-insert is provided attached to the delivery wire, in a wound-down configuration. The delivery wire is composed of a nitinol core wire, which is ground at the distal end to result in a flexible, tapered profile. The device is constrained by the release catheter, which is sheathed by a flexible delivery catheter. A black positioning marker on the delivery catheter aids in proper placement of the device in the fallopian tube.

The delivery handle controls the device delivery and release mechanism. The thumbwheel on the delivery handle retracts both the delivery catheter and the release catheter. The button allows the physician to change the function of the thumbwheel from retracting the delivery catheter to retracting the release catheter. The delivery wire is detached from the micro-insert by rotating the system.

Split Introducer

The split introducer is placed into the sealing cap of the working channel of the hysteroscope, and is intended to help protect the Essure Micro-insert as it is being passed through the sealing cap of the hysteroscope working channel.

B. Mechanism of Action

1. Placement at Utero-Tubal Junction (UTJ)

The Essure Micro-insert is intended for placement into the fallopian tube with the implant portion of the device spanning the utero-tubal junction (UTJ). For purposes of micro-insert placement, the UTJ is defined as the portion of the fallopian tube, just as it enters the uterus. Placement at the UTJ is expected

to aid in anchoring since it most consistently represents the narrowest portion of the fallopian tube. Expulsion of the Essure Micro-insert has occurred when micro-insert placement was too proximal. If the device is placed without any trailing portion of the device in the uterus, then direct visualization of device location is not possible.

2. Tissue In-Growth

The effectiveness of the Essure Micro-insert in preventing pregnancy is believed to be due to a combination of the space-filling design of the device and a local, occlusive, benign tissue response to the PET fibers. The tissue response is the result of a chronic inflammatory and fibrotic response to the PET fibers. It is believed that the tissue ingrowth into the device caused by the PET fibers results in both device retention and pregnancy prevention.

3. Permanency of Tubal Occlusion (and Sterilization)

The long-term nature of the tissue response to the Essure micro-insert is not known. The majority of the clinical data regarding PET in the fallopian tube is based on 12-24 months of implantation, with little data at 36 months. Therefore, beyond 24 months, the nature of the cellular fibrotic response and the ability of the response and the device to maintain occlusion are not known.

