CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208564Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	May 29, 2018
From	Shelley R. Slaughter, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	208564
Applicant	TherapeuticsMD
Date of Submission	November 29, 2017
PDUFA Goal Date	May 29, 2018
Proprietary Name	Imvexxy™
Established or Proper Name	Estradiol Vagina Insert
Dosage Form(s)	Intravaginal Insert
Applicant Proposed Indication(s)/Population(s)	Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
Applicant Proposed Dosing Regimen(s)	Insert at dosage strength or 4 mcg or 10 mcg) administered intravaginally daily for 2 weeks, then administered intravaginally two times per week (approximately 3 to 4 days apart)
Recommendation on Regulatory Action	Approval with a class postmarketing requirement to conduct a phase 4 observational study to determine the long-term general and endometrial safety and chronic use exposure of low dose vaginal estrogen alone products to include Imvexxy
Recommended Indication(s)/Population(s) (if applicable)	Recommend the indication as proposed in postmenopausal women.
Recommended Dosing Regimen(s) (if applicable)	Recommended Dosing and Regimen, as proposed.

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Estrogens without and with progestogens are indicated to treat symptoms (vasomotor and vulvar and vaginal atrophy) due to menopause. With the application of Noncontraceptive Estrogen Class Labeling across all estrogen-containing products irrespective of dosage strength or route of administration, FDA has determined that in the absence of data to establish otherwise, all such products are associated with the same risks. The most serious risks associated with estrogen-alone products, such as estradiol vaginal inserts, include increased risks of endometrial hyperplasia, cerebro-cardiovascular disease and probable dementia. Users of estrogen plus progestogen products are also at increased risk for invasive breast cancer. Noncontraceptive Estrogen Class Labeling recommends mitigating actions to decrease the risks of these serious associated adverse outcome including the addition of progestogen opposition of the effects of estrogen on the endometrium in nonhysterectomized women, appropriate endometrial assessment of women demonstrating persistent vaginal spotting or bleeding, use of the lowest approved dosage strength of the approved estrogen product, and use for the shortest duration appropriate to the woman's treatment goals and individuals risks. In conjunction with the implementation of Noncontraceptive Estrogen Class Labeling, applicants are asked to conduct a long-term endometrial and general safety trial of at least one year minimum duration to assess the risk to the endometrium associated with the proposed product (i.e. demonstrate that rates of observed endometrial hyperplasia and/or cancer are consistent with those seen with other estrogen-alone products. The applicant of this proposed product estradiol vaginal inserts (4 mcg and 10 mcg dosage strengths) did not conduct such a trial and additionally the applicant did not have long-term drug exposure data.

FDA has become aware that prevailing clinical advice (from certain professional organization, "experts", and clinical researchers) for the treatment of signs and symptoms of vulvar vaginal atrophy due to menopause have advocated, inconsistent with the Boxed Warning in Noncontraceptive Estrogen Class Labeling, that administration of a progestogen is not necessary for women treated with certain vaginally-administered "low" dose estrogen-alone products. These recommendations appear to be based largely on pharmacokinetic data (serum estrogen concentrations) and with one exception, short-term clinical trials, but, importantly, do not take into account the potential for adverse endometrial effects (endometrial hyperplasia and/or cancer) due to direct local exposure to vaginally-applied estrogens. Because clinical guidance from professional organization, "experts", and researchers influences the practice of individual healthcare providers and the care their patients receive, there is compelling reason to believe that healthcare providers are following the noted new clinical advice and are not generally administering a progestogen for endometrial protection, despite the information and advice provided in class labeling. Therefore, Noncontraceptive Estrogen Class Labeling for certain vaginally-administered "low" dose estrogen-alone products alone may not provide adequate risk communication about and risk mitigation against endometrial cancer in real world clinical practice. Given this circumstance, it is essential to have long-term endometrial safety data to adequately guide prescribers' decisions concerning endometrial surveillance and the need for progestogen therapy. FDA is proposing a Class Postmarketing Required (PMR) study from all holders of vaginally-administered "low" dose estrogen-alone products. Given the scope and duration of the necessary long-term study(ies) to characterize endometrial safety of "low" dose estrogen products administered vaginally, holders may elect to collaborate in the conduct of such a study(ies).

As a condition of approval of NDA 208564, FDA requires a PMR study to characterize the long-term endometrial safety of the 4 mcg and 10 mcg strengths of Imvexxy (estradiol vaginal inserts) in (b) (4) women. FDA will also require the same Class PMR study from all current holders of "low" dose estrogen-alone products.

In addition to the conduct of a Class PMR to address endometrial safety, in order to address additional deficiencies remaining after the original review period of this NDA, FDA proposed that the applicant address the long-term general safety and long-term drug exposure via a 505(b)(2) route with review of published literature and the appropriate scientific bridging to rely on such literature. The Division of Epidemiology II (DEPI II) in the Office of Epidemiology and Surveillance (OSE) reached the conclusion that the proposed PMR study methods are generally acceptable pending the FDA-recommended changes; however, final determination of the study's acceptability will not be made until the applicant selects an appropriate data source that would allow implementation of the methods described in the proposal. DEPI II provided comments on the protocol to guide the applicant's final protocol. The Clinical Review Team in conjunction with DEPI II has concluded that the applicant has provided appropriate literature and adequate scientific justification to support long-term general safety and long-term drug exposure for the 4 mcg and 10 mcg dosage strengths of estradiol vaginal inserts.

With the information, as described [Class PMR and acceptable support of long-term general safety and long-term drug exposure via the 505(b)(2) pathway] provided in the resubmission; along with two PMCs (PMC 1-develop and validate a new regulatory method capable of detecting known and unknown estradiol-related impurities in the drug product and PMC 2-devlopment and validation of an analytical method capable of detecting and quantitating known and unknown estradiol-related impurities and establish revised acceptance criteria for estradiol-related impurities, if necessary, according to the new analytical method); and Noncontraceptive Estrogen Class Labeling, the Cross-Disciplinary Review Team believes that NDA 208564 for the 4 mcg and 10 mcg dosage strengths of estradiol vaginal inserts, can be approved.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Menopause is a natural condition of aging in a woman that represents the time when her menstrual periods permanently cease and she is no longer capable of reproduction (i.e. she is no longer fertile). Operational menopause is defined by the absence of menstrual periods for 12 consecutive months without any other biological or physiological cause. Menopause results from diminished ovarian primordial follicles, failure of monthly development of an ovarian dominant follicle and ovulation, and eventual exhaustion of primordial follicles. This process is accompanied by greatly diminished ovarian production of the sex hormone estrogen (as well as progesterone) resulting in both very low serum concentrations of estrogens and cessation of menstruation. Menopause may be characterized by the following symptoms:	Moderate to severe menopausal symptoms including the symptoms of vulvar and vaginal atrophy, though not life-threatening, constitute a significant public health concern often requiring medical intervention.

	• Vasomotor symptoms (or hot flashes) - feeling of warmth and excessive sweating (throughout the day), thought to result from the effects of estrogen withdrawal on hypothalamic thermoregulating system. Night sweats may interfere with the woman's ability to sleep at night. • Vulvar and vaginal atrophy symptoms – vaginal dryness, dyspareunia (pain with intercourse) and vaginal irritation resulting from withdrawal of estrogen stimulation to the lower genital tract (vulva and vagina) While not life threatening moderate to severe menopausal symptoms can be debilitating, affecting the woman's ability to carry out her day-to-day normal personal and or employment-related activities. The 2010. Census estimates 53.1 million women, age 50 or above living in the U.S.[1] About 75% - 80% of postmenopausal women experience hot flashes on and off up to a decade post menopause. About 46% of women suffer from moderate to severe vasomotor symptoms requiring medical intervention. An additional 40% of menopausal women experience symptoms of vulvar and vaginal atrophy.[2] The proposed product is intended to treat moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause	
Current Treatment Options	The following are approved products for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause: • Estrogen alone therapy: ▪ Premarin® (conjugated estrogens) Vaginal Cream	Several estrogen-alone and non-estrogen products are approved specifically to treat moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause. Additionally, Vagifem (estradiol vaginal insert)

[1] https://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf
[2] https://www.sciencenews.org/sn-magazine/january-20-2018

	(intravaginally applied estrogen cream) ▪ Enjuvia® (synthetic conjugated estrogens, B) Tablets (oral estrogen tablet) • Estrogen agonist/antagonist therapy: ▪ Osphena® (ospemifene) Tablets (oral estrogen agonist/antagonist tablet) • Prasterone ▪ Intrarosa® (prasterone) Vaginal Insert (intravaginally applied steroid insert).	is approved for the general indication of atrophic vaginitis due to menopause and is used in the gynecologic medical community to treat the moderate to severe vulvar and vaginal atrophy symptom of dyspareunia. These products offer low to moderate dosage-strength estrogen or non-estrogen vaginally-administered or orally-administered options for the treatment of these symptoms
Benefit	• If approved, the lowest dosage strength of Imvexxy™ (estradiol vaginal insert), 4 mcg, would be the lowest dosage strength of an estradiol-alone product approved to treat moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause.	Imvexxy is efficacious in the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy.
Risk and Risk Management	Noncontraceptive Estrogen Class Labeling include in the Boxed WARNINGS and/or WARNINGS AND PRECAUTIONS sections, the following serious adverse outcome risks with long-term (chronic) use: <u>Estrogen-alone therapy</u>: • Endometrial Cancer • Cardiovascular Disorders (Stroke, Coronary Heart Disease and Venous Thromboembolism) • Ovarian Cancer • Probable Dementia Estrogen plus progestogen therapy: • Cardiovascular Disorders • Probable Dementia • Breast Cancer • Ovarian Cancer Noncontraceptive Estrogen Class Labeling, applied to all estrogen	In the face of recommendations to not prescribe progestogen opposition therapy to a woman with a uterus who is also using certain "low" dose and vaginally administered estrogen-alone therapy, which is counter to recommendations offered in Noncontraceptive Estrogen Class Labeling, FDA is concerned that its recommended mitigations strategies are no longer effective. To provide adequate advice regarding the current clinical recommendations by certain professional groups and experts, FDA believes that endometrial safety with respect to the risk for endometrial cancer with vaginally-administered low dose estrogen-alone products use, must be addressed in a postmarketing observational study evaluating the risk of endometrial cancer in nonhysterectomized postmenopausal women

	products and in part to some non-estrogen products (particularly those acting at the estrogen receptor) approved to treat moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause, recommends risk mitigating strategies such as: including the addition of progestogen opposition of the effects of estrogen in nonhysterectomized women, appropriate endometrial assessment of women demonstrating persistent vaginal spotting or bleeding, use of the lowest approved dosage strength of the approved estrogen product and use for the shortest duration appropriate to the woman's treatment goals and individuals risks. FDA has become aware that some professional organizations and individual experts are now advocating that certain "low" dose vaginally-administered estrogen-alone products can be administered without an opposing progestogen. Such recommendation is counter to that provided in Noncontraceptive Estrogen Class Labeling and thus negates the risk mitigation strategies recommended in that labeling.	(across all applicable age groups) who use "low" dose vaginal estrogen unopposed by progestogen therapy. The study should include safety data from the U.S. and other countries where the products are prescribed to ensure sufficient study sample size. The proposed study data source(s), domestic and international, should 1) include vaginal estrogen users across the entire postmenopausal age range, and 2) allow linkage to national cancer registries or adequate medication chart adjudication to confirm endometrial cancer cases. The median duration of follow-up should be at least 3 to 5 years after the first use of an unopposed vaginal estrogen product. FDA has requested the above PMR of this applicant.

2. Background

2.1 Original Review Cycle for NDA 208564

With the original 505(b)(2) NDA submission, the applicant sought approval for the 4, 10, (b) (4) mcg dosage strengths of estradiol vaginal insert for the indication of treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

To support the NDA, the applicant conducted five (5) clinical trials including three (3) phase 1 trials, one (1) phase 2 trial proof-of-concept trial and one (1) double-blind, and placebo-controlled 12-Week phase 3 trial (Trial TXV14-01) with the to-be-marketed formulation.

NDA 208564 was submitted by TherapeuticsMD on July 7, 2016. The NDA received a complete response (CR) decision on May 5, 2017. Deficiencies discussed in the CR Letter included the following:

- Clinical Safety

  1. Your application does not provide long-term endometrial safety data for the 4, 10, (b) (4) mcg estradiol vaginal inserts. Sufficient assessment of endometrial histology to support chronic use is critical to the safety evaluation of unopposed estrogen and to ensure adequate labeling for the safe use of your product. In making this determination, we have considered the following:
    - Treatment of moderate-to-severe dyspareunia, due to menopause, involves a chronic duration.
    - Unopposed estrogen use in a postmenopausal woman with a uterus increases the risk of endometrial hyperplasia/cancer.
    - 12-week safety data from Trial TXV14-01 are inadequate to assess long-term endometrial safety of your estradiol vaginal insert.
    - Long-term endometrial safety data with your product are necessary to ensure its safe use.
      - Clinical practice allows the chronic treatment of local vaginal symptoms related to menopause, such as dyspareunia, with vaginally administered estrogen without opposing progestin therapy to mitigate the risk of endometrial hyperplasia and cancer in women with a uterus.
      - Proliferative changes of the endometrium were seen with your product in some women at 12 weeks of treatment compared to none on placebo. Based on these 12-week endometrial changes, it is unclear, without long-term data, whether your product could be used without an opposing progestin even if it is intended for local vaginal use.

- Long-term endometrial safety information with your product in labeling is essential to guide prescribers' decisions regarding endometrial surveillance and the need for progestin therapy with the chronic use of your product in a woman with a uterus.
- If long-term endometrial data are not reassuring and indicate that your product must be co-administered with a progestin for adequate endometrial protection, then the safety and efficacy of the co-administered drugs will need to be demonstrated.

2. The safety evaluation of your product is expected to quantify and characterize the general safety of the drug over a reasonable duration consistent with its intended chronic use. Such extended duration of exposure is needed to adequately characterize the pattern of drug-related adverse reactions over time or to detect adverse reactions that may occur only with a longer duration of treatment.

To address the deficiencies [1and 2], you will need to conduct and provide data from a long-term endometrial trial of sufficient size and duration to adequately characterize endometrial safety with your product. This trial should also collect and characterize the long-term general safety profile of your product. You are encouraged to request a meeting with us to discuss the details of such a trial.

The reader is also referred to the CDTL Original Cycle Review archived May 04, 2017 for a summary discussion of the pre-decisional discipline reviews, discussion and conclusions in the original review cycle.

2.2 Notable Post-Decisional Regulatory Activity for NDA 208564

Significant post-decisional regulatory activity includes the following:

- **June 14, 2017** – Type A meeting was held with TherapeuticsMD. Per the applicant the stated purpose was to "gain clarification regarding the Agency's Complete Response Letter and the recommendation to provide additional endometrial and general safety data.". The meeting package contained the applicant's plan for the resubmission of NDA 208564 (b) (4) for approval of the 4 mcg and 10 mcg dosage strengths of estradiol vaginal inserts, following the Agency's draft 2005 labeling Guidance for Industry , entitled "FDA Guidance for Industry, "Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommended Prescribing Information for Health Care Providers and Patient Labeling", along with a limitation of use statement that the product was "NOT STUDIED FOR LONGER THAN 12 WEEKS". Also included in the meeting package, was a proposal with study synopsis for a postmarketing 12-month long-term study of the 4 mcg and 10 mcg estradiol vaginal inserts.

The discussion included, but was not limited to, the following:

Question 1: Does the Division agree that, consistent with the draft 2005 Labeling Guidance, the current estrogen class labeling comprehensively communicates the long-term safety of estrogen drug products, including vaginal estradiol products with higher systemic absorption than TX-004HR [estradiol vaginal inserts]?

FDA Response:
The Agency's recommended estrogen-alone and estrogen plus progestin (progestogen) class labeling communicates in the BOXED WARNINGS and WARNINGS and PRECAUTIONS sections, long-term endometrial and general safety findings and recommendations based on data obtained with approved estrogen-alone and estrogen plus progestin drug products. In the absence of adequate and sufficient data to advise otherwise, estrogen-alone and estrogen plus progestin class labeling has been applied to all estrogen-alone and estrogen plus progestin (progestogen) products, irrespective of dosage strength or route of administration, which are approved for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause and/or treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) due to menopause. Additional non-class efficacy and safety findings may be included in the labeling for each individual product based on their respective clinical trial(s) conducted to support the indication(s).

However, we have become aware that prevailing clinical guidelines for the treatment of signs and symptoms of vulvar vaginal atrophy due to menopause have recommended, inconsistent with the Boxed Warning, that administration of a progestogen is not necessary for women treated with certain vaginally-administered "low" dose estrogen-alone products. These recommendations appear to be based largely on pharmacokinetic data (serum estrogen concentrations) and with one exception, short-term clinical trials, but, importantly, do not take into account the potential for adverse endometrial effects from local exposure to vaginally-applied estrogens. Because clinical guidelines are influential in guiding patient care, there is compelling reason to believe that health care providers follow their recommendations of not generally administering a progestogen for endometrial protection, despite the information and advice provided in class labeling. Therefore, class labeling for certain vaginally-administered "low" dose estrogen-alone products alone may not provide adequate risk communication about and risk mitigation against endometrial cancer in real world clinical practice. Given this circumstance, it is essential to have long-term endometrial safety data with your product in labeling, at the time of approval, to adequately guide prescribers' decisions concerning endometrial surveillance and the need for progestogen therapy.

Question 2: Does the Division agree that the current class labeling would be appropriate for the 4 µg and 10 µg strengths of TX-004HR?

FDA Response:

The current class labeling will not be sufficient to support approval of your product with only 12 weeks of endometrial data for the reasons explained in our response to Question 1.

Question 3: Does the Division agree that the proposed clinical study is properly designed to provide the requested long-term endometrial and general safety of TX-004HR?

FDA Response:
To address the deficiencies precluding approval, you will need to conduct a pre-approval endometrial and general safety trial with TX-004HR of a minimum of one year duration, for the reasons outlined in our May 5, 2017, Complete Response letter. Based on the context of use of these products in the real-world, generally without a progestogen, data of sufficient duration of use with locally administered "low" dose estrogen-alone products are important to ensuring the safe use of these products. Be advised that we are deliberating the adequate duration of endometrial safety evaluation for these approved and investigational estrogen-alone products, which would include your product; such safety evaluation may span multiple years.

DBRUP provided comments and recommendation on the proposed 12-month, phase 3 Trial TXV17-01 protocol, and requested that TherapeuticsMD submit a final protocol for review and comment.

Question 4: Notwithstanding the study synopsis proposing to evaluate vaginal dryness associated with VVA, does the Division agree that only safety data needs to be collected in the proposed postmarketing long-term safety study?

FDA Response:
No. See our response to Question 3.

Question 5: Does the Division agree with TherapeuticsMD's proposal for resubmission of NDA 208564?

FDA Response:
No, we do not agree. Refer to our responses to Questions 3 and 4. We do not agree with your proposed postmarketing clinical trial for the 4 mcg and 10 mcg estradiol vaginal inserts.

An overall discussion occurred between the Agency and TherapeuticsMD in the Type A meeting:

- TherapeuticsMD noted that the Women's Health Initiative (WHI) Observational Sub-trial has collected data on real-world use of vaginal estradiol products and may be able to provide safety data to better understand and support the safe use of estrogen-alone products administered vaginally.

- TherapeuticsMD discussed the research of one of its consultants, Dr. James Liu, which concluded that TX-004HR, which is administered to the lower third of the vagina, will not appreciably result in uptake and effect on the endometrium.

- **July 7, 2017** - Office of Surveillance and Epidemiology (OSE) was consulted to review manuscript of the WHI Observational Sub-trial, as discussed at the June 14, 2017 Type A Meeting, and provide assessment of data. Additionally, OSE was asked to review a 2016 publication by Mørch et al.[3] on the risk of endometrial cancer with "low dose" vaginally administered estrogen products in postmenopausal women.

  OSE concluded that the WHI study and the Mørch study both suggest a potential elevated risk for endometrial cancer with low dose vaginal estrogen use. Unfortunately, neither study reported the risk estimates by dose or duration of use, and neither was able to meet FDA's regulatory need in determining a suitable cut-off dose for effective and safe "low-dose" vaginal estrogen use. The evidence suggests a higher risk for endometrial cancer risk with vaginal estrogen use among postmenopausal women with VVA symptoms. However, given the limitations of the WHI study and the incomplete reporting of the Mørch study results, a definite conclusion can't be drawn on the association between use of "low" dose vaginally-administered estrogen products and risk of endometrial cancer. The reader is encouraged to refer to the OSE review archived in DARRTS on October 20, 2017, for detailed findings.