Indications for Use

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

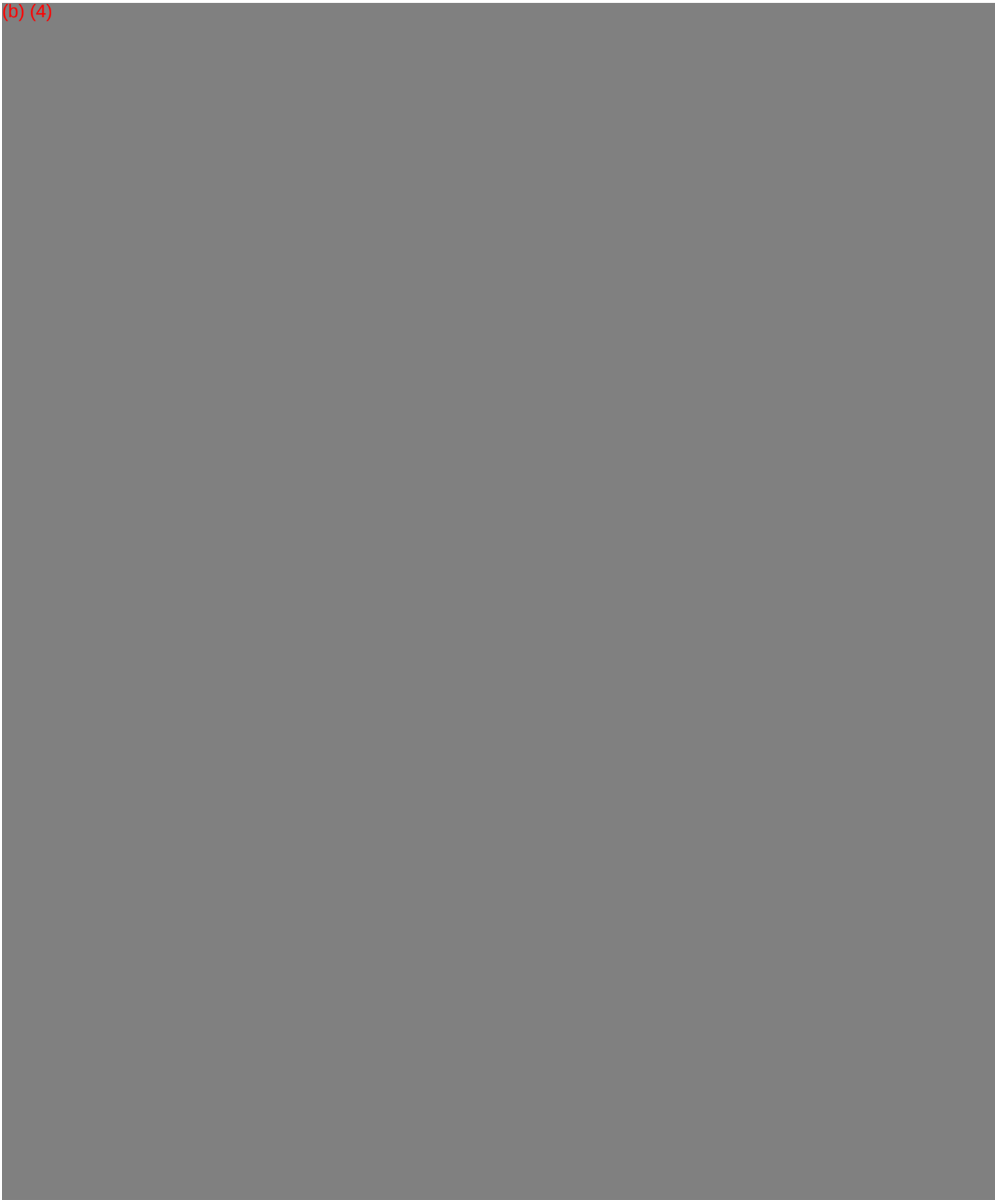
PS Order

On September 24, 2015, FDA convened a meeting of the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee (see transcript), and the panel recommended additional data collection via postmarket surveillance. On February 29, 2016, FDA issued a 522 order for the Essure Permanent Birth Control System.

PS Study Protocol Overview:

(b) (4)

(b) (4)



Study Element	Description
Real-World Evidence (RWE)	N/A
Study Design	Open-label, non-randomized, prospective observational cohort study of two cohorts of subjects who chose to undergo either hysteroscopic sterilization (Essure) or laparoscopic tubal sterilization.
Study Hypothesis	There is no hypothesis testing.
Study Population	The study population will include subjects of reproductive age, between 21 and 45 years of age who have not been pregnant within the past 6 weeks. The study population will include women who chose to undergo hysteroscopic sterilization (Essure) and who meet the criteria as outlined in the Essure Instructions for Use (IFU). Women seeking laparoscopic tubal sterilization must be considered appropriate surgical candidates by the investigator.
Sample Size	2,800 women (1,400 per arm) enrolled at 50-75 sites. (b) (4) [redacted]
Study Endpoints	Follow-up measures will include adverse event assessment, medical history including gynecological procedures, patient reported outcome (PRO) measures for chronic pelvic pain and abnormal uterine bleeding, bloodwork for women with certain adverse events, and analysis of removed Essure devices. Key Endpoints: Pain: The proportion of subjects reporting AEs of chronic lower abdominal and/or pelvic pain after insertion of Essure System (ESS305) (b) (4) [redacted] Bleeding: The proportion of subjects reporting AEs of abnormal uterine bleeding after insertion of Essure System (b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted] Total incidence of new onset or worsening abnormal bleeding events will be based on AE reporting. Hypersensitivity/allergy/autoimmune disorders: The proportion of subjects with adjudicated new onset (b) (4) [redacted] allergic/hypersensitivity reactions (b) (4) [redacted]

Study Element	Description
	(b) (4) Proportion of subjects undergoing invasive gynecologic surgery (b) (4) (b) (4) including Essure insert removal (b) (4) (b) (4) Additional endpoints: • Patient reported outcome measures (b) (4) (b) (4) • Rates of AEs
Length of Follow-up and Frequency of Follow-up Assessments	(b) (4) (b) (4) 36 months.
Enrollment Plan and Follow-up Measures	(b) (4)
Statistical Plan	(b) (4)

Study Element	Description
	(b) (4)

Timeline for Study Implementation (approved on September 2, 2016: PS160001/A002)

Milestone:	Date:
Expected date of study initiation	September 2016
Expected monthly number of study sites with IRB approvals	Approximately 8 sites/month
Expected date of initiation of subject enrollment	May 2017
Expected number of subjects enrolled per month	Approximately 78 patients/month (when all sites activated)
Expected date of enrollment completion	May 2020
Expected date of study follow-up completion	May 2023
Expected date for final report submission	September 2023

PS Study Interim Status/Results and Assessments:

Study Elements

Number of IRB Approvals

Description

- As of December 1, 2017: 56
- As of March 4, 2018 (interactive review): 67
- As of April 11, 2018 (interactive review): 68

Assessment

- Interactive review was initiated twice during the review of this report to request updated enrollment information (see Attachment 1 and Attachment 2).
- The number of IRB approvals is increasing as the study continues to enroll sites. **Acceptable.**

Number of study sites enrolled

Description

- As of December 1, 2017: 49 sites have been activated, 34 sites have enrolled subjects.
- As of March 4, 2018 (interactive review): 60 sites have been activated, 44 sites have enrolled subjects (b) (4)
- As of April 11, 2018 (interactive review): 62 sites have been activated, 51 sites have enrolled subjects.