- **July 19, 2017** - TherapeuticsMD submitted a Request for Dispute Resolution to the Office of Drug Evaluation 3, based on their opinion that:

  1. "DBRUP never advised TherapeuticsMD that the 505(b)(2) application would be deficient without endometrial and general safety data from a long-term (e.g., 12-month) study of TX-004HR, though the Division knew that the Company's clinical development program did not include a long-term endometrial and general safety study of TX-004HR.
  2. TherapeuticsMD's 505(b)(2) application for TX-004HR is not deficient because it provides or references all of the long-term endometrial and general safety data that is required.
  3. Based on its numerous communications and interactions with DBRUP and the 2003 Clinical Evaluation Guidance, TherapeuticsMD conducted a 12-week, phase 3 clinical trial (Trial TXV14-01) of TX-004HR that evaluated efficacy and safety, including endometrial biopsies at Baseline and Week 12. There were no cases of endometrial hyperplasia or endometrial cancer and no signal of exogenous endometrial stimulation in the 12-week clinical trial.

[3] Mørch LS, Kjaer SK, Keiding N, Lokkegaard E, Lidegaard O. The influence of hormone therapies on type I and II endometrial cancer: A nationwide cohort study. Int J Cancer. 2016; 138(6):1506-15

4. The current estrogen class labeling proposed for TX-004HR adequately communicates the long-term safety of the product and therefore supports approval of TherapeuticsMD's 505(b)(2) application. All currently approved estrogen products have labeling based on this guidance. The proposed labeling for TX-004HR likewise is based on and is consistent with the 2005 Labeling Guidance.

5. There were no cases of endometrial hyperplasia or endometrial cancer in the 12-week clinical trial. Twelve weeks is a valid and reliable measurement for endometrial evaluation based on the dosing regimen for TX-004HR that includes a daily loading phase for two weeks at the start of treatment (when the estradiol level will ostensibly be highest), followed by a maintenance phase of one insert administered vaginally twice weekly thereafter.

6. Endometrial proliferation was only reported in one subject in the 10 mcg arm (1/91) with no reported proliferation in the 4 mcg arm. This incidence rate is well within background rates of the general postmenopausal population and lower than the rates reported in the placebo groups of other studies in a similar population (ranging from 3.2% to 10.7%). One case of endometrial proliferation is not suggestive of a signal for endometrial stimulation and, in any event, endometrial proliferation is not a signal for endometrial cancer.

7. The 4 mcg dose of TX-004HR, when approved, will be the lowest dose available for postmenopausal women with VVA who may seek treatment for moderate to severe dyspareunia."

- **July 21, 2017** - TherapeuticsMD submitted a "Formal Dispute Resolution Request - Withdrawal Without Prejudice" after discussion with representatives from the Center for Drug Evaluation and Research's Dispute Resolution Team.

- **August 3, 2017** - Agency sent a General Advice letter to TherapeuticsMD with the following information:
    - We are currently conducting a comprehensive review of the published literature regarding the use of vaginal estrogen products and the risk of endometrial hyperplasia or cancer. Our review will include the findings from the WHI-Observational Study; we are working with the study's investigators to gain a full understanding of its strengths and limitations in assessing the risk of endometrial cancer in users of vaginal estrogen products relative to non-users.
        - To aid in our review, we request that you submit, by September 18, 2017, all literature references that provide an evaluation of vaginal estrogen use and risk of endometrial hyperplasia or cancer, regardless of positive or negative findings, to your NDA. In this submission, also provide your critical review and interpretation of the body of literature overall and by dose, if the information is available. The findings of the 2016 Mørch et al. publication identified below should be discussed in your review:

    - Mørch LS, Kjaer SK, Keiding N, Lokkegaard E, Lidegaard O. The influence of hormone therapies on type I and II endometrial cancer: A nationwide cohort study. Int J Cancer. 2016; 138(6):1506-15.
  - We propose a meeting with you in November 2017 to provide you a status update of our review of the published literature and discuss potential next steps for your application."

- **September 14, 2017** - TherapeuticsMD submitted a Clinical Information Amendment: Response to the General Advice Letter dated August 3, 2017 Request for a Literature Review.
  - See the Medical Officer Review, Subsection 8.2 Review of the Safety Database, archived on November 15, 2017, for a summary of the quality of evidence provided by TherapeuticsMD in the September 14, 2017 amendment.
  - See also the Memorandum to the File, archived November 15, 2017, for a full discussion of the information submitted in the September 14, 2017 Clinical Information Amendment.

- **September 19, 2017** - Type B 2017 CMC Meeting was held with TherapeuticsMD. See the archived meeting minutes for specific FDA CMC recommendations. FDA also provided the following general comments:
  - We acknowledge the challenges encountered with developing robust analytical procedures for the determination of assay, impurities and dissolution of your drug product. Although we find the current tests and acceptance criteria adequate for quality control purposes, the methods do not appear to be suitably robust for regulatory use, i.e., they cannot be readily replicated in another laboratory. We also acknowledge that the current USP monograph for estradiol vaginal inserts, which is based on a tablet-like formulation, may not be suitable for your liquid-filled soft gelation capsule-based formulation.
  - The Agency expects that robust analytical procedures will be established, and that you will work with the USP to revise the monograph.
  - While we recommend that these issues be addressed prior to resubmission of the NDA, we understand that resolution of the problems will require some time. Depending on the planned timing of the NDA submission, we would consider accepting the development and validation of robust analytical procedures as post-marketing commitments. We recommend that you propose a timeline for completing the necessary activities. In any case, the relevant sections of Module 3 should be updated to reflect any changes to the analytical procedures and (re)validation activities.
- **November 03, 2017** – Type C guidance meeting was held with TherapeuticsMD to update the sponsor on the status of the FDA review of the published literature

submitted by the sponsor on September 14, 2017. The following items were discussed:

Question 1: Given the supplemental information provided to the NDA since issuance of the CRL, does the Division agree that TherapeuticsMD's proposal for resubmission of NDA 208564 adequately addresses the CRL?

FDA Response:

At this time, we understand that you propose to resubmit NDA 208564 to support approval of estradiol vaginal inserts 4 mcg and 10 mcg with non-contraceptive estrogen class labeling, and to conduct a post-marketing 12-month endometrial safety trial.

We have reviewed in detail the Crandall et al. and the Mørch et al. papers, conducted a thorough review of the literature, and considered your summary of that literature. At this time, we find that the available information does not support definitive conclusions regarding the endometrial safety of long-term use of unopposed vaginal estrogen products in postmenopausal women for the treatment of a moderate to severe symptom of vulvar and vaginal atrophy due to menopause.

The objective of this meeting is to engage in discussion regarding the types of information that would support resubmission of NDA 208564. Listed below are the two deficiencies identified in the May 2017 Complete Response (CR) letter. Also provided are examples of the types of information that you may submit to address these deficiencies as stated in the CR letter, as well as alternative approaches that we would like to discuss with you. We remind you that the adequacy of your resubmission will be a review issue.

1. *Your application does not provide long-term endometrial safety data for the 4, 10, (b) (4) mcg estradiol vaginal inserts. Sufficient assessment of endometrial histology to support chronic use is critical to the safety evaluation of unopposed estrogen and to ensure adequate labeling for safe use of your product.*

   The CR letter indicates that to address this deficiency, you will need to conduct and provide data from a long-term endometrial trial of sufficient size and duration to adequately characterize endometrial safety with your product. We recognize the challenges with conducting a sufficiently long and large enough clinical trial to address this concern, as well as the fact that there are uncertainties with regard to the long-term endometrial safety of approved low-dose vaginal estrogen products. Therefore, an alternative approach could be to conduct a required post-marketing, observational study to identify the incidence of endometrial cancer associated with long-term use of unopposed low dose vaginal estrogen products in postmenopausal women for the indication of treatment of a moderate to severe symptom (dyspareunia or vaginal atrophy) of vulvar and vaginal atrophy due to menopause. We are considering a

post-marketing required study (PMR) for such an observational study with these products. The proposed study data source(s), domestic or international, should 1) include vaginal estrogen users across the entire postmenopausal age range, and 2) have linkage to national cancer registries to identify confirmed endometrial cancer cases. The median duration of study follow up should be 3 to 5 years or longer after first use of an unopposed vaginal estrogen product, with adequate numbers of long-term users to assess the risk in this population, and adequate post-exposure follow-up to capture the outcome. Appropriate comparison groups are needed to allow risk estimates for endometrial cancer, such as non-users and users of combined low dose vaginal estrogen plus progestogen. Key baseline covariates, such as body weight, should be measured and controlled to reduce confounding. (b) (4)

Should you decide to pursue this option; final details of the PMR should be agreed-to by the Agency.

Discussion:

- FDA indicated that a required PMR long-term observational study to identify the incidence of endometrial cancer associated use of unopposed low dose vaginal estrogen products in postmenopausal women for the indication of treatment of a moderate to severe symptom (dyspareunia or vaginal atrophy) of vulvar and vaginal atrophy due to menopause is an acceptable approach to provide long-term endometrial safety data for your estradiol vaginal insert.
- The Food and Drug Administration (FDA) indicated that it was premature to discuss the PMR in detail.
  - To address the CR letter deficiency for endometrial safety, FDA recommended that TherapeuticsMD provide a synopsis of their proposal for the required post-marketing study in the resubmission.
- TherapeuticsMD acknowledged the need for a PMR and stated their intention to work closely with the Agency on protocol development.
  - TherapeuticsMD committed to providing a protocol synopsis in their resubmission.
- FDA reiterated that the data sources selected for the PMR study should be able to support a hypothesis testing safety study, with the capability of capturing and confirming cancer cases. Drug exposure should reflect the real-world user experience. The study should be sufficiently powered and provide follow-up of at least 3 years.

2. *The safety evaluation of your product is expected to quantify and characterize the general safety of the drug over a reasonable duration consistent with its intended chronic use. Such extended duration of exposure is needed to adequately characterize the pattern of drug-related adverse reactions over time or to detect adverse reactions that may occur only with a longer duration of treatment.*

   The CR letter indicates that the long-term endometrial trial that would satisfy Deficiency #1 above could adequately characterize the general safety of your product. An alternative approach could be reliance on published literature via the 505(b)(2) regulatory pathway to support general safety and chronic use drug exposure for estradiol vaginal inserts 4 mcg and 10 mcg (the existing literature, however, will not be able to adequately characterize endometrial safety - see our comments above). Reliance on the published literature requires that you provide a "bridge" to the published literature. Such a bridge can be a scientific-supported rationale that the literature is scientifically sound and relevant to the proposed product, thereby supporting that reliance on the literature is scientifically appropriate. If the published literature describes a brand name product(s), then your application will rely on FDA's finding of safety and effectiveness for that listed drug(s), and you will also have to provide any necessary patent certifications or statements to address such reliance. Refer to the 505 (b)(2) Regulatory Pathway section below.

   In summary, if estradiol vaginal inserts 4 mcg and 10 mcg were to be approved based on reliance on the published literature to support general safety and chronic use drug exposure, you would receive non-contraceptive estrogen class labeling for general safety information, and a requirement for a post-marketing study to adequately characterize endometrial safety with long-term use of your product.

   Discussion:

   - TherapeuticsMD indicated that the published literature that will be submitted to support general safety of their proposed product is largely non-product specific. FDA reiterated that if the published literature describes a listed drug(s), that is considered reliance on FDA's finding of safety for that listed drug(s) and TherapeuticsMD should provide an appropriate patent certification or statement for each listed drug relied upon. FDA also reiterated that the "bridge" to the published literature is a scientific rationale establishing that reliance on the studies described in the literature is scientifically appropriate.

- FDA explained that TherapeuticsMD's proposal to provide data from cross-study comparisons between their proposed product and listed drugs to demonstrate similar or lower exposure is generally not acceptable for establishing relative bioavailability between products, but may be included as part of their scientific rationale to rely on the published literature to support general safety of the proposed product.
- FDA emphasized that comparison of estrogen exposure through cross study comparisons should not be the sole source of evidence to address the lack of long-term general safety information as outlined in the Complete Response Letter. The cross-study comparison will only provide a broad qualitative overview of the relative systemic exposure of the proposed product and other estrogen products used in the literature and may be considered as part of the Sponsor's scientific bridge to the literature. A cross-study comparison will not provide a precise comparison of systemic estrogen exposures.
- TherapeuticsMD acknowledged the Agency's advice and committed to submitting a full overview of studies in the literature that will be used to support the general safety of their product, as well as their scientific justification for reliance on such literature. The NDA resubmission will include a mapping table.

3. Product Quality

In the original review cycle, Office of Product Quality (OPQ) Review Team concluded that, in its present form, TherapeuticsMD's 505(b)(2) New Drug Application 208564, for estradiol vaginal inserts, 4 mcg, 10 mcg, (b) (4) per vaginal insert is not ready for approval. Labeling (package insert, container/carton) negotiations have not been completed, and in its present form, the labeling does not comply with the requirements under 21 CFR 201. There were no other chemistry, manufacturing and control (CMC) approvability issues. See the OPQ Original Cycle Review Summary of Dr. Mark Seggel, archived in Panorama April 17, 2017. Because of Clinical CR deficiencies (see Background -Regulatory History above), labeling deficiencies and comments were not conveyed to the applicant during the original review cycle.

Though other than labeling there were no other chemistry, manufacturing or control (CMC) CR issues, CMC non-approvability issues were provided to the applicant as "Additional Comments" in the Agency's May 5, 2017 CR letter. These comments were:

- We remind you that the current USP includes a monograph for Estradiol Vaginal Inserts. We understand that the current USP monograph may not be a suitable public standard for your new drug product. However, there is an expectation that your product will conform to the compendial monograph requirements. Alternatively,

deviations from the monograph requirements should be identified on your product labels. We recommend that you petition the USP with proposed revisions to the monograph in order to accommodate your new drug product. Please see the following link for more information about that USP process: http://www.usp.org/usp-nf/pending-monographs.

- Specifically, we note differences in assay test method and acceptance criteria, the dissolution test method and acceptance criteria, and in the procedure for determining related substances.

- The proposed analysis of estradiol-related compounds and degradation impurities by HPLC-MS may be acceptable for quality control purposes in the firm's laboratory but is currently unacceptable for regulatory purposes because the method does not work with a similar mass spectrometer in two different locations. It is therefore incumbent upon you to propose methods that are suitable for regulatory purposes.

- With regard to the dissolution test method, we recommend that you perform dissolution method validation in accordance with US<1092>, The Dissolution Procedure: Development and Validation, and adopt appropriate acceptance criteria.

As noted in the above discussion of post-decisional regulatory activity, CMC met with the applicant on September 19, 2017 to discuss the above OPQ items and communicated the following to the applicant:

- The Agency expects that robust analytical procedures will be established, and that you will work with the USP to revise the monograph.

- While we recommend that these issues be addressed prior to resubmission of the NDA, we understand that resolution of the problems will require some time. Depending on the planned timing of the NDA submission, we would consider accepting the development and validation of robust analytical procedures as post-marketing commitments. We recommend that you propose a timeline for completing the necessary activities. In any case, the relevant sections of Module 3 should be updated to reflect any changes to the analytical procedures and (re)validation activities.

OPQ has determined that because the TherapeuticsMD product is a different formulation that is quite distinct from the tablet formulation (i.e., Vagifem) upon which the USP monograph is based, and because a new, lower strength (4 mcg) is proposed, the USP monograph is not a suitable public standard for TherapeuticsMD's new drug product. TherapeuticsMD should therefore petition the USP with proposed revisions to the monograph in order to accommodate TXMD's new drug product.

In response to May 5, 2017 Additional Comments in the CR Letter and the September 19, 2017, Type C Advice Meeting, TherapeuticsMD proposed the following post-marketing commitments (PMC) (per email correspondence dated January 23, 2018; see Attachment IV).

1. Develop, and if feasible, validate new regulatory methods for known and unknown estradiol impurities (related compounds) in the drug product.

2. Perform a revalidation of the dissolution method TxMD-003 in accordance with requirements of USP using one batch of each strength of the for-market formulations manufactured by the proposed commercial manufacturer.

TherapeuticsMD further proposes that PMC 1 will be closed upon submission of a Prior Approval Supplement and completion of PMC 2 will be reported in the first NDA annual report.

These PMCs are acceptable from the OPQ perspective. The following Product Quality PMC/PMR Development Templates were archived in DARRTS for NDA 208564:

- PMC 1 (#3407-1) – Develop and validate a new regulatory method capable of detecting known and unknown estradiol-related impurities in the drug product
  Archived in DARRTS on May 14, 2018

  - Review issue and study goal
    The current analytical method (HPLC/MS) for the detection of the estradiol-related impurities has been shown to be capable of detecting and quantitating the targeted known impurities of estradiol based on the detection technique used. Mass spectrometric detection is capable of the detecting impurities based molecular mass if and only if the impurity is ionized by the selected ionization technique and polarity. Therefore, mass spectrometric technique is not considered appropriate techniques for detection of non-targeted or unknown impurities.

    The current impurity method in conjunction with assay method has been accepted as a quality control method that provide sufficient information to assure safety and efficacy from the CMC perspective. However, the method is not capable of identifying all impurities including nontargeted, and unknown as well as properly quantitating the total estradiol related impurities.

    The applicant should develop and validate a new analytical method capable of detecting and quantitating all known and unknown estradiol-related impurities in the drug product. The applicant should also submit a revised drug product specification updated for estradiol-related impurities
    according to the new method.

  - Type of study – Other
  - Agreed-upon study
    - Development and validation of an analytical method capable of detecting and quantitating known and unknown estradiol-related impurities.
    - Establish revised acceptance criteria for estradiol-related impurities, if necessary, according to the new analytical method

Based on FDA feedback on the development report, the applicant will finalize method validation and submit a Prior Approval Supplement providing for changes to the analytical methods and acceptance criteria for drug product impurities.

- Timetable
  - Development Report Submission: June 2018
  - Study Completion: November 2018
  - Final Report Submission: November 2018

- PMC 2 (#3407-2) – Perform a revalidation of the dissolution method TxMD-003 in accordance with requirements of USP using one batch of each strength of the for-market formulations manufactured by the proposed commercial manufacturer. Archived in DARRTS on May 04, 2018
  - Review issue and study goal
    Dissolution method (dissolution and analytical testing method) was reviewed and found acceptable in the first review cycle. However, there was a concern that the analytical method is not robust for regulatory use. Dissolution method validation had acceptance criteria for certain validation parameters that were more permissive than those recommended in the USP <1092> which may impact quality of data obtained. The applicant should perform dissolution method validation per USP <1092> and adopt appropriate acceptance criteria for validation parameter
  - Type of study
    Dissolution testing
  - Agreed-upon study:
    Revalidate dissolution test method in accordance with USP <1092>, The Dissolution Procedure: Development and Validation.
  - Timetable
    - Development Report Submission: June 2018
    - Final Report Submission: Submitted in the first NDA Annual Report

With respect to the drug substance, in the resubmission, the Applicant has submitted slightly revised specifications (see Drug Substance review archived in Panorama on March 1, 2018). The specifications were updated to be consistent with the drug substance manufacturer; that is, to include a footnote (“a”) that, at a minimum, one lot is tested annually for microbial limits. No other changes were made with respect to drug substance specifications. OPQ concluded that the specifications remain adequate to ensure control of the drug substance.

OPQ concludes that sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. The commercial drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status. The claimed categorical exclusion from the environmental assessment requirements is granted. OPQ

recommends approval from the CMC standpoint. For complete details of the OPQ evaluation of CMC issues with the original and resubmission of NDA 208564, the reader is referred to OPQ Review Summaries 1 and 2 by Dr. Mark Seggel, archived in Panorama April 17, 2017 and May 22, 2017, respectively.

▪ Nonclinical Pharmacology/Toxicology

In the original review cycle, Dr. Hatfield the non-clinical pharmacology and toxicology reviewer summarized the applicant's intent to rely on published literature for the nonclinical toxicology, genotoxicity and carcinogenicity sections of this NDA. This will inform Sections 8 and 13 of the labeling. The safety of estradiol is well-established and documented in the published literature following many years of clinical use. There are also a number of approved products that contain estradiol as the active pharmaceutical ingredient at the same or similar doses, and for the same or similar indication as TX-004HR (e.g. Vagifem, Femring, Estrace, and Estring). As such, the applicant did not conduct any nonclinical studies of their own for estradiol, and proposes to rely on relevant published literature to support the nonclinical safety of estradiol, and to inform nonclinical sections of labeling. Dr. Hatfield concluded that the literature that the applicant has submitted is adequate to support the nonclinical safety of estradiol without relying on previous findings of safety for an approved product. The applicant also conducted a 28-day repeat dose toxicity study in rabbits to evaluate the safety of the novel excipient (b) (4), which has been used in other approved products. However, there were no previously listed intravaginal dosage routes in the FDA Inactive Ingredient Database and the amount proposed for estradiol vaginal insert is considerably higher than the maximum potency amounts listed for topical cream/gel administration, or oral gel administration. The results of the completed study demonstrated that test article containing (b) (4) was not a vaginal irritant compared to control, and that the amount of (b) (4) present in the formulation is acceptable for use in the drug product. The 28-day repeat dose toxicity study in rabbits also bridges to literature data that documents the safety of estradiol via other routes of administration, and supports the vaginal use of this product. From a Preclinical Pharmacology/Toxicology standpoint, there were no approvability issues and the nonclinical data supported approval.