Assessment

- According to the protocol, the sponsor plans to enroll 50-75 sites. The study has met this target and progress is **acceptable**. However, in order to achieve subject enrollment goals, the sponsor has communicated a plan to increase the target number of sites, and FDA has advised them to do so (b) (4)

Number of subjects enrolled

Description

- Enrollment began on May 3, 2017.
- As of December 1, 2017: 205/2800 (7.3%), including 92 in Essure arm and 113 in BTL arm.
- (b) (4)
- As of March 4, 2018 (interactive review): 337/2800 (12.0%), including 141 in Essure arm and 196 in BTL arm.
- As of April 11, 2018 (interactive review): 416/2800 (14.9%), including 176 in Essure arm and 240 in BTL arm.

Assessment

- The enrollment rate between December 2017 – March 2018 was 132 subjects in 3 months, or approximately 44 subjects per month. The enrollment rate between March 2018 – April 2018 was 79 subjects in 38 days, or approximately 62 subjects per month. Therefore, the enrollment rate is increasing. The timeline specifies a goal of approximately 78 subjects/month once all sites have been activated (anticipated date: May 2018). Therefore, the study status based on current enrollment rate is **Progress Adequate**, (b) (4)
  (b) (4)
- (b) (4)

(b) (4) FDA will continue to assess enrollment during the review of the 24-month report, due September 2, 2018.

- (b) (4)

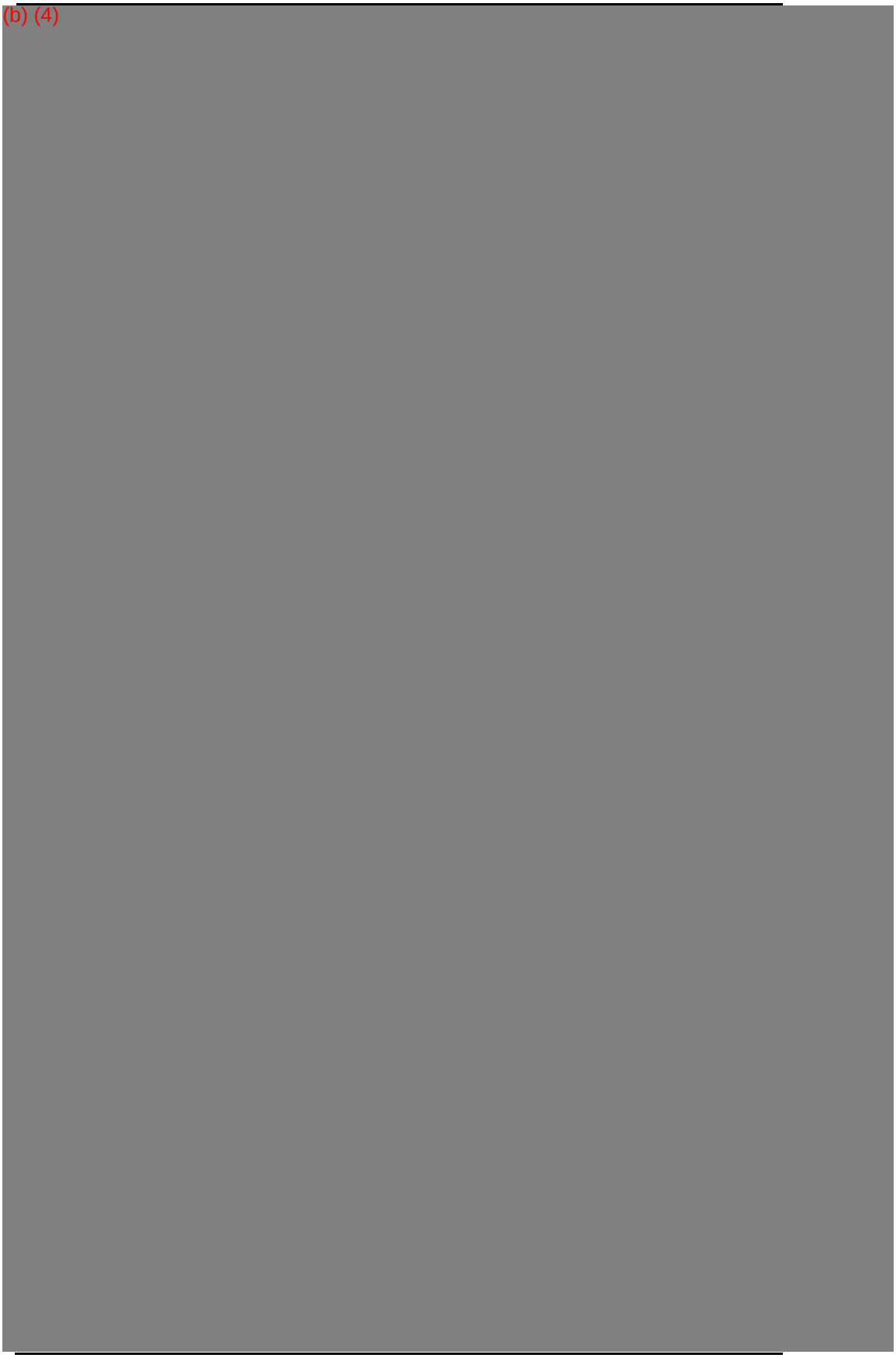
Follow-up rate

Description

(b) (4)

(b) (4)

(b) (4)



(b) (4)

Timeline

Description

- N/A

Assessment

- (b) (4)

Summary of Interim Study Results for the 522 Webpage (updated on April 25, 2018)

Study Elements	Description
Number of study sites enrolled	As of April 11, 2018, 62 sites have been enrolled.
Number of subjects enrolled	As of April 11, 2018, 416 patients have been enrolled (176 in the Essure arm and 240 in the laparoscopic tubal ligation arm).

PS Study Tracking Information:

1. What is the Overall Study Status? Check only one.

	Plan Pending	FDA has not approved the study protocol, and it has been less than 6 months since issuance of the order.
	Plan Overdue	FDA has not approved the study protocol, and it has been 6 months or more since issuance of the order.
	Study Pending	The protocol has been approved, but no subjects have been enrolled.
X	Progress Adequate	The study has begun, and the study progress is consistent with the protocol (e.g., meeting enrollment schedule, follow-up rates, endpoints evaluated).
	Progress Inadequate	The study has begun, but the study progress is inconsistent with the protocol (e.g., not meeting enrollment schedule, missing timepoint evaluations, poor follow-up rates, not all endpoints evaluated).
	Completed	The sponsor has fulfilled the condition of approval, and FDA has closed the study. This is a final study status.
	Terminated	The sponsor has not fulfilled or cannot fulfill the condition of approval (e.g., study questions are no longer relevant, sponsor withdraws PMA, data cannot answer 522 question), and, after all appropriate efforts to fulfill the condition of approval have been exhausted, FDA has terminated the study. This is a final study status.
	Other	Used when the study status does not fit another category (e.g., not marketing the device and have no plans to market the device, change in ownership underway, redesigning device and need PMA approval prior to use in a PAS, pending separate study being used to address condition of approval). This is an interim study status.

Deficiency List:

None

Advisory

1. Please be advised that your study status will be marked as "Progress Adequate" on the Section 522 Postmarket Surveillance Studies webpage (www.fda.gov/522studies).
2. (b) (4)

(b) (6)

cc: (b) (6)

Document History:

Date	Activity	Initials
4/25/18	Drafted	(b) (6)
4/25/18	Reviewed with comments	
4/26/18	Revised	
4/26/18	Reviewed/Cleared	
4/26/18	Revised	
4/26/18	Reviewed/Cleared	
4/27/18	Advisory language cleared via email	
4/27/18	Finalized	

Reviewer's Sign-Off	
Branch Chief Sign-Off	

Attachment List

Attachment 1: Interactive Review Response (March 5, 2018)

Attachment 2: Interactive Review Response (April 23, 2018)

Attachment 3: Internal Meeting (April 2, 2018)

Attachment 4: Minutes from In-Person Meeting (February 8, 2018)

Attachment 5: FDA Feedback Regarding In-Person Meeting Minutes

Attachment 6: Teleconference Minutes (April 18, 2018)

Attachment 1: Interactive Review Response (March 5, 2018)

From: (b) (6)
To:
Cc:
Subject: RE: PS160001/R003 Interactive Review Request
Date: Monday, March 05, 2018 2:08:16 PM
Attachments: image007.png

Dear (b) (6)
Please find the information requested below.

The numbers below are current through end of day 04Mar2018.