In the NDA 208564 resubmission, there is no new or updated nonclinical information. The applicant continues to seek approval via the 505(b)(2) pathway and intends to rely in part on published literature (estradiol) for the nonclinical toxicology, genotoxicity and carcinogenicity sections of this NDA, rather than the Agency's findings of safety and efficacy of an approved estradiol product. The submitted nonclinical literature will inform Sections 8 and 13 of the labeling. The literature originally submitted by the applicant is still considered adequate to support the nonclinical safety of estradiol without relying on previous findings of safety for an approved product. From a Pharmacology/Toxicology standpoint, the review team still recommends approval.

▪ Clinical Pharmacology

In the original review cycle, the Office of Clinical Pharmacology Review Team concluded that the NDA was acceptable. See their review archived in DARRTS on April 7, 2017.

To address the long-term general safety, as well as chronic exposure for this proposed chronically-administered estradiol product, the applicant proposed to rely on published literature via the 505(b)(2) pathway. The Office of Clinical Pharmacology performed a qualitative comparison of estrogen systemic exposure which relied on estrogen systemic exposure with use of the estradiol vaginal insert versus estrogen systemic exposure with use of oral estradiol tablets as presented in 1997 publication from Price et al4 versus. estrogen systemic exposure based on "FDA's previous findings of efficacy and safety" (i.e. the product labeling) with Premarin use. Additionally, information from the bioequivalence review of ANDA 040275 was reviewed as supportive of the Office of Clinical Pharmacology's review and conclusions, but not required.

The following Tables 1 and 2 presents these comparisons for estradiol and unconjugated estrone, respectively.

[4] Price TM, Blauer KL, et al. Single-Dose Pharmacokinetics of Sublingual Versus Oral Administration of Micronized 17-β Estradiol. Obstetrics & Gynecology; 1997; 89(3); 340-345.

Table 1: Estradiol Pharmacokinetics of Estrogen Products

Product	AUC0-24hr (pg.hr/mL)	Cmax (pg/mL)
Estradiol oral tablets, 1 mg[a]	823	34.0
TX-004HR vaginal insert, 10 mcg[b]	138.2	10.9
TX-004HR vaginal insert, 4 mcg[b]	91.7	6.5

[a] Price TM, Blauer KL, Hansen M, et al. Single-Dose Pharmacokinetics of Sublingual Versus Oral Administration of Micronized 17-β Estradiol. Obstetrics & Gynecology; 1997; 89(3); 340-345.
[b] NDA 208564; PK Sub-Study TXV14-01; baseline-unadjusted values on Day 1

Table 2: Unconjugated Estrone Pharmacokinetics of Estrogen Products

Product	AUC0-24hr (pg.hr/mL)	Cmax (pg/mL)
Estradiol oral tablets, 1 mg[a]	2923	169
TX-004HR vaginal insert, 10 mcg[b]	462.7	23.5
TX-004HR vaginal insert, 4 mcg[b]	290.2	15.8

[a] Price TM, Blauer KL, Hansen M, et al. Single-Dose Pharmacokinetics of Sublingual Versus Oral Administration of Micronized 17-β Estradiol. Obstetrics & Gynecology; 1997; 89(3); 340-345.
[b] NDA 208564; PK Sub-Study TXV14-01; baseline-unadjusted values on Day 1

The overall Office of Clinical Pharmacology Findings were as follows:

- A review of the analytical methods for each study was not possible and is therefore a limitation of this cross-study review. The fold changes are suggestive of higher estrogen exposure from estradiol oral tablets and Premarin oral conjugated estrogens; however, a direct, quantitative comparison to the proposed estradiol vaginal insert is not feasible due to the cross-study nature of comparison.
- In a cross-study comparison, the Office of Clinical Pharmacology Review - Addendum shows that the systemic estradiol exposure is 6.0- and 3.1-fold higher in AUC0-24 and

Cmax, respectively, with estradiol oral tablet, 1 mg (data from Price et al. publication), compared to TX-004HR, 10 mcg (data from sponsor's NDA).

- In a cross-study comparison, the Office of Clinical Pharmacology Review - Addendum shows that the systemic unconjugated estrone exposure is 6.3- and 7.2-fold higher in AUC0-24 and Cmax, respectively, with estradiol oral tablet, 1 mg (data from Price et al. publication), compared to TX-004HR, 10 mcg (data from sponsor's NDA).
- TX-004HR 4 mcg is known to have a lower systemic exposure than TX-004HR 10 mcg; therefore, systemic estrogen exposure from the 4 mcg dose is also lower than estradiol oral tablet, 1 mg.
- The Clinical Pharmacology review (DARRTS April 20, 2018) summarized a cross-study comparison showing that the systemic estradiol, estrone, and estrone conjugate exposure from Premarin, 2 x 0.3 mg oral tablets (data from approved label of NDA 04-782) was generally higher compared to TX-0004HR 10 mcg.

The Office of Clinical Pharmacology Division of Clinical Pharmacology-3 recommends approval from a Clinical Pharmacology perspective.

▪ Clinical Microbiology

Issues regarding revision of the drug substance specification to include a footnote ("a") that, at a minimum, one lot is tested annually for microbial limits, are discussed under Section 3 Product Quality. No Clinical Microbiology consult was necessary or requested.

▪ Clinical/Statistical- Efficacy

During the original review cycle three dosage strengths of estradiol vaginal insert were found to be efficacious with a statistically significant increase in the percentage of superficial vaginal cells and statistically significant decrease in the percentage of vaginal parabasal cells and statistically significant decrease in vaginal pH and statistically significant decrease in the mean change in severity from baseline. Table 10 from the CDTL Review in the original cycle, is reproduced below as Table 3.

Table 3: Efficacy Summary of Trial TXV14-01, modified Intent-to-Treat Population (mITT)

Co-Primary Endpoint	TX-004HR 4 mcg	TX-004HR 10 mcg	TX-004HR 25 mcg	Placebo
Dyspareunia				
Baseline				
(n)	186	188	186	187
Mean (SD)	2.7 (0.48)	2.6 (0.48)	2.7 (0.44)	2.7 (0.46)
Week 12				
(n)	178	176	174	183
Mean (SD)	1.18 (0.97)	1.03 (0.95)	1.03 (0.97)	1.45 (1.03)
Change from Baseline*				
LS Mean (S.E.)**	-1.50 (0.07)	-1.64 (0.07)	-1.67 (0.07)	-1.25 (0.07)
Difference from. placebo***	-0.25	-0.38	-0.42	--
p-value vs. placebo***	0.0156	0.0002	<0.0001	--
%Superficial Cells				
Baseline				
(n)	186	188	186	187
Mean (SD)	1.3 (1.24)	1.2 (1.23)	1.3 (1.16)	1.3 (1.31)
Week 12				
(n)	170	171	174	172
Mean (SD)	18.7 (19.54)	18.5 (19.95)	24.9 (24.23)	7.0 (14.7)
Change from Baseline (SD)				
Mean	-1.54 (1.04)	-1.68 (0.96)	-1.72 (0.94)	-1.28 (1.04)
LS Mean (SE)	17.50 (1.54)	16.72 (1.54)	23.20(1.53)	5.63 (1.54)
Difference vs. placebo****	11.87	11.09	17.57	--
p-value vs. placebo****	<0.0001	<0.0001	<0.0001	--
% Parabasal Cells				
Baseline				
(n)	186	188	186	187
Mean (SD)	52.3 (39.2)	51.3 (38.0)	53.5 (38.3	52.0 (39.2)
Week 12				
(n)	170	171	174	172
Mean (SD)	12.0 (22.3)	7.8 (18.5)	6.6 (16.6)	45.2 (40.3)
Change from Baseline				
Mean (SD)	-41.1 (41.6)	-43.8 (37.8)	-46.2 (40.0)	-6.3 (29.8)
LS Mean (SE)	-40.63 (1.75)	-44.07 (1.75)	-45.55 (1.74)	-6.73 (1.75)
Difference from. Placebo****	-33.90	-37.34	-38.82	--
p-value vs. placebo****	<0.0001	<0.0001	<0.0001	--

Co-Primary Endpoint	TX-004HR 4 mcg	TX-004HR 10 mcg	TX-004HR 25 mcg	Placebo
Vaginal pH				
Baseline				
(n)	186	188	186	187
Mean (SD)	6.3 (0.87)	6.3 (0.83)	6.3 (0.91)	6.3 (1.04)
Week 12				
(n)	170	171	174	174
Mean (SD)	1.1 (0.98)	0.9 (0.92)	1.0 (0.99)	1.4 (1.02)
Change from Baseline				
Mean	-1.33 (1.11)	-1.41 (1.03)	-1.37 (1.14)	-0.28 (0.07)
LS Mean (SE)	-1.32 (0.07)	-1.42 (0.07)	-1.34 (0.07)	
Difference vs. placebo	-1.03	-1.14	-1.06	--
p-value vs. placebo***	<0.0001	<0.0001	<0.0001	--

* Last Observation Carried Forward (LOCF)
**Difference vs. placebo is the (Week 12 mean for TX-004 minus baseline mean for TX-004) minus (Week 12 mean for placebo minus baseline mean for placebo).
*** ANCOVA: treatment as the main factor and baseline value as the covariate.
**** MMRM = Mixed Model Repeated Measures

Source: Adapted from Statistical Review Tables 6, 9, 10 and 11 page 10, 14 and 15; Medical Officer Review Tables 18 and 19, pages 57 and 58 and NDA 208564 Clinical Trial Report for TXV14-01, Table 25 page 84 of 3533

Abbreviations: mITT = modified Intent-to-Treat, LS = least square, SE = standard error, MMRM = mixed model repeated measures.

No additional efficacy studies were required or submitted to support the resubmission of the NDA. (b) (4)

- **Safety**

The applicant submitted an Integrative Summary of Safety (ISS) pooling the results of phase 2 Trial TXV13-01 and phase 3 Trial TXV14-01 to explore adverse events, vital signs and other clinical findings from physical examinations of women exposed to estradiol vaginal inserts up to 12 weeks of use. The clinical review team reviewed only phase 3 Trial TXV 14-01 to support the safety of estradiol vaginal insert up to 12 weeks of use. The reader is referred to the CDTL NDA 208564 Review archived in DARRTS on May 4, 2017 for the review of the 12-week safety data.

However, the applicant provided no information on long-term general and endometrial safety and chronic exposure for estradiol vaginal insert 4mcg, 10 mcg (b) (4) mcg. In the CR letter, FDA advised that "sufficient assessment of endometrial histology to support chronic use is critical to the safety evaluation of unopposed estrogen and to ensure adequate labeling for the safe use of your product. In making this determination, we have considered the following:

- Treatment of moderate-to-severe dyspareunia, due to menopause, involves a chronic duration.

- Unopposed estrogen use in a postmenopausal woman with a uterus increases the risk of endometrial hyperplasia/cancer.
- 12-week safety data from Trial TXV14-01 are inadequate to assess long-term endometrial safety of your estradiol vaginal insert.
- Long-term endometrial safety data with your product are necessary to ensure its safe use.
    - Clinical practice allows the chronic treatment of local vaginal symptoms related to menopause, such as dyspareunia, with vaginally administered estrogen without opposing progestin therapy to mitigate the risk of endometrial hyperplasia and cancer in women with a uterus.
    - Proliferative changes of the endometrium were seen with your product in some women at 12 weeks of treatment compared to none on placebo. Based on these 12-week endometrial changes, it is unclear, without long-term data, whether your product could be used without an opposing progestin even if it is intended for local vaginal use.
        - Long-term endometrial safety information with your product in labeling is essential to guide prescribers' decisions regarding endometrial surveillance and the need for progestin therapy with the chronic use of your product in a woman with a uterus.
        - If long-term endometrial data are not reassuring and indicate that your product must be co-administered with a progestin for adequate endometrial protection, then the safety and efficacy of the co-administered drugs will need to be demonstrated.
- The safety evaluation of your product is expected to quantify and characterize the general safety of the drug over a reasonable duration consistent with its intended chronic use. Such extended duration of exposure is needed to adequately characterize the pattern of drug related adverse reactions over time or to detect adverse reactions that may occur only with a longer duration of treatment.
- To address the deficiencies [1and2], you will need to conduct and provide data from a long-term endometrial trial of sufficient size and duration to adequately characterize endometrial safety with your product. This trial should also collect and characterize the long-term general safety profile of your product. You are encouraged to request a meeting with us to discuss the details of such a trial.

On June 14, 2017, the Agency met with TherapeuticsMD in Type A so that the company might "gain clarification regarding the Agency's Complete Response Letter and the recommendation to provide additional endometrial and general safety data." FDA explained its position that the Agency's recommended estrogen-alone and estrogen plus progestin (progestogen) class labeling communicates in the BOXED WARNINGS and WARNINGS and PRECAUTIONS

sections, long-term endometrial and general safety findings and recommendations based on data obtained with approved estrogen-alone and estrogen plus progestin drug products. In the absence of adequate and sufficient data to advise otherwise, estrogen-alone and estrogen plus progestin class labeling has been applied to all estrogen-alone and estrogen plus progestin (progestogen) products, irrespective of dosage strength or route of administration, which are approved for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause and/or treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) due to menopause. Additional non-class efficacy and safety findings may be included in the labeling for each individual product based on their respective clinical trial(s) conducted to support the indication(s).

However, we have become aware that prevailing clinical guidelines for the treatment of signs and symptoms of vulvar vaginal atrophy due to menopause have recommended, inconsistent with the Boxed Warning, that administration of a progestogen is not necessary for women treated with certain vaginally-administered "low" dose estrogen-alone products. These recommendations appear to be based largely on pharmacokinetic data (serum estrogen concentrations) and with one exception, short-term clinical trials, but, importantly, do not take into account the potential for adverse endometrial effects from local exposure to vaginally-applied estrogens. Because clinical guidelines are influential in guiding patient care, there is compelling reason to believe that health care providers follow their recommendations of not generally administering a progestogen for endometrial protection, despite the information and advice provided in class labeling. **Therefore, class labeling for certain vaginally-administered "low" dose estrogen-alone products alone may not provide adequate risk communication about and risk mitigation against endometrial cancer in real world clinical practice. Given this circumstance, it is essential to have long-term endometrial safety data with your product in labeling, at the time of approval, to adequately guide prescribers' decisions concerning endometrial surveillance and the need for progestogen therapy**.

On September 14, 2017, TherapeuticsMD submitted a Clinical Information Amendment (Sequence-0031) presenting a systematic literature search conducted on the use of vaginal estrogens and the risk of endometrial hyperplasia or cancer.

On October 20, 2017, the Division of Epidemiology II (DEPI II) completed an assessment of the quality of evidence provided by TherapeuticsMD including an epidemiological assessment of the recently published Women's Health Initiative (WHI) Observational Study (Crandall CJ, et al. 2017)[5], and the Danish study (Mørch LS, et al, 2016)[6].

The DEPI II Review concluded that "The WHI study and the Danish study **both suggest a potential elevated risk for endometrial cancer with low dose vaginal estrogen use.** Unfortunately, neither study reported the risk estimates by dose or duration of use, and neither was able to meet FDA's regulatory need in determining a suitable cut-off dose for effective

[5] Crandall CJ, Hovey KM, Andrews CA, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative observational study. Menopause; 25(1) (published ahead of print).

[6] Mørch LS, Kjaer SK, Keiding N, et al. The influence of hormone therapies on type I and II endometrial cancer: A nationwide cohort study. Int J Cancer. 2016;138(6):1506-1515.

and safe "low-dose" vaginal estrogen use. **We conclude that current evidence suggests a higher risk for endometrial cancer risk with vaginal estrogen use among postmenopausal women with VVA symptoms. However, given the limitations of the WHI study and the incomplete reporting of the Danish study results, a definite conclusion can't be drawn on the association between VE use and risk of endometrial cancer.**" See the DEPI II review archived October 20, 2017 for a discussion of the DEPI II assessment of the WHI Observational Study and the Danish study.

On November 15, 2017, the Clinical Team completed an assessment of the quality of evidence provided by TherapeuticsMD in the September 14, 2017 systematic literature search conducted on the use of vaginal estrogens and the risk of endometrial hyperplasia or cancer. Thirty-seven (37) articles/ abstracts were identified that included information regarding vaginal estrogen use and endometrial histology. Of the 37 articles/ abstracts identified, 20 were randomized, controlled clinical trials with drug exposure duration ranging from 2-weeks up to 52-weeks. In addition, the Clinical Information Amendment included prospective interventional, prospective observational, and retrospective observational/ registry studies. Non-US approved estriol vaginal products and non-estrogen prasterone vaginal inserts are not included in the publications reviewed.

Overall, the breath of the literature review conducted by TherapeuticsMD appeared complete in its scope for reports of endometrial histology, including endometrial hyperplasia or endometrial cancer, and the use of vaginal estrogens in postmenopausal women.
The Clinical Team did not identify additional major publications of randomized, controlled clinical trials utilizing US approved vaginally administered estrogen-alone drug products (for example, conjugated estrogens or estradiol). The Clinical Team did not agree with TherapeuticsMD's assessment that the published literature "does not support a risk of endometrial hyperplasia or endometrial cancer with vaginal estrogens. The Clinical Team concluded that safety data from published literature in the September 14, 2017 Clinical Information Amendment is not adequate to determine the general and endometrial safety and chronic use drug exposure safety risk of low-dose vaginal estrogens. "Therefore, this available published literature does not support definitive conclusions regarding the endometrial safety of vaginally administered unopposed low-dose vaginal estrogen products in postmenopausal women with moderate to severe vulvar and vaginal atrophy." See the Clinical Memorandum to the File, dated November 15, 2017 for a discussion of the literature search conducted by TherapeuticsMD on the use of vaginal estrogens and the risk of endometrial hyperplasia or cancer.

Following review of the applicant's September 14, 2017 Clinical Information Amendment (as discussed above), FDA met again with the applicant at a November 3, 2017 Advice Meeting. FDA acknowledged that the Agency recognized 1) the challenges with conducting a sufficiently long and large enough clinical trial to address the CR long term and endometrial safety concern and 2) the fact that there are uncertainties with regard to the long-term endometrial safety of approved low-dose vaginal estrogen products. FDA offered that an alternative approach to conducting a clinical trial could be to conduct a required post-marketing, observational study to identify the incidence of endometrial cancer associated with long-term use of unopposed low dose vaginal estrogen products in postmenopausal women for

the indication of treatment of a moderate to severe symptom (dyspareunia or vaginal dryness) of vulvar and vaginal atrophy due to menopause.

FDA stated that it is considering a post-marketing required study (PMR) for such an observational study with these products. FDA indicated that a required PMR long-term observational study to identify the incidence of endometrial cancer associated use of unopposed low dose vaginal estrogen products in postmenopausal women for the indication of treatment of a moderate to severe symptom (dyspareunia or vaginal atrophy) of vulvar and vaginal atrophy due to menopause is an acceptable approach to provide long-term endometrial safety data for your estradiol vaginal insert. The proposed study data source(s), domestic or international, should 1) include vaginal estrogen users across the entire postmenopausal age range, and 2) have linkage to national cancer registries to identify confirmed endometrial cancer cases. The median duration of study follow up should be 3 to 5 years or longer after first use of an unopposed vaginal estrogen product, with adequate numbers of long-term users to assess the risk in this population, and adequate post-exposure follow-up to capture the outcome. Appropriate comparison groups are needed to allow risk estimates for endometrial cancer, such as non-users and users of combined low dose vaginal estrogen plus progestogen. Key baseline covariates, such as body weight, should be measured and controlled to reduce confounding. (b) (4)

The CR letter indicated that the proposed long-term endometrial clinical trial (or alternatively the required PMR observational study) that would address the deficiency with respect to the lack of long-term endometrial safety could also adequately characterize the general safety of estradiol vaginal inserts. However, at the November 3, 2017 Advice Meeting, FDA offered an alternative approach of reliance on published literature via the 505(b)(2) regulatory pathway to support general safety and chronic use drug exposure for estradiol vaginal inserts 4 mcg and 10 mcg (noting that the existing literature would not be able to adequately characterize endometrial safety). Reliance on the published literature requires that that the applicant provide a "bridge" to the published literature. Such a bridge could be a scientific-supported rationale that the literature is scientifically sound and relevant to the proposed product, thereby supporting that reliance on the literature is scientifically appropriate. If the published literature describes a brand name product(s), then NDA 208564 would rely on FDA's finding of safety and effectiveness for that listed drug(s), and the applicant would also have to provide any necessary patent certifications or statements to address such reliance

Finally, FDA indicated that if estradiol vaginal inserts 4 mcg and 10 mcg were to be approved based on reliance on the published literature to support general safety and chronic use drug exposure, the product would receive Noncontraceptive Estrogen Class Labeling for general safety information, and as a condition of approval there would be a requirement for a post-marketing study to adequately characterize endometrial safety with long-term use of estradiol vaginal inserts.