- Number of sites approved for participation: 84 (b) (4)
  (b) (4)
- Number of IRB approvals: 67
- Number of clinical sites activated: 60 Sites activated (b) (4)
- Number of sites with subjects enrolled: 44
- Number of subjects enrolled (by arm): 337 Total = 141 Essure and 196 LTS

Please let me know if you have additional questions.

Thank you,
(b) (6)

Freundliche Grüße / Best regards,

(b) (6)

//////////////////

Bayer U.S. LLC
Development, Pharmaceuticals
Essure & Devices
921 Parker Street
Berkeley CA 94710
United States
(b) (6)

Web: http://www.bayer.us

From: (b) (6)
Sent: Friday, March 02, 2018 1:27 PM
To: (b) (6)
Cc:
Subject: PS160001/R003 Interactive Review Request
Importance: High

Dear (b) (6)

I am reviewing the 18-month interim report and I have a concern I'd like to resolve interactively.

The interim report is dated February 28, 2018, but has a data cutoff date of December 1, 2017. Therefore, the information in the report is outdated. In order for FDA to assess the current study

progress, please send an enrollment update as of March 1, 2018 or later. Please include the following information: number of sites approved for participation, number of IRB approvals, number of clinical sites activated, number of sites with subjects enrolled, and number of subjects enrolled (by arm).

Please send via email by March 9, 2018. Please let me know if you have any questions or concerns.

Thank you!

(b) (6)

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

(b)(4)

The information contained in this e-mail is for the exclusive use of the intended recipient(s) and may be confidential, proprietary, and/or legally privileged. Inadvertent disclosure of this message does not constitute a waiver of any privilege. If you receive this message in error, please do not directly or indirectly use, print, copy, forward, or disclose any part of this message. Please also delete this e-mail and all copies and notify the sender. Thank you.

Attachment 2: Interactive Review Response (April 23, 2018)

From: (b) (6)
To:
Cc:
Subject: RE: PS160001/R003 Interactive Review Request (reply requested by 4/10)
Date: Monday, April 23, 2018 11:08:29 AM
Attachments: image001.png

Dear (b) (6)
Please see response below.

Feel free to contact me if you have additional questions.

Thank you,
(b) (6)
Freundliche Grüße / Best regards,

(b) (6)

////////////////////

Bayer U.S. LLC
Development, Pharmaceuticals
Essure & Devices
921 Parker Street
Berkeley CA 94710
United States
(b) (6)
Web: http://www.bayer.us

From: (b) (6)
Sent: Tuesday, April 17, 2018 12:52 PM
To: (b) (6)
Cc:
Subject: RE: PS160001/R003 Interactive Review Request (reply requested by 4/10)

Hi (b) (6)
Thank you for the responses. I have additional comments, below. We can discuss further during the tcon tomorrow.

(b)(4)

(b)(4)

Thank you,
(b) (6)

From: (b) (6)
Sent: Wednesday, April 11, 2018 12:27 AM
To: (b) (6)
Cc:
Subject: RE: PS160001/R003 Interactive Review Request (reply requested by 4/10)

Dear (b) (6)
Please find the responses to your queries below.

Thank you,
(b) (6)

Freundliche Grüße / Best regards,

(b) (6)

////////////////////

Bayer U.S. LLC
Development, Pharmaceuticals
Essure & Devices
921 Parker Street
Berkeley CA 94710
United States
(b) (6)

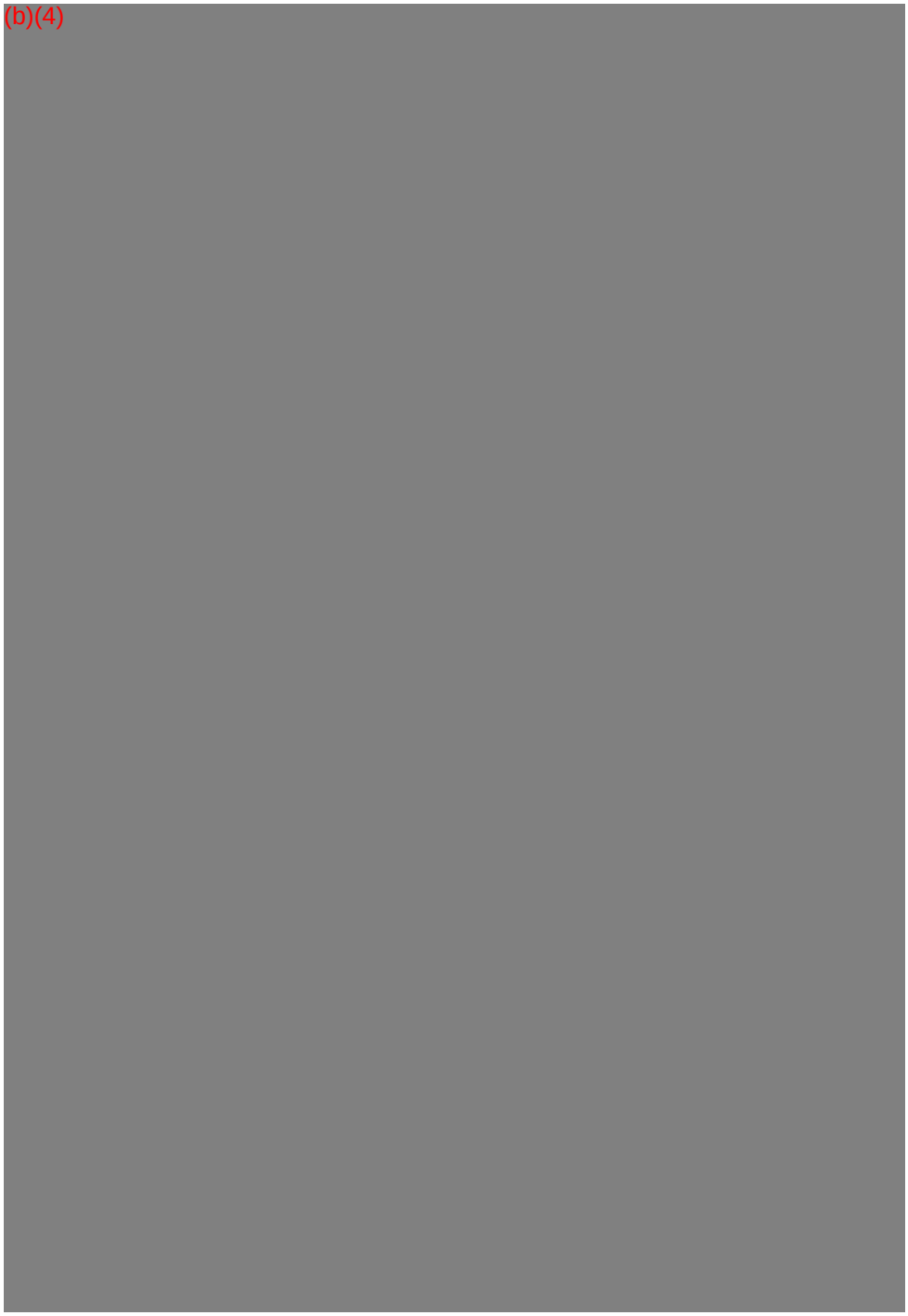
Web: http://www.bayer.us

From: (b) (6)
Sent: Tuesday, April 03, 2018 1:31 PM
To: (b) (6)
Cc:
Subject: PS160001/R003 Interactive Review Request (reply requested by 4/10)
Importance: High