6 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Literature to Support Long-Term General Safety and Chronic Drug Exposure:

No new safety data was included in the resubmission of NDA 208564.

Consistent with the guidance provided by the Agency at the November 3, 2017 Advice Meeting, TherapeuticsMD resubmitted their NDA with support of long-term general safety and chronic drug exposure of the 4 mcg and 10 mcg dosage strengths of estradiol vaginal inserts, based on literature which support the Agency's Draft 2005 Guidance for Industry, entitled " Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommended Prescribing Information for Health Care Providers and Patient Labeling" (henceforth referred in this review as Draft 2005 Noncontraceptive Estrogen Class Labeling)[7] and other published literature on higher dosage strength estrogen products[8] via the 505(b)(2) regulatory pathway. The applicant's scientific support (bridge) for reliance on the published literature is based on the scientific- rationale that the literature is scientifically sound and supports a well-established

[7] Food and Drug Administration, Draft Guidance for Industry, "Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommended Prescribing Information for Health Care Providers and Patient Labeling." November 2005

[8] Price TM, Blauer KL, Hansen M, Stanczyk F, Lobo R, Bates GW. Single-dose pharmacokinetics of sublingual versus oral administration of micronized 17β-estradiol. Obstet Gynecol 1997; 89:340-5.

long-term and chronic use safety profile of estrogens, spanning greater than 50 years of use. Such literature is based on estrogen products with substantially higher dosage strengths (up to 10^5-fold) compared to the proposed 4 and 10 mcg dosage strengths of estradiol vaginal inserts. The applicant's bridge between the referenced literature and the proposed 4 and 10 mcg dosage strengths of estradiol vaginal inserts consists of three major elements:

1. The proposed 4 and 10 mcg dosage strengths of estradiol vaginal inserts are part of the estrogen class of products, which have been studied and reported upon in the referenced literature.
2. FDA's recognition of the scientific soundness of the literature forming the basis for Noncontraceptive Estrogen Class Labeling.
3. The proposed 4 and 10 mcg dosage strengths of estradiol vaginal inserts and the systemic exposure from use of these products are both lower than the estrogen products studied and reported upon in the referenced literature.

The following literature is submitted (listed in alphabetical order) and relied-upon in part to support the estradiol vaginal insert 505(b)(2) application with respect to long-term general safety and chronic drug exposure:

1. Anderson GL, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures. The Women's Health Initiative Randomized Trial. JAMA 2003;290:1739-1748
2. Bailar JC. Thromboembolism and oestrogen therapy. Lancet 1967;2(7515):560
3. Bennion LJ, et al. Effects of oral contraceptives on the gallbladder bile of normal women. N Engl J Med 1976;294(4):189-92
4. Beral V et al. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet 2015;385(9980):1835-1842.
5. Chlebowski RT, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. JAMA, 2003. 289:3243-3253.
6. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350(9084):1047-59
7. Collaborative Group for the Study of Stroke in Young Women. Oral contraception and increased risk of cerebral ischemia or thrombosis. N Engl J Med 1973:288:871-878
8. Curb JD, et al. Venous thrombosis and conjugated equine estrogen in women without a uterus. Arch Intern Med 2006;166:772-780
9. Cushman M, et al. Estrogen plus progestin and risk of venous thrombosis JAMA 2004;292:1573-1580

10. Grady D, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II). JAMA 2002;288:49-57

11. Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. Circulation 2006;113:2425-2434

12. Hsia J, et al. Conjugated equine estrogens and coronary heart disease. Arch Intern Med 2006;166:357-365

13. Hulley S, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605-613

14. Inman WHW, et al. Thromboembolic disease and the steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs. Br Med J 1970; 2(5703):203–209

15. Mack TM, et al. Estrogens and endometrial cancer in a retirement community. N Engl J Med 1976;294(23):1262-7

16. Mann JI, Inman WHW. Oral contraceptives and death from myocardial infarction. Br Med J 1975;2(5965):245-8

17. Pfeffer RI, Van Den Noort S. Estrogen use and stroke risk in postmenopausal women. Am J Epidemiol 1976;103(5):445-56

18. Rosenberg L, et al. Myocardial infarction and estrogen therapy in post-menopausal women. N Engl J Med 1976. 294:1256–1259

19. Rossouw JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007;297:1465-1477

20. Shumaker SA, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women. Women's Health Initiative Memory Study. JAMA 2004;291:2947-2958

21. Smith DC, et al. Association of exogenous estrogen and endometrial carcinoma. N Engl J Med 1975;293(23):1164-7

22. Stefanick ML, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA 2006;295:1647-1657

23. Stolley PD, et al. Thrombosis with low-estrogen oral contraceptives. Am J Epidemiol 1975;102(3):197-208

24. Surgically confirmed gallbladder disease, venous thromboembolism, and breast tumors in relation to postmenopausal estrogen therapy. A report from the Boston Collaborative Drug Surveillance Program, Boston University Medical Center. N Engl J Med 1974;290(1):15-9

25. Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. Br Med J, 1969. 2(5658):651-7.

26. Weiss NS, et al. Increasing incidence of endometrial cancer in the United States. N Engl J Med, 1976. 294(23):1259-62.

27. Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med 1975;293(23):1167-70.

Additionally, the applicant submitted Table 3 in NDA 208564 Section 1.11.4 Multiple Module Information Amendment to delineate which sections of the labeling for estradiol vaginal insert is reliant on the submitted published literature. This table is presented in modified form below as Table 4 of this review.

Table 4: Literature Support of Estradiol Vaginal Insert Long-Term Safety [505 (b)(2) mapping Table]

Relevant Section of Labeling[a]	Literature Relied Upon	Comments
Section 5 WARNINGS AND PRECAUTIONS		
5.2 Cardiovascular Disorders		
Stroke	Publication # 11 - Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. Circulation 2006;113:2425-2434.	Referenced in Current Estrogen Class Labeling
	Publication # 19 - Rossouw JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007;297:1465-1477.	Referenced in Current Estrogen Class Labeling
	Publication # 7 - Collaborative Group for the Study of Stroke in Young Women. Oral contraception and increased risk of cerebral ischemia or thrombosis. N Engl J Med 1973:288:871-878*	Historical Reference – Contraceptive Estrogens[b]
	Publication #17 - Pfeffer RI, Van Den Noort S. Estrogen use and stroke risk in postmenopausal women. Am J Epidemiol 1976;103(5):445-56*	Historical Reference – Noncontraceptive estrogen therapy[c]

Table 4: Literature Support of Estradiol Vaginal Insert Long-Term Safety [505 (b)(2) mapping Table] - continued

Relevant Section of Labeling[a]	Literature Relied Upon	Comments
Section 5 WARNINGS AND PRECAUTIONS		
5.2 Cardiovascular Disorders		
Coronary Heart Disease	Publication #12 - Hsia J, et al. Conjugated equine estrogens and coronary heart disease. Arch Intern Med 2006;166:357-365	Referenced in Current Estrogen Class Labeling
	Publication # 19 - Rossouw JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007;297:1465-1477.	Referenced in Current Estrogen Class Labeling
	Publication #13 - Hulley S, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605-613	Referenced in Current Estrogen Class Labeling
	Publication #10 - Grady D, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II). JAMA 2002;288:49-57	Referenced in Current Estrogen Class Labeling
	Publication #18 - Rosenberg L, et al. Myocardial infarction and estrogen therapy in post-menopausal women. N Engl J Med 1976. 294:1256–1259	Historical Reference – Noncontraceptive estrogen therapy.[c] See the MOR summary review Table 4 archived May 29, 2018. Limitations of this article: 1. dose of oral estrogen not identified; 2. duration of use not identified; 3. Incomplete patient demographic information; 4. potential for recall bias.
	Publication # 16 - Mann JI, Inman WHW. Oral contraceptives and death from myocardial infarction. Br Med J 1975;2(5965):245-8	Historical Reference - Contraceptive Estrogens*

Table 4: Literature Support of Estradiol Vaginal Insert Long-Term Safety [505 (b)(2) mapping Table] - continued

Relevant Section of Labeling[a]	Literature Relied Upon	Comments
Section 5 WARNINGS AND PRECAUTIONS		
5.2 Cardiovascular Disorders		
Venous Thromboembolism (VTE)	Publication #8 - Curb JD, et al. Venous thrombosis and conjugated equine estrogen in women without a uterus. Arch Intern Med 2006;166:772-780	Referenced in Current Estrogen Class Labeling
	Publication # 9 - Cushman M, et al. Estrogen plus progestin and risk of venous thrombosis JAMA 2004;292:1573-1580	Referenced in Current Estrogen Class Labeling
	Publication #25 - Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. Br Med J, 1969. 2(5658):651-7.	Historical Reference – Contraceptive Estrogens[b]
	Publication #2 - Bailar JC. Thromboembolism and oestrogen therapy. Lancet 1967;2(7515):560	Historical Reference – Noncontraceptive estrogen therapy.[c] See the MOR summary review Table 4 archived May 29, 2018. Limitations of this article: The safety information is relative to the synthetic estrogen diethylstilbesterol (5 mg). This information is not relevant to estradiol vaginal estrogens 4 and 10mcg.

Table 4: Literature Support of Estradiol Vaginal Insert Long-Term Safety [505 (b)(2) mapping Table] - continued

Relevant Section of Labeling[a]	Literature Relied Upon	Comments
Section 5 WARNINGS AND PRECAUTIONS		
5.3 Malignant Neoplasms		
Endometrial Cancer	Publication # 27 - Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med 1975;293(23):1167-70	Historical Reference – Noncontraceptive estrogen therapy.[c] See the MOR summary review Table 4 archived May 29, 2018. This publication retrospective case control study was contributory to the understanding that unopposed estrogen use is associated with increased risk of endometrial adenocarcinoma. Fifty seven percent [57% (n=54)] of 94 cases of endometrial adenocarcinoma or adenoacanthoma recorded conjugated estrogens (CE) use; risk ratio (RR) 7.6 with a one-sided 95 % confidence interval (CI) of 4.7 versus 15% (n=29) of controls. Limitations of the study include no discussion of the specific estrogen dosage strength. However, dosage strengths of conjugated estrogens in early to late 1960s or early 1970s in general exceeded 1.25 mg.

Table 4: Literature Support of Estradiol Vaginal Insert Long-Term Safety [505 (b)(2) mapping Table] - continued

Relevant Section of Labeling[a]	Literature Relied Upon	Comments
Section 5 WARNINGS AND PRECAUTIONS		
5.3 Malignant Neoplasms		
Endometrial Cancer	Publication #21 - Smith DC, et al. Association of exogenous estrogen and endometrial carcinoma. N Engl J Med 1975;293(23):1164-7	Historical Reference – Noncontraceptive estrogen therapy.[c] See the MOR summary review Table 4 archived May 29, 2018. This publication retrospective case control study was contributory to the understanding that unopposed estrogen use is associated with increased risk of endometrial adenocarcinoma. Forty-eight percent [48% (n=152)] of 317 women with endometrial cancer used estrogen compared with 17% (54) of 317 controls. Risk of endometrial cancer was 4.5 times greater in women exposed to estrogens. Limitations of the study include: no discussion of the specific estrogen product, dosage strength or duration. This published literature is considered to be of limited relevance to 4 and 10 mcg estradiol vaginal insert.
	Publication #15 - Mack TM, et al. Estrogens and endometrial cancer in a retirement community. N Engl J Med 1976;294(23):1262-7	Historical Reference – Noncontraceptive estrogen therapy.[c] See the MOR summary review Table 4 archived May 29, 2018. This publication retrospective case control study was contributory to the understanding that unopposed estrogen use is associated with increased risk of endometrial adenocarcinoma. RR for any estrogen use estimated to be 8.0 (95% CI, 3.5-18.1); RR for conjugated estrogen use (< 0.625 mg, > 0.625 mg) 5.6 (95% CI, 2.8-11.1). Increased risk was shown for invasive and noninvasive cancer and dose-response effect was demonstrated. Risk for endometrial cancer exceeds the baseline risk from any other single cancer. Limitations include study relied on medical records for women seen at a single medical care community. This published literature is considered to be of limited relevance to 4 and 10 mcg estradiol vaginal insert.

Table 4: Literature Support of Estradiol Vaginal Insert Long-Term Safety [505 (b)(2) mapping Table] - continued

Relevant Section of Labeling[a]	Literature Relied Upon	Comments
Section 5 WARNINGS AND PRECAUTIONS		
5.3 Malignant Neoplasms		
Endometrial Cancer	Publication #26 - Weiss NS, et al. Increasing incidence of endometrial cancer in the United States. N Engl J Med, 1976. 294(23):1259-62.	Historical Reference – Noncontraceptive estrogen therapy.[c] See the MOR summary review Table 4 archived May 29, 2018. This summary report of published data collected between 1969 and 1973 of population-based cancer reporting system serving eight areas of the country, was contributory to the understanding that unopposed estrogen use is associated with increased risk of endometrial adenocarcinoma. Limitations of this publication include: specific estrogen is not identified, dose of estrogen not identified and duration of use not identified. This published literature is considered to be of limited relevance to 4 and 10 mcg estradiol vaginal insert.

Table 4: Literature Support of Estradiol Vaginal Insert Long-Term Safety [505 (b)(2) mapping Table] - continued

Relevant Section of Labeling[a]	Literature Relied Upon	Comments
Section 5 WARNINGS AND PRECAUTIONS		
5.3 Malignant Neoplasms		
Breast Cancer	Publication #22 - Stefanick ML, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA 2006;295:1647-1657	Referenced in Current Estrogen Class Labeling
	Publication #5 - Chlebowski RT, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. JAMA, 2003. 289:3243-3253.	Referenced in Current Estrogen Class Labeling
	Publication #6. - Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997;350(9084):1047-59	Historical Reference – Noncontraceptive estrogen therapy.[c] See the MOR summary review Table 4 archived May 29, 2018. This 1997 epidemiologic study was contributory to the general understanding of breast cancer and the duration of estrogen use. The study is a reanalysis of worldwide epidemiological evidence on relationship between risk of breast cancer and hormone therapy use in 52,705 women with breast cancer and 108,411 women without breast cancer from 51 studies in 21 countries. The relative risk of breast cancer increased by factor of 1.02 (95% CI, 1.01-1.04) for each year of use. Relative risk of breast cancer was 1.35 (95% CI, 1.21-1.49) for women who used hormone therapy for 5 years or longer. Risk of having breast cancer is increased in women using hormone therapy and increases with increasing duration of use Effect is reduced after cessation of use, and largely disappears after about 5 years

Table 4: Literature Support of Estradiol Vaginal Insert Long-Term Safety [505 (b)(2) mapping Table] - continued

Relevant Section of Labeling[a]	Literature Relied Upon	Comments
Section 5 WARNINGS AND PRECAUTIONS		
5.3 Malignant Neoplasms		
Breast Cancer-	Publication # 24 - Surgically confirmed gallbladder disease, venous thromboembolism, and breast tumors in relation to postmenopausal estrogen therapy. A report from the Boston Collaborative Drug Surveillance Program, Boston University Medical Center. N Engl J Med 1974;290(1):15-9	Historical Reference – Noncontraceptive estrogen therapy.c See the MOR summary review Table 4 archived May 29, 2018. This 1974 retrospective hospital survey provides extremely limited information with respect to the general understanding of breast cancer. One hundred three women 45 to 69 years of age with discharge diagnosis of biopsy proven breast tumor for the first time were analyzed [(N=103); 51 newly diagnosed cases of breast cancer and 52 cases of benign breast tumors] vs. 744 age-matched controls. No significant association between estrogens and newly diagnosed breast cancer or benign breast tumors was present. Dose and duration of estrogen use was not provided,
Ovarian Cancer	Publication # 1 - Anderson GL, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures. The Women's Health Initiative Randomized Trial. JAMA 2003;290:1739-1748 Publication # 4 - Beral V et al. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet 2015;385(9980):1835-1842.	Referenced in Current Estrogen Class Labeling Referenced in Current Estrogen Class Labeling

Table 4: Literature Support of Estradiol Vaginal Insert Long-Term Safety [505 (b)(2) mapping Table] - continued

Relevant Section of Labeling[a]	Literature Relied Upon	Comments
Section 5 WARNINGS AND PRECAUTIONS		
5.4 Probable Dementia		
Probable Dementia	Publication # 20. Shumaker SA, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women. Women's Health Initiative Memory Study. JAMA 2004;291:2947-2958	Referenced in Current Estrogen Class Labeling
5.5 Gallbladder Disease		
Gallbladder Disease	Supportive Publication # 4 - Bennion LJ, et al. Effects of oral contraceptives on the gallbladder bile of normal women. N Engl J Med 1976;294(4):189-92	General Knowledge Included in Estrogen Class Labeling
5.6 Hypercalcemia		
Hypercalcemia		General Knowledge Included in Estrogen Class Labeling

Table 4: Literature Support of Estradiol Vaginal Insert Long-Term Safety [505 (b)(2) mapping Table] - continued

Relevant Section of Labeling[a]	Literature Relied Upon	Comments
5.7 Visual Abnormalities		
Visual Abnormalites	Supportive Publication # 14 - Inman WHW, et al. Thromboembolic disease and the steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs. Br Med J 1970; 2(5703):203–209 Supportive Publication #23 - Stolley PD, et al. Thrombosis with low-estrogen oral contraceptives. Am J Epidemiol 1975;102(3):197-208	General Knowledge Included in Estrogen Class Labeling General Knowledge Included in Estrogen Class Labeling
5.8 Addition of a Progestin When a Woman Has Not Had a Hysterectomy		
Addition of a Progestin When a Woman Has Not Had a Hysterectomy		General Knowledge Included in Estrogen Class Labeling
5.9 Elevated Blood Pressure		
Elevated Blood Pressure		General Knowledge Included in Estrogen Class Labeling
5.10 Hypertriglyceridemia		
Hypertriglyceridemia		General Knowledge Included in Estrogen Class Labeling

Table 4: Literature Support of Estradiol Vaginal Insert Long-Term Safety [505 (b)(2) mapping Table] - continued

Relevant Section of Labeling[a]	Literature Relied Upon	Comments
5.11 Hepatic Impairment and/or Past History of Cholestatic Jaundice		
Hepatic Impairment and/or Past History of Cholestatic Jaundice		General Knowledge Included in Estrogen Class Labeling
5.12 Hypothyroidism		
Hypothyroidism		General Knowledge Included in Estrogen Class Labeling
5.13 Fluid Retention		
Fluid Retention		General Knowledge Included in Estrogen Class Labeling
5.14 Hypocalcemia		
Hypocalcemia		General Knowledge Included in Estrogen Class Labeling
5.15 Exacerbation of Endometriosis		
Exacerbation of Endometriosis		General Knowledge Included in Estrogen Class Labeling
5.16 Hereditary Angioedema		
Hereditary Angioedema		General Knowledge Included in Estrogen Class Labeling
5.17 Exacerbation of Other Conditions		
Exacerbation of Other Conditions		General Knowledge Included in Estrogen Class Labeling
5.18 Laboratory Tests		
Laboratory Tests		General Knowledge Included in Estrogen Class Labeling
5.19 Drug Laboratory Test Interactions		
Drug Laboratory Test Interactions		General Knowledge Included in Estrogen Class Labeling

Table 4: Literature Support of Estradiol Vaginal Insert Long-Term Safety [505 (b)(2) mapping Table] - continued

Relevant Section of Labeling[a]	Literature Relied Upon	Comments
Section 6 ADVERSE REACTIONS		
6.1 Clinical Trials Experience		
Cardiovascular Disorders [see Warnings and Precautions (5.2)]	See relied upon literature cited for Sub-Section 5.2 above	See comments above regarding Referenced Publications in Current Estrogen Class Labeling - Sub-Section 5.2.
Malignant Neoplasms [see Warnings and Precautions (5.3)]	See relied upon literature cited for Sub-Section 5.2 above	See comments above regarding Referenced Publications in Current Estrogen Class Labeling - Sub-Section 5.3
Section 13 NONCLINICAL TOXICOLOGY		
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	See Pharmacology and Toxicology Original Cycle Review archived in DARRTS March 29, 2017	The literature submitted to support this labeling sub-section was considered adequate from the reviewer's standpoint
14 CLINICAL STUDIES		
14.2 Women's Health Initiative Studies	See literature supporting Sub-Sections 5.2 and 5.3	See comments above regarding Referenced Publications in Current Estrogen Class Labeling - Sub-Sections 5.2 and 5.3
14.3 Women's Health Initiative Memory Study	See literature supporting Sub-Section 5.4	See comments above regarding Referenced Publications in Current Estrogen Class Labeling - Sub-Sections 5.4

[a]Sections included are only those directed or influenced by the class of estrogen-alone products. Labeling sections-dependent upon original data are not included.