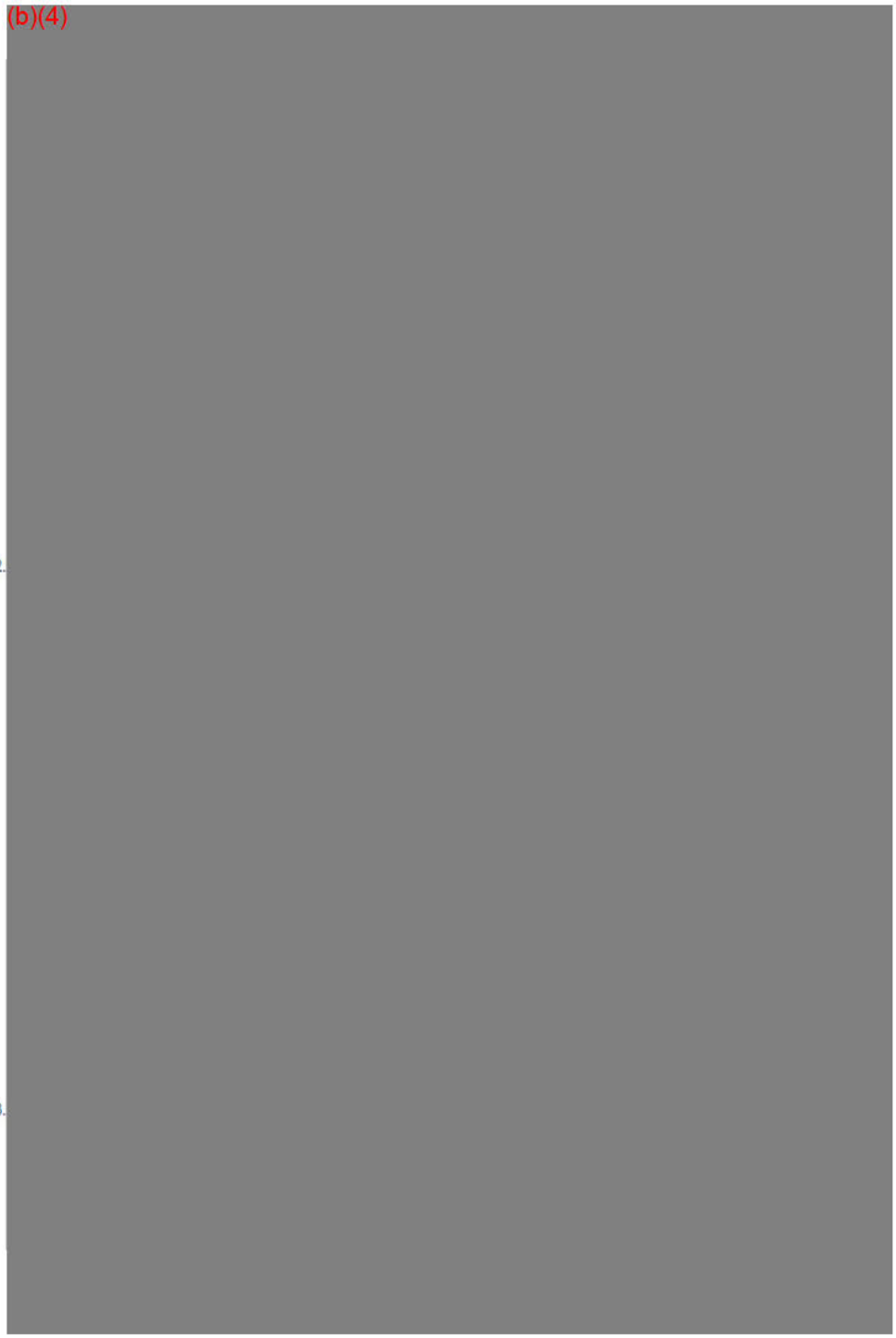
Dear (b) (6)
Regarding the review of PS160001/R003, I have additional requests that I would like to resolve interactively:

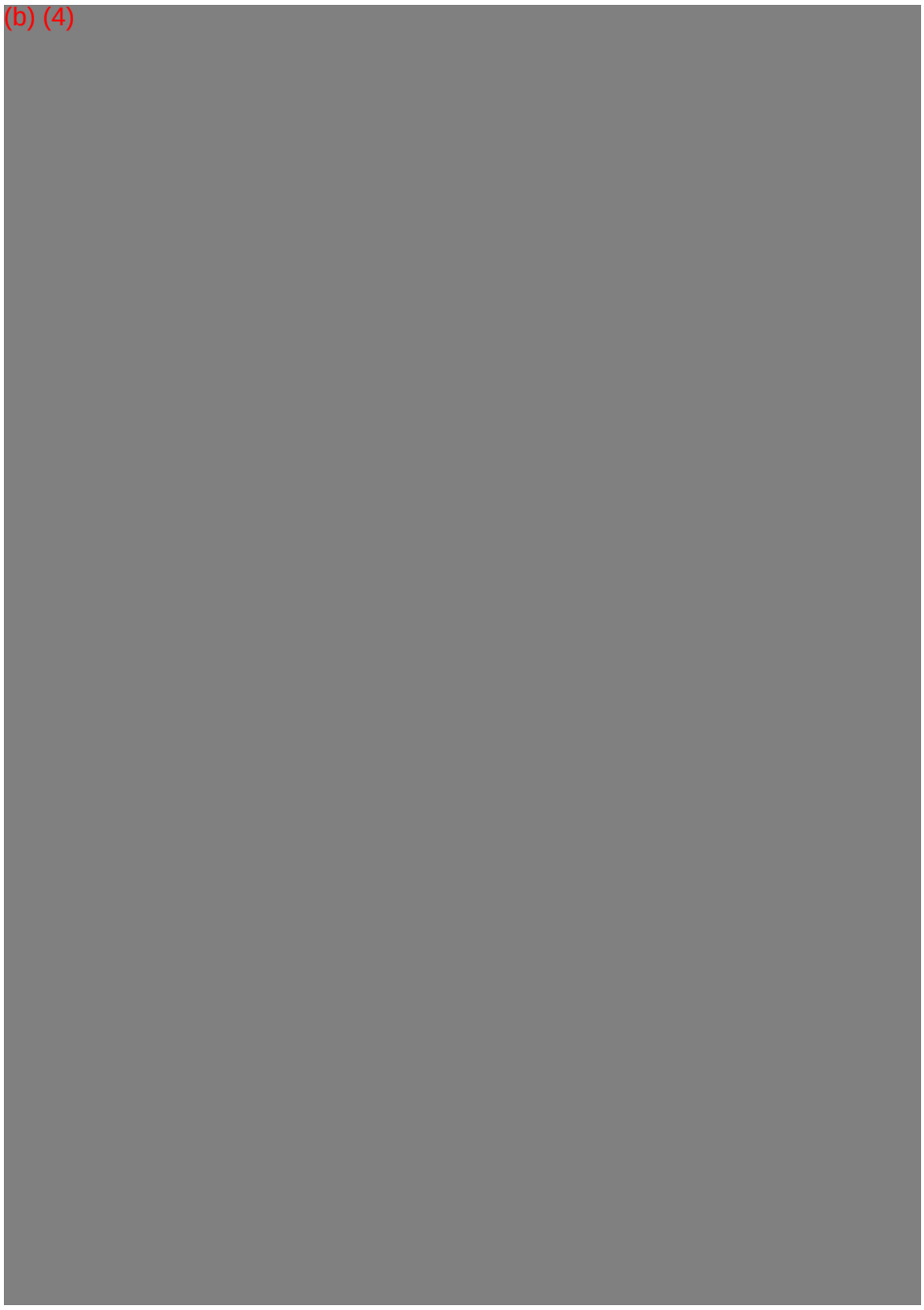
1. (b)(4)