[b]Historical reference to oral contraceptive product – Information on the safety of oral contraceptive product use is considered by the clinical team to not be directly relevant to safety on estrogen products used in menopausal symptom therapy, particularly vaginally-administered lower dosed estrogen products such as estradiol vaginal insert. This determination is based on: 1) Oral contraceptive products contain different active ingredients, ethynyl estradiol or mestranol; 2) Synthetic contraceptive estrogens have a different mechanism of action than estradiol used for hormone therapy, 3) In general, synthetic contraceptive estrogens are approximately 10-fold more potent than the natural estrogen estradiol, and 4) The dosage strength of oral estrogen used in combination with progestins for contraceptive products are substantially higher than the dosage strengths of the estrogen products used in menopausal symptom therapy.

[c]Historical reference to noncontraceptive oral estrogen therapy – The Clinical Team considers these historical publication references to be of limited relevance to the long-term safety of 4 and 10 mg estradiol vaginal inserts

because the dosage strengths of oral estrogens are unknown, multiple fold greater than the proposed vaginal insert product.

Source: Adapted from NDA 208564 Resubmission, Module 1 Regional, Submodule 1.11 Information Amendment Information Not Covered Under Module 2 to 5, Submodule 1.11.14 Multiple Module Information Amendment, Appendix B: Literature Citation and 505(b)(2) Mapping Table, Table 3.

Conclusion regarding support of long-term general safety and chronic exposure

The applicant submitted 27 published articles to support long-term general safety and chronic exposure of the 4 mcg and 10 mcg dosage strength of estradiol vaginal insert. The scientific rationale (bridge) supporting that reliance on the articles is scientifically sound and appropriate include: 1)the proposed 4 and 10 mcg dosage strengths of estradiol vaginal inserts are part of the estrogen class of products, which have been studied and reported upon in the referenced literature; 2) FDA's recognition of the scientific soundness of the literature forming the basis for Estrogen Class Labeling; 3)The proposed 4 and 10 mcg dosage strengths of estradiol vaginal inserts and the systemic exposure from use of these products are both lower than the estrogen products studied and reported upon in the referenced literature. With respect to general (systemic) long-term safety and chronic exposure, the Clinical team is in concurrence with the applicant that the scientific rationale is sound and appropriate.

The clinical team assessed each of the 27 publications included in the NDA resubmission to support general (systemic) long-term safety and chronic exposure of the estradiol vaginal insert. The reader is encouraged to read Medical Officer Review (MOR) of Theresa van der Vlugt MD, archived in DARTTS on May 26, 2018, for detailed discussion of the articles provided in the resubmission. This clinical team previously reviewed 12 of the 27 publications, which were used as the primary support of the 2005 Draft Guidance for Industry, entitled "FDA Guidance for Industry, "Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommended Prescribing Information for Health Care Providers and Patient Labeling". By including these articles as the basis for Noncontraceptive Estrogen Class Labeling, the team made the determination that these publications provided safety information that is relevant to all estrogen hormone therapy dosage strengths and all routes of administration (oral, transdermal, vaginal) to include the 4 mcg and 10 mcg estradiol vaginal inserts. The twelve articles primarily informed the Boxed Warnings and Warning and Precautions Sections of Noncontraceptive Estrogen Class Labeling. Nine (9) of the 12 publications, forming the basis for the Noncontraceptive Estrogen Class Labeling, report results of the Women's Health Initiative (WHI) estrogen-alone and estrogen plus progestin subtrials (Anderson GL, et al 2003; Chlebowski RT, et al. 2003; Curb JD, et al. 2006, Cushman M, et al. 2004; Hendrix SL, et al. 2006; Hsia J, et al. 2006; Rossouw JE, et al. 2007; Shumaker SA, et al. 2004; and Stefanick ML, et al. 2006). Data from the additional three (3) of the previously reviewed 12 publications forming the basis of the 2005 Draft Noncontraceptive Estrogen Class Labeling, address Section 5 Warnings and Precautions, Subsection 5.2 Cardiovascular Disorders, Coronary Heart Disease (Hulley S, et al. 1998 and Grady D, et al. 2002), and Subsection 5.3 Malignant Neoplasms, Ovarian Cancer (Beral V, et al. 2015).

Additionally, 8 of the 27 publications are considered contributory to our current understanding of 1) the risk of unopposed estrogen use in a postmenopausal woman with a uterus [Ziel HK et al 1975 (Publication # 27), Smith DC et al. 1975 (Publication # 21), Mack TM et al. 1976 (Publication # 15), and Weiss NS et al. 1974 (Publication # 26)]; 2) effects of estrogen on breast safety [Collaborative Group on Hormone Factors in Breast Cancer 1997 (Publication # 6) and Boston University Medical Center 1974 (Publication # 24)]; 3) effects of estrogen on the risk of stroke in postmenopausal women [Pfeiffer RI et al 1976 (Publication # 17)]; and 4) effects of estrogen on the risk for coronary heart disease in postmenopausal women [Rosenberg L et al 1976 (Publication # 18)]. The Clinical Team considers these 8 publications to be relevant to the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts, but with limitations.

The remaining 6 observational case control publications regarding oral contraceptive use, and the one (1) letter to the editor (diethylstilbestrol use in prostate cancer), provided by the applicant in the resubmission, are not considered by the Clinical Review Team to be relevant to the 4 mcg and 10 mcg estradiol vaginal inserts (see Table 4).

Overall, the Clinical Team deems 20 of the 27 publications provided in the resubmission and identified in Table 4 to be either "relevant" or "relevant with limitations" in providing support for the long-term general safety and long-term drug exposure of the 4 mcg and 10 mcg dosage strengths of estradiol vaginal inserts.

▪ Advisory Committee Meeting

No Advisory Committee input was requested or necessary to reach an approvability decision on estradiol vaginal inserts.

▪ Pediatrics

A full waiver of Pediatric Research Equity Act (PREA) requirement was granted by Pediatric Review Committee (PeRC) in the original review cycle. Granting of the full waiver was based on the fact that vulvar and vaginal atrophy due to menopause is a condition that qualifies for waiver because studies would be impossible or highly impractical. On October 30, 2017 in internal communications, PeRC indicated that they would not have to revisit the waiver for the resubmission of NDA 208564.

▪ Other Relevant Regulatory Issues

Financial disclosure information and the results of the Office of Scientific Investigations (OSI) audits were reviewed in original review cycle. No outstanding regulatory issues remain from these or any other regulatory items.

The proprietary name Imvexxy was approved on February 27, 2018

▪ Labeling

Prescribing Information (PI)
Estrogen vaginal inserts will receive Noncontraceptive Estrogen Class Labeling. The product is recommended for treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause. The clinical studies section will reflect results from single clinical Trial TX 14-01. The final Agency recommended PI, as provided to the applicant on May 16, 2018, is attached to this review.

Patient Package Insert (PPI) and Instructions for Use
The recommended PPI and IFU reflects the information provided in the PI in patient-friendly language. The final Agency recommended PPI, as provided to the applicant on May 16, 2018, is attached to this review.

On May 18, 2018 TherapeuticsMD indicated their concurrence with all labeling recommendations provided by the FDA on May 16, 2018.

Carton and Container Labeling:
DMEPA recommended the following be implemented prior to approval of NDA 208564:

1. Blister Carton Labeling, Blister Card Insert Labeling, and Professional Sample Carton Labeling:

    - The strength statement on the carton labeling is presented in a small font and the two strengths can be better differentiated to decrease risk of wrong strength medication errors. Specifically, we recommend you consider increasing the font size of the strength statements (for example, 4 mcg and 10 mcg) and further differentiating the strengths in accordance with 21 CFR 201.15(a)(6), taking into account all pertinent factors including typography, layout, contrast, boxing, bolding, and other printing features.
    - To better differentiate the strengths, we continue to recommend that the colors used to denote the strength statement do not overlap with the colors used in the carton trade dress.

2. Blister Carton Labeling (commercial configuration)
    1. As currently presented, the carton labeling lacks a linear barcode. The linear barcode is often used for additional verification before dispensing in the outpatient setting and before drug administration in the inpatient setting; therefore, it is an important safety feature that should be visible on the label whenever possible according to 21CFR 201.25(c)(2) and section 201(k) of the FD&C Act (21 U.S.C. 321(k)). We recommend that the linear and 2D barcodes are visible on the outside of the carton labeling. Both the linear and 2D barcodes should be surrounded by sufficient white space to allow scanners to read the barcodes properly in accordance with 21 CFR 201.25(c)(1)(i). In addition, both the linear and 2D barcodes should be presented in close proximity to each other to minimize confusion users may experience with multiple barcodes.

3. Remove all reference to [redacted] (b) (4), as this language is considered promotional.

On May 18, 2018 TherapeuticsMD indicated their concurrence with all labeling recommendations provided by the FDA on May 16, 2018

▪ Postmarketing Recommendations

Postmarketing Requirements (PMRs) and Commitments (PMCs)

PMR:
As a condition of an approval action, the applicant will be required to conduct the following study (see Section 8 of this review):

- An observational study evaluating the risk of endometrial cancer in nonhysterectomized (with a uterus) postmenopausal women who use "low" dose vaginally-administered estrogen unopposed by a progestogen. The study should include safety data from the U.S. and other countries where the holder's products are being prescribed to ensure sufficient study sample size. The proposed study data source(s), domestic and international, should 1) include users of vaginally-administered estrogens across the entire postmenopausal age range, and 2) allow linkage to national cancer registries or adequate medication chart adjudication to confirm endometrial cancer cases. The median duration of follow-up should be at least 3 to 5 years after the first use of an unopposed vaginal estrogen product. Appropriate comparison groups should be selected to allow risk estimates for endometrial cancer. Wherever feasible, key baseline covariates, such as body mass index (BMI), smoking and family history of cancer, should be measured and controlled to reduce confounding.

PMC
The applicant also agreed to two postmarketing commitments (see Section 3 of this review) to:

1. Develop and validate a new regulatory method capable of detecting known and unknown estradiol-related impurities in the drug product.

2. Perform a revalidation of the dissolution method TxMD-003 in accordance with requirements of USP using one batch of each strength of the for-market formulations manufactured by the proposed commercial manufacturer

▪ Recommended Comments to the Applicant

Each Discipline Review Team has recommended that NDA 208564 be approved. The plan is to send a "Decisional Letter" to the applicant on May 29, 2017.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHELLEY R SLAUGHTER
05/29/2018

CHRISTINE P NGUYEN
05/29/2018
I concur with the approval recommendation of this application, and with Dr. Slaughter's summary review.

Cross-Discipline Team Leader (CDTL) Review

Date	April 28, 2017
From	Shelley R. Slaughter, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	208564
Type of Submission	Original 505(b)(2)
Applicant	TherapeuticsMD
Date of Submission	July 7, 2016
PDUFA Goal Date	Original –May 7, 2017
Proprietary Name / Established (USAN) names	[redacted] (b) (4) Estradiol Vaginal Insert
Dosage forms / Strength	Vaginal insert/ 4, 10 [redacted] (b) (4) mcg
Proposed Indication(s)	Per Form 356h "Treatment of moderate to severe dyspareunia), a symptom of vulvar and vaginal atrophy, due to menopause."
Recommendation:	Approval is **not** recommended.

1. Introduction and Executive Summary

With this 505(b)(2) original NDA submission, the applicant is seeking approval for (b) (4) (tentative name approval) for the indication of treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

To support the NDA, the applicant conducted five (5) clinical trials including three (3) phase 1 trials, one (1) phase 2 trial proof-of-concept trial and one (1) double-blind, and placebo-controlled 12-Week phase 3 trial (Trial TXV14-01) with the to-be-marketed formulation.

Key focus items for the application review were:

1. Efficacy
   As (b) (4) is an estradiol product, (administered as a vaginal insert) and estradiol is an active ingredient in several estrogen alone and estrogen plus progestin products, a single trial was acceptable to support efficacy in the U.S.

   Primary efficacy data from Trial TVX14-01 demonstrate that the 4 mcg, 10 mcg, and 25 mcg estradiol vaginal insert dosage groups compared to placebo, demonstrates an improvement (i.e., statistically significant increase) in the percentage of superficial vaginal cells **and** improvement (i.e., statistically significant decrease) in the percentage of vaginal parabasal cells **and** improvement (i.e., statistically significant decrease) in vaginal pH **and** improvement (i.e., statistically significant decrease) in the mean change in severity from baseline for moderate to severe dyspareunia. Therefore the clinical trial data support effectiveness of each strength of the estradiol vaginal insert in the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Refer to Efficacy – Section 7 of this review.

   The statistically significant findings for efficacy are consistent with a positive estrogen effect, but do not correlate with the mean serum estrogen concentrations obtained for the pharmacokinetic (PK) sub-group of Trial TXV14-01. In particular for the 4 mcg dose of estradiol vaginal insert, mean (SD) concentrations of estradiol, estrone and estrone conjugate 3.92 (2.43), 15.33 (4.80) and 237.7, respectively do not differ from the same analytes in the placebo groups, 4.94 (2.61), 19.37 (8.78) and 275.9 (153.67). This suggest that serum estrogen concentrations would not be appropriate surrogates in representing the characteristics of low dose estrogen products and should not be used to compare these product with other estrogen products. Such comparisons moving forward should most likely use tissue concentrations and not serum concentrations. Whether tissue drug product analyte concentrations can be used in such a manner, should be explored.

2. Safety
   No data was submitted by the applicant to support the long-term general and endometrial safety and to satisfy the Division recommendation for premarket exposure in women using a product intended for chronic use (ICH E1 guideline). The

applicant evaluated the endometrium at the completion of phase 3 Trial TXV14-01, which was appropriate. However, because treatment of the symptoms of vulvar and vaginal atrophy involves in most instance long-term, if not life-long commitment to therapy, the Division, in general, also recommends evaluation of the endometrium in a long-term endometrial and general safety trial. Refer to Safety – Section 8 of this review.

3. Labeling

As the recommendation for (b) (4) estradiol vaginal insert is not to approve, no labeling negotiations were pursued with the applicant. However, some aspect of the applicants initially proposed labeling revisions deserve comment.

- Per FDA recommendation on the established name for the dosage form, (b) (4) is to be designated as an estradiol vaginal insert.
- TherapeuticsMD disagrees with the designation and states that estradiol vaginal insert does not adequately describe the dosage form for (b) (4) as it does not convey the nature of the dosage form. They propose that "estradiol (b) (4) is more descriptive and less confusing to healthcare providers, pharmacies, and patients."
- The Agency does not accept (b) (4) and has informed TherapeuticsMD that their product, once approved, would have the established name, estradiol vaginal inserts.
- (b) (4)
- The Clinical review team disagrees with the (b) (4) Refer to Item 2, Introduction and Executive Summary – Section 1 and Safety – Section 8 of this review.
- (b) (4) TherapeuticsMD initially (b) (4)

(b) (4)

From: (b) (4)

.

To: (b) (4)

.

- The Clinical Review Team disagrees with (b) (4) See Item 2, Section 1- Introduction and Executive Summary and Section 8-Safety of this review.

- With the rationale that (b) (4) TherapeuticsMD changed the following language in labeling (b) (4)

  From: (b) (4)

  To: (b) (4)

- The Clinical Review Team disagrees with (b) (4)

2. Background and Regulatory History

- **May 10, 2013** – TherapeuticsMD submitted IND 118439 with two phase 1 protocols designed to investigate the pharmacokinetics and bioavailability of estradiol vaginal insert (10 mcg and 25 mcg) compared to 10 mcg and 25 mcg Vagifem® (estradiol vaginal insert), respectively.
- **July 8, 2013** – The Division of Bone Reproductive and Urologic Products (DBRUP) provided an Advice Letter to TherapeuticsMD advising the sponsor that for the proposed phase 1 studies, the sponsor should follow the Agency's Draft 2003 Clinical Trial Guidance for the definition of postmenopausal status, enrollment criteria, and washout periods for women entering the trial who had previous use of estrogen alone or estrogen plus progestogen therapy.
- **July 18, 2014** – DBRUP provided a Written Response Only for a Type C Advice Meeting request from TherapeuticsMD on May 8, 2014 in response to the Agency's July 8, 2013 Advice Letter. The following questions and responses regarding clinical/statistical issues are highlighted:

  Question: "Does the Agency concur that the design of the proposed Phase 3 study is acceptable and sufficient for the Phase 3 evaluation of TX-004HR for the stated indication?"

  FDA Response:
  "No, we do not concur. We have the following general comments:

  - We do not agree with your proposal, as stated in subsection 10.9.4 of your draft protocol, to allow "as needed" use of a vaginal lubricant during the conduct of Study TXV14-01.
  - Per the Agency's 2003 draft clinical evaluation Guidance for Industry, we recommend that the endometrial tissue obtained by endometrial biopsy at screening, during the conduct of the study, and at the end-of-study be processed in the same manner by a central laboratory. For the evaluation of protection of the endometrium, we recommend concurrent readings by three independent expert pathologists from institutions with independent fiduciary and organizational reporting. Each pathologist should be blinded to the treatment group and to the readings of the other pathologists. We also recommend that standardized criteria be used for the diagnosis of endometrial hyperplasia, and that endometrial polyps be fully characterized as to glandular proliferation and atypia. The concurrence of two of the three pathologists is accepted as the final diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis would be used as the final diagnosis. The standardized criteria for histologic evaluation, and the Agency's 2003 draft clinical evaluation guidance can be viewed at http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133343.pdf

- We do not agree with your draft protocol proposal to have assessment of "treatment unscheduled biopsy" or End-of-Treatment (or early withdrawal if after week 10 of drug administration) endometrial biopsies by two primary pathologists with involvement of a third pathologist only in cases of disagreement by the two initial readers regarding the presence of endometrial hyperplasia, endometrial polyp, or endometrial cancer. Refer to our previous bulleted comment regarding evaluation of endometrial pathology.
- Your draft protocol does not address the administration of a progestogen following collection of the end-of-study endometrial biopsy (or early withdrawal endometrial biopsy after week 10).
- Data collected for secondary endpoints will not be used to determine effectiveness of your drug product. (b) (4) .
- You propose to study multiple doses of TX-004HR (4 mcg, 10 mcg and 25 mcg) compared to placebo.
  - Clarify whether you intend to submit your new drug application for multiple dose strengths and if so, how those different dose strengths will be given to patients.
  - Provide your rationale of dose selection and the dosage and administration instructions at the time of your new drug application submission. These should be well supported by the Phase 3 data.
- Should you decide to conduct a single study to support the indication, the evidence of efficacy needs to be at an alpha level of at least 0.01. In addition, in the statistical analysis plan, we recommend the mixed model for repeated measures (MMRM) instead of last observation carried forward (LOCF) for handling missing values. The latter could be used for sensitivity analysis.
- You should submit a final protocol for our review and comment. Provide the following with your protocol:
  - Complete information regarding the use of "non-hormonal medications" that the Medical Monitor can approve if the study participant experiences hot flashes.
  - A copy of the Pathology Committee Charter which includes "Instructions and other additional information regarding performing the endometrial biopsies, submission of samples and reporting" designed "to ensure uniformity and interpretation".
  - Specify the following regarding PK characterization:
    - blood sampling time points
    - a proposal on how the baseline will be characterized
    - number of subjects"

Question: "Does the Agency agree with the sample size calculation for the Phase 3 study as described in Section 9.4.2?"

FDA Response:
"No, we do not agree. In order to have a subject's data included in the efficacy analysis for proposed Study TXV14-01, the subject should have identified at baseline, moderate to severe pain with sexual activity (dyspareunia) as most bothersome to her and have a baseline percentage of superficial cells that does not exceed 5% and have a vaginal pH greater than 5.0.

For powering the study with respect to the co-primary endpoint of severity of dyspareunia, you assumed effect size in terms of percent change (41.2%), while the required efficacy is the mean change from baseline. Justify that the sample size of 120 is adequate for the mean change."

- **August 6, 2014** – TherapeuticsMD submitted phase 3 Trial TXV14-01
- **October 27, 2014** – DBRUP provided an Advice Letter to TherapeuticsMD addressing the protocol for phase 3 Trial TXV 14-01. Items addressed include:
  - The inclusion criterion related to an evaluable screening endometrial biopsy needs to take into consideration the age of the woman, the number of years since menopause and any recent use of a hormone therapy product. For example, a screening endometrial biopsy in a postmenopausal woman who has not recently used hormone therapy and is 60 to 75 years of age or 10 or more years post-menopause, should not commonly demonstrate a finding of proliferative endometrium, weakly proliferative endometrium, or disordered proliferative endometrium. Such a woman should ideally not be randomized into Study TXV14-01 for the treatment of the symptoms of vulvar and vaginal atrophy. We recommend that you propose entrance criteria for an "acceptable result from an evaluable screening endometrial biopsy" that factors in the age of the woman and/or the number of years since menopause and recent hormone therapy use.
  - Subjects who have a Body Mass Index (BMI) less than or equal to 38 kg/m^2
  - Concerns regarding the proposed permitted non-hormonal medications in Trial TXV14-01 (at the discretions of the investigator) for use by postmenopausal women. Such non-hormonal products included some which were not approved for the treatment of moderate to severe vasomotor symptoms (VMS). The only nonhormonal approved product is Brisdelle™ (paroxetine) capsule, 7.5 mg daily. Administer only Brisdelle™, 7.5 mg daily, to trial participants experiencing 7-8 moderate to severe hot flashes per day.
  - Postmenopausal woman experiencing mild hot flashes should not receive therapy.
  - Three independent expert pathologists should concurrently evaluate End-of-Treatment [or early withdrawal (when treated ≥10 weeks)] endometrial biopsies. Each of these three pathologists should be blinded to the study treatment group and to the readings of the other pathologists.
  - The protocol should be more specific as to additional follow-up that should occur if two attempts at end-of-study endometrial biopsy results in insufficient tissue for diagnosis.

- Clarify whether progestin treatment is planned after 12-weeks of treatment with your estrogen only product in postmenopausal women with intact uteri.

- **November 26, 2014, 2014** – TherapeuticsMD submitted an amended protocol for Trial TXV 14-01.

- **February 9, 2015** – DBRUP provided Therapeutics MD with an Advice Letter stating:

  - We do not concur with the proposed procedure regarding "appropriate treatment" when a study participant is diagnosed with endometrial hyperplasia, either during the study conduct or at the end-of-study. It is your responsibility to assure that appropriate treatment for a diagnosis of endometrial hyperplasia is provided, either by the study Investigator or by the woman's primary care physician, and to follow these women who have developed on-study or end-of study endometrial hyperplasia until this adverse event is resolved.
  - Clarify whether progestin treatment is planned after 12-weeks of treatment with your estrogen-only product in postmenopausal women with intact uteri.

  The Clinical Review Team notes that to this point in the estradiol vaginal development, discussions with the sponsor had focused on the design and conduct of the phase 3 efficacy trial. The Division failed to prospectively advise/remind the sponsor that in order to support chronic use of their product, they would need to conduct a long-term general and safety trial.

- **December 15, 2015** – Type B pre-NDA teleconference meeting between DBRUP and TherapeuticsMD (requested October 12, 2015). Discussions included, but were not limited to the following:

  - DBRUP did not agree with a submission that only addressed "de minimis nonclinical requirements" or that the proposed NDA constitutes a 505(b)(1) application. If the sponsor had not conducted (and did not plan to conduct) studies of their own to support the complete nonclinical safety of their product, or have a right of reference to the required studies, then the sponsor would need to rely on 1) published literature, and/or 2) FDA's previous finding of safety for a listed drug, in order to support the nonclinical safety and labeling for their product. Two options for providing nonclinical information under the 505(b)(2) pathway were discussed:
    - Submit published literature for information necessary to inform Section 8 (Use in Specific Populations) and Section 13 (Nonclinical Toxicology) of labeling. If relevant clinical data in the literature are more informative than animal data, this could be used as an alternative, provided it does not reference a specific product.
    - Refer to a Listed Drug. Under this option, labeling language from the listed drug can be used for your product as long as you establish a bridge demonstrating that your product and the listed drug are sufficiently similar. No literature submissions would be necessary.

- DBRUP noted that the proposed pharmacokinetic (PK) studies appear to be sufficient for filing the NDA. However, the acceptability of the data generated from these studies will be a review issue. Bioanalytical method validation and performance should be in compliance with the Agency's Bioanalytical Method Validation Guidance

  (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf).

  All bioanalytical method validation and study (performance) reports should be submitted at the time of the original NDA submission. FDA reminded TherapeuticsMD to submit Sections 2.7.1 Summary of Biopharmaceutics and Analytical Methods and 2.7.2 Summary of Clinical Pharmacology in the NDA. Include all bioanalytical method validation and study (performance) reports in Section 2.7.1. Therapeutics MD agreed to submit the above information in the appropriate sections of the NDA.

- TherapeuticsMD stated:

  - The Clinical Program consists of five studies: three single-dose PK studies, one 14-day Phase 2 safety and efficacy study, and one pivotal, 12-week, Phase 3, safety and efficacy study. Per the Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (April 2009), our application meets the exception situation in which sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety, would be sufficiently detailed to serve as the narrative portion of the Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS), respectively, while still concise enough to meet the suggested size limitations for Module 2. At this time, TherapeuticsMD does not anticipate formal integrated analyses due to the types of studies performed. However, should any tables, figures, and datasets be created for integrated analyses, these would be placed in section 5.3.5.3, as appropriate. The narrative portions will be submitted only once (in 2.7.3 and 2.7.4) and leaf elements will be provided in both locations (Modules 2 and 5, if needed) as instructed in the guidance. Does the Division agree that sections 2.7.3 and 2.7.4 may serve as the narrative portions of the ISE and ISS as described in the FDA guidance, with any appendices of tables, figures, and datasets located in section 5.3.5.3, as needed?

- DBRUP provided agreement that the proposed NDA application would meet the exception situation set forth in the Agency's 2009 Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, in which the narrative portion of section 2.7.3, Summary of Clinical Efficacy, under Module 2 Common Technical Document Summaries, 2.7 Clinical Summary, could be sufficiently detailed to serve as the narrative portion of the Integrated Summary of Efficacy (ISE). In addition to the Summary of Clinical Safety in section 2.7.4, we recommend

that your proposed NDA application include an Integrated Summary of Safety (ISS) in section 5.3.5.3 under Module 5 Clinical Study Reports.

- FDA agreed that the legacy report and data compilation (scanned, no electronic datasets) for the rabbit preclinical safety study report (b) (4)/1013/G/T077 was acceptable for NDA submission.
- TherapeuticsMD provided a proposed Clinical Study Data Standardization Plan following the Agency's template in Appendix B. For the phase 1 studies, the sponsor proposed to use legacy format tabulation data and data definition files in define.pdf format per Study Data Specifications (SDS) version 2.0 as the exchange standards, with no Clinical Data Interchange Standards Consortium (CDISC) terminology standard. For the phase 2 study, the sponsor proposed legacy format tabulation datasets with data definition file in define.pdf format and annotated case report form (CRF) as blankcrf.pdf per SDS version 2.0, and legacy format analysis datasets with define.pdf and SDS version 2.0 for the exchange standards, with no CDISC terminology standard. For the phase 3 study, the sponsor proposed Standard Data Tabulation Model Implementation Guide (SDTM IG) version 3.1.3, Analysis Data Module Implementation Guide (ADaM IG) version 1.0, annotated CRF as blankcrf.pdf per SDS version 2.0 and define.xml version 1.0 as the exchange standards, with CDISC controlled terminology.
- The Agency responded that the Agency would prefer define.xml version 2. If the sponsor submits the define.xml version 1, they should also submit define.pdf for printing purposes SAS programs to generate analysis datasets and efficacy results for the primary and key secondary analyses should also be submitted with data.
- In response to TherapeuticsMD request for agreement from the Agency that no label comprehension study was need, FDA responded that a comprehensive use-related risk analysis of the proposed product to inform whether a labeling comprehension study would be needed. The proposed product and package design does raise concerns for FDA regarding the potential for wrong route of administration errors (e.g., oral administration of the insert). The absence of an applicator for use with the proposed product may suggest to patients that the 'inserts' can be given by routes other than vaginal. Therefore, the Agency recommended the sponsor perform a use-related risk analysis to identify the use-related risks associated with the proposed product. The risk analysis should include an evaluation of all the steps involved in using your product, the errors that users might commit or the tasks they might fail to perform (consider known problems for similar products), and the potential negative clinical consequences of use errors. The use-related risk analysis should also discuss the risk-mitigation strategies the sponsor employed (e.g., labeling interventions). The sponsor's risk analysis should evaluate the risk for wrong route of administration errors and consider how this risk can be mitigated. The use-related risk analysis will inform whether a labeling comprehension study is needed to validate the proposed risk mitigation strategies. The risk analysis, along with any data you may

have to support the design of your user interface, should be included in your original NDA submission.

- TherapeuticsMD proposed to submit a 505(b)(1) NDA containing the following:
  - Module 1: to include all information required by regulation (21 CFR 314)
  - Module 2:
    - 2.2 – Introduction
    - 2.3 - Quality Overall Summary
    - 2.4 – Nonclinical Overview - not applicable (only one nonclinical study was conducted)
    - 2.5 - Clinical Overview
    - 2.6 – Nonclinical Written and Tabulated Summaries - not applicable (only one nonclinical study was conducted)
    - 2.7 – Clinical Summaries provided, with 2.7.3 and 2.7.4 serving as the narratives for the integrated summaries as described in Question 6
  - Module 3: to include all chemistry, manufacturing and controls information required by regulation (21 CFR 314.50) or by agreement with the Division
  - Module 4: to contain the local tolerance study report, (b) (4) /1013/G/T077, as described in Question 4
  - Module 5: to contain the five clinical study reports as described in Question 6

  TherapeuticsMD requested agreement from the Agency that their proposal constitutes a complete 505(b)(1) application for review?

- In response, FDA indicated that the Agency did not agree that the proposed NDA constitutes a 505(b)(1) application. If the sponsor owns or has a right of reference to all of the data/information that they will be relying upon for approval, then the application would be a 505(b)(1) application. The nonclinical section would need to be supported by the required studies (that the sponsor conducted or through right of reference to the application containing the full study reports) to determine the nonclinical safety of the proposed product. If the sponsor intends to rely, in part, on information required for approval that comes from studies not conducted by the sponsor or for the sponsor or for which the sponsor has not obtained a right of reference (e.g., reliance on the FDA's finding of safety and/or effectiveness for a listed drug or published literature), then the marketing application will be a 505(b)(2) application. Refer to the 505(b)(2) REGULATORY PATHWAY section below for information about submitting a 505(b)(2) NDA.

  Additionally, the Agency did not agree that the Summary of Clinical Summary in section 2.7.4 will serve as the narrative portion of the Integrated

Summary of Safety (ISS) under Module 5. The Agency advised that the sponsor include under Module 5, an Integrated Summary of Safety (ISS) including phase 2 Clinical Trial TXV13-01 and phase 3 Clinical Trial TXV14-01.

From a technical standpoint (not content related), the placement of files in the eCTD structure, is acceptable. For archival purposes, submit a pdf file of any labeling document submitted in word and make sure the leaf title includes "word", so reviewers can quickly identify the word version of the document.

- FDA further stated that the sponsor's application would be a 505(b)(2) application because the sponsor did not own or have right of reference to the information needed to meet all the nonclinical and labeling requirements for an NDA. The sponsor should refer to the previous discussion for details regarding submission of published literature or reliance on a listed drug to support the 505(b)(2) application.
- TherapeuticsMD stated that they intend to submit a 505(b)(2) application.

The Clinical Review Team notes that the Division failed to advise the sponsor at the preNDA meeting that in order to support chronic use of their product, they would need to conduct a long-term general and safety trial.

- **July 7, 2016** – NDA 208564 was submitted by TherapeuticsMD
- **September 19, 2016** – FDA sent a 74-day Filing Review Issues Identified letter to TherapeuticsMD. The following issues were presented:
  - ***Clinical***
    - Your application does not provide long-term (12 months or more) general and endometrial safety data for the 4, 10, (b) (4) mcg estradiol vaginal inserts. Endometrial histology evaluation obtained at or greater than 12 months of use is critical to the safety evaluation of unopposed estrogen.
      - Unopposed estrogen use in a postmenopausal women with a uterus increases the risk of endometrial hyperplasia/cancer.
      - 12-week safety data from Trial TXV 4-01 are inadequate to assess long-term general and endometrial safety of your estradiol vaginal insert.
    - Your application does not provide data on chronic exposure at 6 months and 1 year for the 4, 10, (b) (4) mcg estradiol vaginal inserts.
      - Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause is a chronic use indication in postmenopausal women.
      - The International Council for Harmonisation (ICH) guidelines for exposure for chronically administered drugs recommends exposure of 500 women exposed overall, 300-600 women for 6 months, and 100 women for 1 year at the dose or dose range believed to be efficacious.

- Your draft prescribing and patient information labeling is not consistent with recommended estrogen class labeling per the Agency's 2005 draft Guidance for Industry entitled, "Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Prescribing Information for Healthcare Providers and Patient Labelling."

- ***Clinical Pharmacology***
  - Your application does not provide data from one or more drug interaction studies with commonly used vaginal products, such as antifungals. This type of assessment is important in determining if a local drug interaction can affect systemic estrogen exposure and, therefore, impact safety. Address the potential drug interaction between your proposed estradiol vaginal capsules and commonly used vaginal product(s).
  - You state that Trial ESTR-2036-14 was conducted to assess the effect of normal activity on the bioavailability of proposed estradiol vaginal capsule. You conclude that estrogen concentrations were similar regardless of whether participants were ambulatory or supine for 4 hours, and that the activity level or body position does not affect estradiol absorption.
    - Clarify how many of the 16 participants enrolled in Trials ESTR-2036-14 and ESTR-1K-500-12 were seated, ambulatory (i.e., upright and walking), or a combination of seated and ambulatory. The report for Trial ESTR-2036-14 does not include statistical analysis of estrogen concentrations to compare body position or activity level. Submit statistical analysis for the comparison of body position/activity level (seated, ambulatory, and both) versus supine position for the 16 participants enrolled in both Trials ESTR-2036-14 and ESTR-1K-500-12. Identify participants with identification numbers.
  - It is unclear from your method validation and bioanalytical reports whether the long-term stability covers the entire duration for which the participants' samples were stored (from the first day of sample collection to the last day of analysis). For all the clinical trials, submit a table summarizing the long-term freezer stability for estradiol, estrone, and estrone conjugate in plasma or serum, as appropriate, and the duration of time for which the participants' plasma or serum samples were stored.

3. CMC/Biopharmaceutics/Device

The Chemistry and Biopharmaceutics data for this NDA were reviewed by the Office of Product Quality (OPQ) Review Team as listed in Table 1.

Table 1: Office of Product Quality (OPQ) Review Team

DISCIPLINE	REVIEWER	DIVISION / BRANCH
Drug Substance	Martin Haber	ONDP/DNDAPI/ Br II
Drug Product	Hamid Shafiei	ONDP/DNDP II/Br. V
Process	Jingbo Xiao	OPF/DPA III/Br. VIII
Microbiology	Stephen Langille	OPF/DMA/Br. I
Facility	Vidya Pai	OPF / DIA /Br. III
Biopharmaceutics	An-Chi Lu	ONDP / DB / Br. II
Environmental Analysis (EA)	Hamid Shafiei	ONDP/DNDP II/Br. V
Laboratory (OTR)	Laura Pogue	OPF/DPA/OTR
Application Technical Lead	Mark Seggel	ONDP/DNDPII/Br V
RPM	Thao M. Vu	OPRO/DRBPM I// BrV

Abbreviations: ONDP = Office of New Drug Products; DNDAPI = Division of New Drug Active Pharmaceutical Ingredient; DPA = Division of Pharmaceutical Analysis; DMA = Division of Microbiology Assessment; DIA = Division of Inspectional Assessment; DB = Division of Biopharmaceutics; DNDP = Division of Non-prescription Drug Product; OPF= Office of Process and Facility; DPA = Division of Pharmaceutical Analysis; RPM = Regulatory Project Manager

Much of the following is adapted from the Executive Summary of the OPQ Review.

Drug Substance:
Estradiol used in the manufacture of TherapeuticsMD's estradiol vaginal insert is synthesized by (b) (4), as described in its Type II Drug Master File (DMF) (b) (4) A letter of authorization was provided from (b) (4) to TherapeuticsMD. Estradiol is supplied as the (b) (4). Estradiol (and estradiol (b) (4) is the subject of a USP monograph.

Estradiol, an estrogen, is an estrane (C18) steroid with two hydroxyl groups, one at the C3 position and the other at the 17β position, and three double bonds in the A ring. Estradiol is also known as 17β-estradiol or as estra-1,3,5(10)-triene-3, 17β-diol. Estradiol is the primary female sex steroid. Estradiol (b) (4) is the 17-beta-isomer of estradiol. Previous review (December 2016) and current evaluation of the DMF find it to be adequate.

Drug Product:
Estradiol vaginal inserts, 4 mcg, 10 mcg, (b) (4) mcg, are (b) (4) The capsule fill mass consists of estradiol solubilized in 300 mg of an (b) (4) which is then encapsulated. The (b) (4) is composed of (b) (4) (medium chain triglycerides) and (b) (4) (a mixture of PEG (b) (4) stearate NF, ethylene glycol palmitostearate NF and PEG (b) (4) stearate NF). The capsule fill mass thus contains not more than (b) (4) estradiol by weight.

The soft gelatin capsule shell consists of gelatin, hydrolyzed gelatin, sorbitol sorbitan solution, colorants and water. Each shell is ca. (b) (4) mg. The capsule shells are imprinted with (b) (4) printing ink.

All inactive ingredients are of suitable quality for use in a vaginally administered product. Per

the applicant, the proposed estradiol vaginal insert is designed for "easy insertion, with no need for an applicator, and formulated to dissolve completely and quickly, without requiring vaginal secretions to activate the formulation, minimizing vaginal discharge following administration."

The proposed to-be-marketed estradiol vaginal insert product will be packaged in 18-count and 8-count starter and maintenance blister packs, respectively.

Per the applicant the following supporting information for approval of this new drug application was submitted:

1. Product development, formulation compatibility, and formulation stability studies that support the proposed composition for the commercial drug product.
2. Container closure specifications and relevant supporting information regarding the material compatibility as well as performance of the proposed container closure.
3. Sufficient stability data that supports the proposed expiration period of 24 months.
4. Adequate post-approval stability testing protocols and commitments.
5. Drug product release and stability specification that includes testing and acceptance criteria for all physical and chemical quality attributes necessary for assuring the identity, strength, purity, and quality of the drug product at release and throughout the proposed product shelf-life.
6. Validation reports for key in-house analytical methods.
7. Request for the categorical exclusion from the environmental impact assessment.

The proposed new drug product specification includes tests for appearance, identity, assay ((b) (4) %), content uniformity, related substances ((b) (4), any other individual impurity and total impurities), fill moisture content (nmt (b) (4)%), in vitro dissolution, and microbial limits.

Per the ONDP review, the new drug product specification (tests, methods and acceptance criteria) differs from the USP Estradiol Vaginal Inserts monograph requirements in several aspects. Nevertheless, the proposed new drug product specification appears adequate to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product.

The ONDP review notes that the applicant's proposed HPLC/MS method for the determination of related substances (organic impurities) is different from the HPLC/UV method described in the USP monograph for estradiol vaginal inserts and has been found to be inadequate for determining unknown impurities. Based on risk-based assessment, it has been determined that some degree of inaccuracy in determining the unknown impurities is not expected to have significant impacts on the assurance of the identity, strength, purity and quality of the drug product. However, it would be desirable for the applicant to develop a method closely comparable to the method described in the USP monograph for the determination of organic impurities post-approval (refer to the PMC section of this review document).

Stability data obtained on drug product manufactured at (b) (4) and Catalent support an expiration dating period of 24 months for product stored at 25°C.

Based on ONDP' evaluation, the applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product at release and throughout the proposed expiration dating period of 24 months. From the drug product perspective NDA 208564 is recommended for approval with the expiration dating period of 24 months.

Process:
The drug product manufacturing process includes several unit operations: fill mass preparation, gel mass preparation, encapsulation, drying, washing, polishing, bulk packaging, and blister packaging. Because the active product ingredient is a highly potent category 4 compound and the drug load is very low (b) (4)% w/w), a robust manufacturing process is required for ensuring within-batch consistency.

In the fill manufacturing process, (b) (4) Equipment is in place for insert size sorting, printing, polishing and insert inspection.

Critical manufacturing process parameters have been identified. The overall control strategy is adequate to ensure the within-batch and batch-to-batch consistency of the drug product.

As amended, the information provided for batch formula, manufacturing process controls, and in-process controls are found adequate. In addition, proprietary and confidential information with regard to manufacturing of (b) (4) are found adequate from process perspective.

From a process perspective, NDA 208564 is recommended for approval.

Product Quality Microbiology
Because the route of administration is intravaginal the product is not required to be sterile. The manufacturing process is not an aseptic process. The drug product has a microbial release specification consistent with compendial recommendations and is tested regularly on stability for microbiological quality. No product quality microbiology deficiencies were identified based upon the information provided. From a microbiology perspective, the application is recommended for approval.

Biopharmaceutics
To ensure consistent product performance, an in vitro dissolution test employing USP Apparatus Type 3 at 30 dips per minute and a dissolution medium consisting of 250 mL of 0.1 N HCl with 1.5%, and eventually 0.5%, sodium laurel sulfate at 37°C was developed. The applicant has agreed to an acceptance criterion of (b) (4)(Q) of the labeled contents dissolved in 60 minutes.

To demonstrate that the manufacturing process used by Catalent for the

registration/stability batches and the process used at (b) (4). for clinical and registration/stability batches produces equivalent product, a comparison of the dissolution profiles for (b) (4) manufactured at Catalent (b) (4) was performed. The two-sample T-test concludes that the means at the 30, 60, 90, and 120 minute time points do not differ from each other. Data provided for 4 mcg and 10 mcg products demonstrate that about (b) (4) or more API is dissolved at the first few time points, and although a similarity factor f2 could not be calculated, the in vitro release profiles are considered comparable.