(b)(4)



(b)(4)





(b) (4)

Please reply via email by April 10, 2018. Please let me know if you have any concerns or questions.

Thank you!

(b) (6)

FDA U.S. FOOD & DRUG ADMINISTRATION

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:

(b)(4)

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Attachment 3: Internal Meeting (April 2, 2018)

Participants: (b) (6) [redacted]

Discussion:

1. (b) (4), (b) (5) [redacted]
2. [redacted]

Attachment 4: Minutes from In-Person Meeting (February 8, 2018)

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center – WO66-G609
10903 New Hampshire Ave.
Bldg. 66, Rm. G609
Silver Spring, MD 20993-0002

RE: PS160001 Face-to-face Meeting Minutes
Essure® System for Permanent Birth Control PMA P020014

Dear (b) (6),

Reference is made to the Bayer / FDA face-to-face meeting held on February 8, 2018 regarding the current status of the Essure 522 study, PS160001.

March 2, 2018

(b) (6)
921 Parker St.
Berkeley, CA 94710
Phone: (b) (6)
(b) (6)

Bayer Attendees: (b) (6)
(b) (6)

FDA Attendees: (b) (6)
(b) (6)

On February 8, 2018 a face-to-face meeting between Bayer and FDA was held at the FDA Silver Spring, MD office to discuss the enrollment status of the Essure 522 Study. After introductions, FDA went over general housekeeping, noting that all materials for this meeting are subject to FOIA requests, this meeting was for informational purposes only and they would not be making formal decisions at this time. If decisions are necessary a formal submission is required. The meeting began with the Bayer presentation given by (b) (6)
(b) (6) The presentation covered the (b)(4)
(b)(4)

(b) (4)

(b)(4)

(b)(4)

(b) (4)

(b) (4)

The information contained in this submission is considered confidential, and Bayer therefore requests protection of this information in accordance with 18 USC 1905, 21 USC 331 (1), 5 USC 522.

Please feel free to contact me if you have any questions or need additional information. I can be reached by phone at (b) (6) or by email at (b) (6)

Respectfully,

(b) (6)

Attachment 5: FDA Feedback Regarding In-Person Meeting Minutes

From: (b) (6)
To:
Subject: RE: PS160001 face-to-face meeting minutes
Date: Tuesday, March 06, 2018 1:20:00 PM

Thank you for sending the meeting minutes. We have a couple of clarifying comments and additions regarding the meeting minutes; please see below. No need to submit a revised version of the minutes.

(b)(4)

Please let me know if you have any further questions or comments.

Thank you!
(b) (6)

From: (b) (6)
Sent: Friday, March 02, 2018 1:02 PM
To: (b) (6)
Subject: PS160001 face-to-face meeting minutes

Dear (b) (6)
Attached please find the meeting minutes from the face-to-face meeting held on February 8, 2018 regarding the Essure PS522 Study, PS160001.

Feel free to contact me if you have any questions.

Thank you,
(b) (6)

Freundliche Grüße / Best regards,

(b) (6)

//////////////////

Attachment 6: Teleconference Minutes (April 18, 2018)

Participants: (b) (6)

Discussion:

1. (b)(4)
2.
3.

Next steps:

(b)(4)