Note that the USP Estradiol Vaginal Inserts monograph specifies dissolution testing with Apparatus 1 and a pH 4.75 phosphate buffer dissolution medium, and sampling at 3, 5 and 10 hours.

From a Biopharmaceutics perspective NDA 208564 is recommended for approval. In addition to recommending that the applicant petition the USP to incorporate the new test and acceptance criterion into the compendial monograph, it is recommended that the applicant perform dissolution method validation in accordance with US<1092>, The Dissolution Procedure: Development And Validation, and adopt appropriate acceptance criteria.

Manufacturing Facilities

The identification of the manufacturing facilities, their roles and responsibilities, as well as final recommendations, is presented in Table 2.

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Dr. Pai concluded that all facilities are acceptable to support approval of NDA208564.

Environmental Assessment
The applicant requested a categorical exclusion from the environmental assessment requirements in accordance with 21 CFR 25.31(b). In support of this request, the applicant has calculated an expected introduction concentration EIC-Aquatic of 2.82 x 10-5 ppb. This is well below the 1 ppb threshold. The applicant has also stated that to their knowledge no extraordinary circumstances exist. Although estradiol is a hormonally active compound, the environmental assessment team has advised that the categorical exclusion can be granted.

Overall Recommendations and Conclusion on Approvability
Per the Technical Lead Review of Dr. Mark Seggel, in its present form, TherapeuticsMD's 505(b)(2) New Drug Application 208564, for estradiol vaginal inserts, 4 mcg, 10 mcg, (b) (4) mcg per vaginal insert is not ready for approval. Labeling (package insert, container/carton) negotiations have not been completed, and in its present form, the labeling does not comply with the requirements under 21 CFR 201. Labeling deficiencies and comments will not be conveyed to the applicant during the current review cycle.

Although numerous deficiencies were noted during a recent inspection of the manufacturer of the phase 3 clinical trials materials, (b) (4), the totality of information indicates that those materials were of suitable quality for investigational use. The quality of the investigational product is consistent with the commercial product manufactured by Catalent.

Sufficient information and supporting data have been provided in accordance with 21CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. The commercial drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status. The claimed categorical exclusion from

the environmental assessment requirements is granted.

Because there is a USP drug product monograph for estradiol vaginal inserts, 10 mcg (b) (4) mcg per insert, there is an expectation that the TherapeuticsMD product will meet the compendial monograph requirements. However, because the TherapeuticsMD product is a soft gelatin capsule formulation that is quite distinct from the tablet formulation (i.e., Vagifem) upon which the USP monograph is based, and because a new, lower strength (4 mcg) is proposed, the USP monograph is not a suitable public standard for TherapeuticsMD's new drug product. TherapeuticsMD, should therefore petition the USP with proposed revisions to the monograph in order to accommodate TherapeuticsMD's new drug product.

Dr. Seggel suggested the following comments for the NDA 208564 Action Letter:

- "We remind you that the current USP includes a monograph for estradiol vaginal inserts. We understand that the current USP monograph may not be a suitable public standard for your new drug product. However, there is an expectation that your product will conform to the compendial monograph requirements. Alternatively, deviations from the monograph requirements should be identified on your product labels. We recommend that you petition the USP with proposed revisions to the monograph in order to accommodate your new drug product. Please see the following link for more information about that USP process: http://www.usp.org/usp-nf/pending-monographs."
- Specifically, we note differences in assay test method and acceptance criteria, the dissolution test method and acceptance criteria, and in the procedure for determining related substances.
- The proposed analysis of estradiol related compounds and degradation impurities by HPLC-MS may be acceptable for quality control purposes in the firm's laboratory but is currently unacceptable for regulatory purposes because the method does not work with a similar mass spectrometer in two different locations. It is therefore incumbent upon you to propose methods that are suitable for regulatory purposes.
- With regard to the dissolution test method, we recommend that you perform dissolution method validation in accordance with US<1092>, The Dissolution Procedure: Development and Validation, and adopt appropriate acceptance criteria."

4. Nonclinical Pharmacology/Toxicology

The non-clinical pharmacology and toxicology information presented in the application was reviewed by Kimberly Hatfield, Ph.D., Office of New Drugs (OND), Office of Drug Evaluations 3 (ODE 3), DBRUP. The following is from the Executive Summary of Dr. Hatfield's Nonclinical Pharmacology and Toxicology Review.

The applicant is seeking approval via the 505(b)(2) pathway and intends to rely on published literature for the nonclinical toxicology, genotoxicity and carcinogenicity sections of this NDA. This will inform Sections 8 and 13 of the labeling.

The safety of estradiol is well-established and documented in the published literature following many years of clinical use. There are also a number of approved products that contain estradiol as the active pharmaceutical ingredient at the same or similar doses, and for the same or similar indication as TX-004HR (e.g. Vagifem, Femring, Estrace, and Estring). As such, the applicant has not conducted any nonclinical studies of their own for estradiol, and proposes to rely on relevant published literature to support the nonclinical safety of estradiol, and to inform nonclinical sections of labeling. The literature that the applicant has submitted is adequate to support the nonclinical safety of estradiol without relying on previous findings of safety for an approved product.

The applicant conducted a 28-day repeat dose toxicity study in rabbits to evaluate the safety of the novel excipient (b) (4) (b) (4) has been used in other approved products, but there are no listed intravaginal dosage routes in the FDA Inactive Ingredient Database, and the amount proposed for (b) (4) estradiol vaginal insert is considerably higher than the maximum potency amounts listed for topical cream/gel administration, or oral gel administration. The results of the completed study showed that test article containing (b) (4) not a vaginal irritant compared to control, and that the amount of (b) (4) present in the formulation is acceptable for use in the drug product. The 28-day repeat dose toxicity study in rabbits also bridges to literature data that documents the safety of estradiol via other routes of administration, and supports the vaginal use of this product.

From a Preclinical Pharmacology/Toxicology standpoint, Dr. Hatfield concludes that nonclinical data support approval of NDA 208564.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review was performed by Li, Li Ph.D., and LaiMing Lee, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology (DCP) 3.

Phase 3 Trial TXV14-01 (refer to Efficacy - Section 7 of this review for a discussion of objectives, design and conduct of this trial) included pharmacokinetic (PK) assessment of analytes of estradiol, estrone, and estrone conjugates, in a subset of participating women (N= 72) on Days 1, 14, and 84 (4 days after last dose of drug or placebo) of the trial. This subset consisted primarily of Caucasian women (range 88.9 to 100% in the individual treatment arms), mean age of 58.5 years (range 41 to 75 years of age) with mean body mass index (BMI) of 28.2 kg/m^2 (range 27.2 -28.9 kg/m^2). Blood sampling was obtained pre-dose and 2, 4, 6, 10, and 24 hours post-dose on Days 1 and 14 and one sampling on Day 84.

Because estradiol and free and conjugated estrone are present in women as endogenous compounds, the analyses determined PK parameters as both "baseline-unadjusted" and "baseline-adjusted" values. The Baseline was determined by averaging concentration of the analyte at Screening and on Day 1 before dosing (Time=0). Screening and Day 1 pre-dose concentrations were averaged and considered baseline for each subject, unless either measurement resulted in a non-quantifiable value. In this case, reasonable scientific judgment was utilized to estimate a baseline, endogenous estrogen concentration. This baseline value was subtracted at each time point to determine a new, baseline-adjusted concentration for subsequent PK analysis. If the baseline-adjusted concentration resulted in a

negative number, the negative number was included in the PK analysis. In the calculation of the unadjusted AUC_{0-24} and $C_{avg\ (0-24)}$ for each analyte and for each visit (Day 1 and Day 14), the concentration at time zero was set at 0.0 pg per mL. All other PK parameters, including all PK concentrations and Baseline concentration, are unaffected by this rule.

Because of problematic (unreliable) bioanalytical method for estrogen conjugates, the accuracy of estrogen conjugate PK measurements is in doubt. The incurred sample reanalysis failed with only 33.7% of samples meeting the acceptance criteria. The applicant was unable to identify the root cause of the incurred sample reanalysis (ISR) failure. The reader is referred to the Dr. Lee's review for a discussion of this issue. Dr. Lee recommends not (b) (4) For this reason, this review will emphasize discussion of the analytes estradiol and estrone in the evaluation of Trial TXV14-01.

Baseline concentrations of estradiol, estrone and estrone conjugates for Trial TXV14-01 are presented in the following Table 3.

Table 3: Concentrations of Estradiol, Estrone and Estrone Conjugates at Baseline Determination in Trial TXV14-01

Estradiol				
Estradiol Concentration (pg/mL)	**E_2 Vaginal Insert 4 mcg (N=18)**	**E_2 Vaginal Insert 10 mcg (N=19)**	**E_2 Vaginal Insert 25 mcg (N=18)**	**Placebo (N=17)**
Mean (SD)	3.923 (2.433)	4.948 (3.391)	3.624 (1.697)	4.494 (2.605)
Median, CV (%)	2.79, 62.02	3.66, 68.53	3.31, 46.82	3.78, 57.97
Min, Max	2.00, 11.20	2.09, 15.70	2.00, 8.31	2.00, 10.10
Estrone				
Estrone Concentration (pg/mL)	**E_2 Vaginal Insert 4 mcg (N=18)**	**E_2 Vaginal Insert 10 mcg (N=19)**	**E_2 Vaginal Insert 25 mcg (N=18)**	**Placebo (N=17)**
Mean (SD)	15.33 (4.803)	20.34 (8.567)	16.73 (7.794)	19.37 (8.778)
Median, CV (%)	15.30, 31.33	19.20, 42.12	15.20, 46.58	17.50, 45.33
Min, Max	8.51, 27.40	9.61, 42.60	8.03, 34.50	6.51, 37.00
Estrone Conjugate				
Estrone Conjugate Concentration (pg/mL)	**E_2 Vaginal Insert 4 mcg (N=18)**	**E_2 Vaginal Insert 10 mcg (N=19)**	**E_2 Vaginal Insert 25 mcg (N=18)**	**Placebo (N=17)**
N	18	19	18	16
Mean (SD)	237.7 (180.8)	239.2 (174.2)	343.4 (421.1)	275.9 (152.6)
Median, CV (%)	183, 76.04	179, 72.86	176, 122.6	293, 55.3

Min, Max	25.0, 672	59.3, 670	62.6, 1460	67.2, 627

Source: Clinical Pharmacology Review, Individual Study Reports, Tables 4, 7 and 10, pages 65, 68 and 71 and adapted from NDA 208564, Clinical Trial Report for Trial TXV14-01

At baseline the mean estradiol concentration for each group in the PK subset was less than 5 pg per mL; individual values ranged from 2.00 [the lower limit of quantification; LLOQ)] to 15.70 pg per mL. Mean estrone concentrations were less than 21 pg per mL. The values for estradiol and estrone in this trial are consistent with expected concentrations of these analytes in healthy postmenopausal women, albeit somewhat lower. In a study of hormone concentrations in postmenopausal women with and without (i.e., normal endometrium) endometrial cancer, mean baseline estradiol concentration was 11.7 ± 1.4 pg per mL and mean baseline estrone was 28.5 ± 4.7 pg per mL[1]. In a subsample of adherent participants from the active and placebo-control groups of the estrogen-alone and estrogen plus progestin subtrials of the Women's Health Initiative, who were selected for determination of selected sex hormones at baseline and one year after randomization, mean baseline estradiol levels at baseline was 13.3 pg per mL in the estrogen-alone arm and 10.9 pg per mL in the estrogen plus progestin arm, and mean baseline estrone was 41.4 pg per mL in both arms[2]. Baseline serum estradiol and estrone concentrations correlate with age since menopause, body weight and fat percentage in postmenopausal women.

Table 4 provides baseline-adjusted pharmacokinetic (PK) parameters for estradiol, estrone and estrone conjugates following once daily administration of 4, 10 and 25 mcg of estradiol vaginal insert or placebo (refer to Dr. Lee's review for presentation and discussion of baseline-unadjusted PK parameters for the evaluated analytes following once daily administration of 4, 10 and 25 mcg of estradiol vaginal insert or placebo).

[1] Judd H, Lucas WE, and Yen, SS. Serum 17-beta estradiol and estrone levels in postmenopausal women with and without endometrial cancer. J. Clin Endocrinol Metab 1976;43(2):272-278

[2] Edlefsen K, Jackson RD, et al. The effects of postmenopausal hormone therapy on serum estrogen, progesterone and sex hormone binding globulin levels in healthy post-menopausal women. Menopause 2010;173(3)622-629

Table 4: **Baseline-adjusted Estradiol, Estrone and Estrone Conjugate PK Parameters Following Once Daily Administration of Estradiol Vaginal Insert, 4, 10, and 25 mcg in Trial TXV14-01.**

Estradiol						
Estradiol Parameter	**Day**	**Statistic**	**E_2 Vaginal Insert 4 mcg (N=18)**	**E_2 Vaginal Insert 10 mcg (N=19)**	**E_2 Vaginal Insert 25 mcg (N=18)**	**Placebo (N=17)**
C_{max} (pg/mL)	Day 01	Mean (SD)	2.562(2.173)	5.994(4.441)	26.18(18.19)	2.056(3.479)
		Median, CV	2.33,84.81	5.14,74.08	19.6,69.47	0.895,169.2
		Pairwise test*	0.6074	0.0059	<0.0001	--
	Day 14	Mean (SD)	1.332(1.077)	2.984(1.734)	12.05(7.321)	0.99(1.815)
		Median, CV	1.1,80.88	2.89,58.1	10.8,60.78	0.73,183.4
		Pairwise test*	0.5088	0.0022	<0.0001	--
AUC_{0-24} (h*pg/mL)	Day 01	Mean (SD)	-0.42(46.26)	19.45(22.77)	130.4(111.9)	8.793(32.28)
		Median, CV	7.87,-11100	19.8,117	75.8,85.85	3.01,367.2
		Pairwise test*	0.5018	0.2564	0.0001	--
	Day 14	Mean (SD)	3.348(16.25)	5.662(29.25)	84.58(62.7)	-3.686(30.69)
		Median, CV	1.45,485.3	7.16,516.6	53.8,74.12	-3.65,-832.6
		Pairwise test*	0.4098	0.3629	<0.0001	--
Estrone						
Estrone Parameter	**Day**	**Statistic**	**E_2 Vaginal Insert 4 mcg (N=18)**	**E_2 Vaginal Insert 10 mcg (N=19)**	**E_2 Vaginal Insert 25 mcg (N=18)**	**Placebo (N=17)**
C_{max} (pg/mL)	Day 01	Mean (SD)	0.42(3.045)	3.178(2.987)	5.115(4.776)	6.327(12.81)
		Median, CV	-0.235,724.5	3.4,93.99	5,93.37	1.6,202.4
		Pairwise test*	0.0659	0.3046	0.71	--
	Day 14	Mean (SD)	0.65(3.488)	3.655(8.792)	5.638(4.806)	3.441(5.686)
		Median, CV	-0.05,539.3	2.2,240.6	5.58,85.25	1.8,165.2
		Pairwise test*	0.0938	0.933	0.2249	--
AUC_{0-24} (h*pg/mL)	Day 01	Mean (SD)	-64.12 (81.83)	-25.4 (63.84)	17.46 (89.57)	3.101 (120.8)
		Median, CV	-58.2, -127.6	-15.9, -251.4	20.1, 513.1	-38.6, 3894
		Pairwise test*	0.0612	0.3751	0.6910	--
	Day 14	Mean (SD)	-41.25 (78.04)	-22.56 (141.8)	27.03 (115.3)	-38.01 (91.14)
		Median, CV	-50.5, -189.2	-49.1, -628.4	15.6, 426.6	-25.1, -239.8
		Pairwise test*	0.9120	0.7058	0.0742	--

Estrone Conjugate						
			E_2 Vaginal Insert 4 mcg	**E_2 Vaginal Insert 10 mcg**	**E_2 Vaginal Insert 25 mcg**	**Placebo**
Parameter	**Day**	**Statistic**	**(N=18)**	**(N=19)**	**(N=18)**	**(N=17)**
C_{max} (pg/mL)	Day 01	Mean (SD)	35.41(89.09)	90.24(65.2)	198.6(301.5)	27.12(49.69)
		Median, CV	15.3,251.6	73,72.25	177,151.8	36.7,183.2
		Pairwise test*	0.7444	0.0033	0.0318	--
	Day 14	Mean (SD)	48.16(132.6)	277.8(493.6)	236.1(372.4)	67.05(121.8)
		Median, CV	35,275.4	121,177.7	192,157.8	39,181.7
		Pairwise test*	0.6735	0.1065	0.0928	--
AUC_{0-24} (h*pg/mL)	Day 01	Mean (SD)	-510.1 (2123)	192.1 (821)	883.8 (7001)	-807.7 (1127)
		Median, CV	-322, -416.3	287, 427.3	1420, 792.2	-437, -139.5
		Pairwise test*	0.6199	0.0047	0.3473	--
	Day 14	Mean (SD)	-606.2 (2897)	3364 (7934)	1688 (7209)	-189 (2157)
		Median, CV	-65.1, -477.8	419, 235.9	2300, 427	-368, -1141
		Pairwise test*	0.6439	0.0928	0.3244	--

Source: Clinical Pharmacology Review, Individual Study Reports, Tables 6, 9, and 12, pages 67, 71 and 74; adapted from NDA 208564, Clinical Trial Report for Trial TXV14-01

For the analyte estradiol when compared to the placebo group, the baseline-adjusted C_{max} and AUC_{0-24} were significantly higher for estradiol vaginal insert 25 mcg on both Day 1 and Day 14. For estradiol vaginal insert 10 mcg, baseline-adjusted C_{max}, but not AUC_{0-24}, was significantly higher compared to placebo on both Day 1 and Day 14. Both C_{max} and AUC_{0-24} were lower on Day 14 compared to Day 1. There was no statistical difference in baseline-adjusted AUC_{0-24} and C_{max} between estradiol vaginal insert 4 mcg and placebo on either Day 1 or Day 14.

Estradiol concentrations at Day 84 were similar to Baseline levels for estradiol vaginal insert 4 mcg (4.25 vs 3.92 pg per mL), 10 mcg (4.79 vs 4.95 pg per mL, respectively) and placebo (4.36 vs 4.49 pg per mL) groups. For the estradiol vaginal insert 25 mcg group, the Day 84 concentration was 6.65 pg per mL vs 3.62 pg per mL at Baseline. The current data suggests no significant estradiol accumulation at Day 84.

For the analyte estrone, when compared to the placebo group, the baseline-adjusted C_{max} and AUC_{0-24} for estradiol vaginal insert 10 mcg and 25 mcg groups were similar to the placebo group with no statistically significant differences noted at either day. The estradiol vaginal insert 4 mcg group demonstrated numerically lower estrone PK parameters compared to placebo; however these were not statistically significant.

For the analyte estrone sulfate when compared to the placebo group, the baseline-adjusted C_{max} was significantly higher for estradiol vaginal insert 10 and 25 mcg on Day 1 only. The baseline-adjusted C_{max} on Day 15 for both the 10 and 25 mcg estradiol vaginal inserts were not statistically significantly different from placebo. For the baseline-adjusted AUC_{0-24}

parameter, only the Day 1 evaluation for the 10 mcg estradiol vaginal insert was statistically significantly different from placebo. Baseline-adjusted AUC_{0-24} parameters for Day 14 for the estradiol vaginal insert 10 mcg and both Day 1 and Day 14 for estradiol vaginal insert 25 mcg were not statistically significantly different from placebo.

PK parameter evaluations were also performed in phase 1 Trials ESTR-1K-499-12 and ESTR-1K-500-12. Both trials were comparative PK trials with Vagifem as the reference drug and were conducted outside of the U.S. (Namil Nadu India) in healthy postmenopausal women. Note that the difference in population body mass index in this region of India vs. the U.S could possibly influence the outcome.

Trials ESTR-1K-499-12 and ESTR-1K-500-12 were both open-label, randomized, two-treatment, two period, two-sequence, single-dose, 2-way crossover trials designed to assess the relative bioavailability of 10 mcg (Trial ESTR-1K-499-12) or 25 mcg (Trial ESTR-1K-500-12) estradiol vaginal insert (Test) vs a 10 mcg (Trial ESTR-1K-499-12) or 25 mcg (Trial ESTR-1K-500-12) dose of Vagifem® (Reference). Both trials randomized 36 healthy postmenopausal women (18 women randomized to Test and 18 women randomized to Reference in each period). The trials were conducted in Namil Nadu, India. Trial participants were housed in the clinical facility for two consecutive nights for each of two dosing periods, from at least 11 hours before dosing (at least 10 hours fasting) until after the 24 hours post dose blood draw in each period. All trial participants received the Test ((b) (4) 10 mcg estradiol vaginal insert, manufactured by (b) (4). (b) (4) in Trial ESTR-1K-500-12) and Reference (Vagifem® 10 mcg estradiol vaginal insert, manufactured by Novo Nordisk A/S, Lot No. CE70136 in Trial ESTR-1K-499-12 or 25 mcg estradiol vaginal insert, manufactured by Novo Nordisk A/S, Lot No. CE70169) products, inserted intravaginally, during the trial (one product per dosing period), with a 14-day washout period between dosing periods. Each woman was required to remain in a supine position for 4 hours after dosing and to refrain from strenuous activity until they were checked out of the clinical facility. Trial participants were fasted for an additional four hours after dosing, then provided a standard diet. A total of 13 blood samples were taken at prescribed time points per the trial protocol: -1.00, -0.50, 0.00, 1.00, 2.00, 4.00, 6.00, 8.00, 10.00, 12.00, 14.00, 18.00 and 24.00 hours with reference to the time of insertion of the Test and Reference inserts into the vagina. After completion of Period I of the trial, trial participants entered a 14-day washout period prior to crossing over to Period II. All procedures in Period II were identical to those described for Period I with subjects receiving the alternative treatment.

In Trial ESTR-1K-499-12, plasma samples were analyzed for estradiol and estrone simultaneously using a LC-MS/MS method, and a separate LC-MS/MS method was used for the determination of estrone sulfate in plasma. Analysis was performed at Esoterix Endocrinology, Calabasas, California. The lower limits of quantification for estradiol, estrone, and estrone sulfate were 1.0 pg per mL, 2.5 pg per mL, and 10.0 pg per mL, respectively, during analysis. Pharmacokinetic parameters for baseline-adjusted and baseline-unadjusted estradiol, estrone, and estrone sulfate were determined by performing a non-compartmental analysis. Estimates of the PK parameters area under the concentration-time curve to 24 hours (AUC_{0-24}), peak concentration (C_{max}), and time to reach peak

concentration (T_{max}) were reported. In Trial ESTR-1K-500-12, trial plasma samples were analyzed at Micro Therapy Research Labs Private Limited, Chennai, India. Per the application, trial samples were analyzed for estradiol and estrone using a validated LC-MS/MS method over a concentration range of 1.9960 to 703.1640 pg per mL and 9.9080 to 3490.5920 pg per mL, respectively. Estrone sulfate was determined using a validated LC-MS/MS method over a concentration range of 20.0760 to 5098.6680 pg per mL

Subjects in Trial ESTR-1K-499-12 were healthy adult human postmenopausal female volunteers between 40-65 years of age (mean 50.47 years of age) with a body mass index (BMI) range between 18.50 kg/m^2 and 29.99 kg/m^2 (mean 25.33 kg/m^2) and mean weight of 57.26 kg.. Thirty five (35) women completed the trial.

Table 5 presents a summary of the baseline-adjusted PK parameters arithmetic means ± standard deviation of test product and reference product for estradiol, estrone, and estrone sulfate in Trial ESTR-1K-499-12 (refer to the reviews of Drs. Lee and van der Vlugt for discussion of baseline unadjusted results).

Table 5: Summary of Pharmacokinetic (PK) Parameters (Arithmetic Mean ± Standard Deviation) of Test Product (10 mcg (b) (4) Estradiol Vaginal Insert, TX-004HR) and Reference Product (10 mcg Vagifem®) for Estradiol, Estrone and Estrone Sulfate – Baseline-Adjusted in Trial ESTR-1K-499-12

Estradiol		
Pharmacokinetic Parameter	**Arithmetic Mean ± SD**	
	Test Product (Tx-004HR)	**Reference Product (Vagifem®)**
C_{max} (pg/mL	15.72 ± 7.92	24.19 ± 11.93
AUC_{0-24} (pg hr/mL	53.01 ± 19.56	163.86 ± 72.09
Tmax (hr)	1.98 ± 1.29	10.53 ± 5.58
Estrone		
Pharmacokinetic Parameter	**Arithmetic Mean ± SD**	
	Test Product (Tx-004HR)	**Reference Product (Vagifem®)**
C_{max} (pg/mL	6.85 ± 6.58	8.83 ± 7.15
AUC_{0-24} (pg hr/mL	34.71 ± 27.95	63.00 ± 46.55
T_{max} (hr)	9.12 ± 8.83	11.16 ± 7.24
Estrone Sulfate		
Pharmacokinetic Parameter	**Arithmetic Mean ± SD**	
	Test Product (Tx-004HR)	**Reference Product (Vagifem®)**
C_{max} (pg/mL	13.9 ± 7.0	19.3 ± 11.4
AUC_{0-24} (pg hr/mL	98.0 ± 80.9	177.6 ± 166.2
T_{max} (hr)	6.3 ± 4.6	10.3 ± 5.6

Source: Clinical Pharmacology Review, Individual Study Reports, Tables 1,3 and 5, page 37, 39, and 41; Clinical Review Table 2, page 35 and adapted from NDA 208564, Clinical Trial Report for ESTR-1K-499-12, Tables 11, 12, 17, 18, 23, and 24 page 47 , 52, 53, 57 and 58.

Statistical analyses of geometric least square means, intra-subject coefficient of variation (CV%), Test/Reference (T/R) ratios (expressed as a percentage) and 90% CI for C_{max} and AUC_{0-24} for baseline adjusted and unadjusted data of estradiol, estrone and estrone sulfate,

were performed. The baseline-adjusted comparative bioavailability results for Trial ESTR-1K-499-12 are summarized in Table 6 (refer to the reviews of Drs. Lee and van der Vlugt for discussion of baseline unadjusted results).

Table 6: Statistical Results of 10 mcg (b) (4) Estradiol Vaginal Insert, TX-004HR, Versus 25 mcg Vagifem® for Baseline-Adjusted Estrogens in Trial ESTR-1K-499-12

	PK Parameter	Geometric Least Square Mean		Intra-Subject CV%	T/R Ratio (%)	90% Confidence Interval
		Test Product (T)	Reference Product (R)			
Estradiol (N=34)	**C_{max} (pg/mL)**	14.45	20.20	60.68	71.54**	56.82 - 90.08
	AUC $_{0-24}$ (pg.hr/mL)	49.73	131.04	70.64	37.95**	29.21 - 49.31
Estrone (N=33)	**C_{max} (pg/mL)**	5.16	6.93	47.59	74.50**	61.69 - 89.97
	AUC $_{0-24}$ (pg.hr/mL)	24.20	47.90	73.66	50.51**	38.37 - 66.50
Estrone Sulfate (N=24)	**C_{max} (pg/dL)**	12.3	16.5	48.02	74.55**	59.43 - 93.51
	AUC $_{0-24}$ (pg.hr/dL)	68.5	118.4	73.87	57.87**	41.68 - 80.35

**Comparison was detected as statistically significant ($P < 0.05$).

Source: Clinical Pharmacology Review ,Individual Study Reports, Table 7, page 42-43; Clinical Review Table 4 page 36 and adapted from NDA 208564, Clinical Trial Report for ESTR-1K-499-12, Tables 29, 31and 33, page 62,63 and 64 of 88.

Systemic exposures of estradiol, estrone and estrone sulfate following vaginal administration of (b) (4) estradiol vaginal insert 10 mcg were statistically significantly lower than that of VAGIFEM 10 mcg in healthy postmenopausal women.

Subjects in Trial ESTR-1K-500-12 were healthy adult human postmenopausal female volunteers between 40-65 years of age (mean 49.86 years of age) with a body mass index (BMI) range between 18.50 kg/m^2 and 29.99 kg/m^2 (mean 25.61 kg/m^2) and mean weight of 57.47 kg. Thirty six (36) women completed the trial.

Tables 7 presents a summary of the baseline-adjusted PK parameters arithmetic means ± standard deviation of test product and reference product for estradiol, estrone, and estrone sulfate in Trial ESTR-1K-500-12.

Table 7: Summary of Pharmacokinetic (PK) Parameters (Arithmetic Mean ± Standard Deviation) of Test Product (25 mcg (b) (4) VTX-004HR) and Reference Product (25 mcg Vagifem®) for Estradiol, Estrone and Estrone Sulfate – Baseline-Adjusted in Trial ESTR-1K-500-12

Estradiol		
Pharmacokinetic Parameter	**Arithmetic Mean ± SD**	
	Test Product (Tx-004HR)	**Reference Product (Vagifem®)**
C_{max} (pg/mL	25.33 ± 12.55	51.53 ± 33.23
AUC_{0-24} (pg hr/mL	99.85 ± 57.91	350.5 ± 163.0
T_{max} (hr)	1.92 ± 0.50	12.50 ± 5.66
Estrone		
Pharmacokinetic Parameter	**Arithmetic Mean ± SD**	
	Test Product (Tx-004HR)	**Reference Product (Vagifem®)**
C_{max} (pg/mL	14.19 ± 11.18	30.50 ± 31.40
AUC_{0-24} (pg hr/mL	90.42 ± 85.5	233.6 ± 215.5
T_{max} (hr)	6.34 ± 4.64	13.35 ± 6.73
Estrone Sulfate		
Pharmacokinetic Parameter	**Arithmetic Mean ± SD**	
	Test Product (Tx-004HR)	**Reference Product (Vagifem®)**
C_{max} (pg/mL	727.6 ±668.3	969.0 ± 814.8
AUC_{0-24} (pg hr/mL	6533 ± 6092	9343 ± 7370
T_{max} (hr)	13.26 ± 6.10	16.22 ± 3.47

Source: Clinical Pharmacology Review, Individual Study Reports, Tables 3and 5, pages 50, 52 and 54 and Clinical Review; Tables 6, page 38 and adapted from NDA 208564, Clinical Trial Report for ESTR-1K-500-12, Tables 10, 11, 16, 17, 22and 23, pages 46, 47, 53 and 59.

Statistical analyses of geometric least square means, intra-subject coefficient of variation (CV%), Test/Reference (T/R) ratios (expressed as a percentage) and 90% CI for Cmax and AUC0-24 for baseline adjusted and unadjusted data of estradiol, estrone and estrone sulfate, were performed. The baseline-adjusted results for Trial ESTR-1K-500-12 are summarized in Table 8. Refer to the reviews of Drs. Lee and van der Vlugt for discussion of baseline unadjusted results.

Table 8: Statistical Results of 25 mcg (b) (4) Estradiol Vaginal Insert Versus 25 mcg Vagifem® for Baseline-Adjusted Estrogens

	PK Parameter	Geometric Least Square Mean		Intra-Subject CV%	T/R Ratio (%)	90% Confidence Interval
		Test Product (T)	Reference Product (R)			
Estradiol (N=36)	**C_{max} (pg/mL)**	23.08	42.70	54.0	54.1	44.2 - 66.1
	AUC_{0-24} (pg.hr/mL)	89.21	292.1	70.4	30.5	23.7 - 39.3
Estrone (N=36)	**C_{max} (pg/mL)**	10.79	23.58	99.6	45.8	33.0 - 63.6
	AUC_{0-24} (pg.hr/mL)	51.25	165.47	157	31.0	19.8 - 48.4
Estrone Sulfate (N=36)	**C_{max} (pg/dL)**	490.0	730.6	58.8	67.1	53.8 - 83.6
	AUC_{0-24} (pg.hr/dL)	4233	7323	82.6	57.8	43.2 - 77.3

**Comparison was detected as statistically significant (P < 0.05).

Source: Clinical Pharmacology Review, Individual Study Reports, Table 8,page 56; Clinical Review Table 8 page 39and adapted from NDA 208564, Clinical Trial Report for ESTR-1K-500-12, Tables 28, 30, and 32 page 65, 66 and 67of 88.

As was the case with (b) (4) estradiol vaginal insert 10 mcg, systemic exposures of estradiol, estrone and estrone sulfate following vaginal administration of (b) (4) estradiol vaginal insert 25 mcg was statistically significantly lower than that of VAGIFEM 25 mcg in healthy postmenopausal women.

Trial TXV13-01 was designated as a phase 2, 14-day trial (proof-of-concept) of 10 mcg only of estradiol vaginal insert. The objectives were to preliminarily evaluate (explore) efficacy and safety of the 10 mcg dose in reducing severity of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause after 14 days of treatment; systemic exposure; and to estimate the effect size and variability of vulvar and vaginal atrophy endpoints.

Enrollment criteria were similar to TXV14-01. Fifty (50) postmenopausal women (24 in the 10 mcg estradiol vaginal insert treatment group and 26 in the placebo vaginal insert treatment group), 40 to 75 years of age, who met the trial entry criteria for VVA at Baseline, were eligible for the trial. Efficacy measures included change from Baseline (Screening) to Day 15 in:

- The percentage of vaginal superficial cells compared to placebo,
- The percentage of vaginal parabasal cells compared to placebo,
- The vaginal pH compared to placebo,

- Severity of the most bothersome VVA symptom identified by the subject at Baseline (vaginal dryness; dyspareunia; vaginal and/or vulvar irritation or itching; dysuria) compared to placebo,

- Vaginal bleeding associated with sexual activity compared to placebo (presence or absence), and

- Investigator's assessment of the vaginal mucosa compared to placebo.

Per the application, two-week treatment with 10 mcg estradiol vaginal insert resulted in a statistically significant greater mean increase in vaginal superficial epithelial cells than did placebo (35% compared to 9%, respectively; p=0.0002), a statistically significant greater mean decrease in vaginal parabasal epithelial cells than did placebo (54% compared to 5%, respectively; p<0.0001), and a statistically significant reduction in vaginal pH than did placebo (0.97 units compared to 0.34 units, respectively; p=0.0002). However, the decrease in severity of the most bothersome symptom self-identified at Baseline was essentially the same for both 10 mcg estradiol vaginal insert and placebo vaginal insert (-1.043 compared to -1.042, respectively; p=0.9951. These results are not presented in tabular form.

Dose response was not evaluated in 14-day Trial TXV13-01. Trial TXV13-01 compared only one dose of estradiol vaginal insert (10 mcg) with the placebo vaginal insert. Dose response was evaluated in 12-Week, phase 3, Trial TXV14-01.

Per the application, erratic patterns and fluctuations in estradiol concentrations for numerous trial participants were reported. In addition, results from reanalysis of specimens produced vastly different results from the original analysis (> 30%) confirming the "lack of validity of the bioanalytical method used." In addition, approximately 40% of the samples failed to meet assay acceptance criteria during the reanalysis. The applicant considers the estradiol concentrations values obtained during this trial "invalid" and therefore, no pharmacokinetic or statistical analysis for estradiol concentrations was conducted.

In the September 19, 2016, 74-day Filing Review Issues Identified letter, the Division indicated, NDA 20864 does not contain data from one or more drug interaction studies with commonly used vaginal products, such as antifungals. This type of assessment is important in determining if a local drug interaction can affect systemic estrogen exposure and, therefore, impact safety. Address the potential drug interaction between your proposed estradiol vaginal capsules and commonly used vaginal product(s).

On October 10, 2016, the applicant acknowledged that concomitant use of TX-004HR and vaginal antifungals can increase or decrease estrogen exposure, but proposed labeling is consistent with other estrogen products (class labeling) with higher systemic exposure and includes ketoconazole and itraconazole (CYP3A4 inhibitors) that may increase estrogen exposure. Per the Office of Clinical Pharmacology, the rationale provided by the applicant addresses the potential metabolic interaction between estradiol and CYP3A4 inhibitors. However, the applicant did not address how physical interactions with excipients from (b) (4) estradiol vaginal insert and other vaginal products can affect estrogen bioavailability. However, the proposed product is an immediate release product that has

demonstrated low systemic exposure and clearance within 24 hrs. The Office of Clinical Pharmacology determined that no drug-drug interactions between (b) (4) estradiol vaginal insert and other vaginal products would be required.

The Office of Clinical Pharmacology has determined that sufficient and appropriate clinical pharmacology and pharmacokinetic information was submitted in the NDA and they find the application acceptable from a Clinical Pharmacology perspective.

6. Clinical Microbiology

Because the route of administration is intravaginal the product is not required to be sterile. See Section 3 of this review.

From a clinical microbiology perspective, NDA208564 is recommended for approval.

7. Clinical/Statistical - Efficacy

The primary review of the efficacy information in NDA 208564 was performed by Theresa van der Vlugt, M.D., Office of New Drugs (OND)/Office of Drug Evaluations (ODE) 3/DBRUP and Statistical Reviewer, Kate Dwyer, Ph.D., Office of Translational Science/Division of Biometrics III.

DBRUP recommends that trials conducted to support the treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause, evaluate the co-primary endpoints of superficial and parabasal cells from a smear of the middle or second third of the side wall of the vagina, vaginal pH, and change in the moderate-to-severe most bothersome symptom of dyspareunia, assessed at baseline. At baseline, enrollees should have 5% or fewer superficial cells, pH greater than 5 and identify dyspareunia as their most bothersome moderate-to-severe symptom of vulvar and vaginal atrophy. To be successful in support of the indication, results should demonstrate for estradiol vaginal insert compared to placebo, an improvement (i.e., statistically significant increase) in the percentage of superficial vaginal cells **and** improvement (i.e., statistically significant decrease) in the percentage of vaginal parabasal cells **and** improvement (i.e., statistically significant decrease) in vaginal pH **and** improvement (i.e., statistically significant decrease) in the mean change in severity from baseline.

The applicant submitted a single randomized and placebo controlled phase 3 trials, Trial TX 14-01 to support the efficacy of estradiol vaginal insert. For the determination of efficacy, this was appropriate.

The primary objective of Trial TXV14-01 was to assess the safety and efficacy at 12 weeks of three doses of TX-004HR (4 mcg, 10 mcg, and 25 mcg) compared to placebo on vaginal superficial cells, vaginal parabasal cells, vaginal pH, and the symptom of moderate to severe dyspareunia (vaginal pain associated with sexual activity) as the most bothersome symptom (MBS) associated with VVA.

Subjects were healthy (no active or ongoing chronic medical conditions/disease and no history of alcoholism or drug abuse) postmenopausal women [meeting criteria of 1 year of

spontaneous menses, or greater than 6 months but less than one year of spontaneous menses (or hysterectomized women less than 55 years of age) with FSH greater than 40 IU per mL], who were to be between 40 and 75 years of age [actual mean trial age 59.1± 6.24 years], with normal mammogram within 9 months of randomization, normal breast exam, normal Pap smear within the last 12 months, BMI less than or equal to 38 kg/m^2 (actual mean trial BMI 26.7 kg/m^2) and normal hematology, clinical chemistry, and urinalysis. The majority of enrolled women were Caucasian (86.7%). Non-hysterectomized women were to have had an acceptable result from an evaluable screening endometrial biopsy demonstrating secretory endometrium; endometrial tissue other (including benign, inactive, or atrophic fragments of endometrial epithelium, glands, stroma, etc.); endometrial tissue insufficient for diagnosis; no endometrium identified; or no tissue identified; at least one pathologist must identify sufficient tissue to evaluate the biopsy. Reports by the evaluating central pathologists of Other findings must specify one of the following: endometrial polyp not present; benign endometrial polyp; or polyp other. Note because endometrial polys are subject to estrogen stimulation, the Clinical Team disagrees with the applicant having enrolled women with any type of endometrial polyp in this trial of an estrogen product. Women were to be sexually active (vaginal penetration within approximately one month of screening and anticipate sexual activity during the conduct of the trial. Only women who met the criteria of having 5% or fewer superficial cells, pH greater than 5 and identified dyspareunia as their most bothersome moderate-to-severe symptom of vulvar and vaginal atrophy were included in the efficacy analyses.

The trial was conducted between November 1, 2014 and September 30, 2015. Seven hundred and sixty-four (764) healthy postmenopausal women were randomized in a 1:1:1:1 ratio to receive:

- 4 mcg estradiol vaginal insert [191 women randomized (batch number: PN0089-10); 175 (91.6%) completers]; 1 insert daily for 2 weeks, then 1 insert twice weekly for 10 weeks
- 10 mcg estradiol vaginal insert [191 women randomized (batch number: PN 0089-08); 174,(91.1%) completers]; 1 insert daily for 2 weeks, then 1 insert twice weekly for 10 weeks
- 25 mcg estradiol vaginal insert [190 women randomized 9 batch number: PN 0089-09); 177 (93.2%) completers]; 1 insert daily for 2 weeks, then 1 insert twice weekly for 10 weeks
- Placebo vaginal insert [192 women randomized (batch number: PN089-07); 178 (92.7%) completers]; 1 insert daily for 2 weeks, then 1 insert twice weekly for 10 weeks

Women received vaginal inserts as a once daily intravaginal treatment for the first 2 weeks and a twice weekly intravaginal maintenance for the following 10 weeks. Participating women were trained by the clinical site staff to self-administer the capsule intra-vaginally. Women were instructed to find their most comfortable position and insert the capsule with the smaller end up into vaginal canal for about 2 inches. The capsule was to be applied approximately the same hour for the first 14 days. Under the twice weekly regimen, the two

drug administrations should be three to four days apart, and should not have exceeded more than twice in a seven-day period. Women were seen in the clinic: Weeks -4 to 0 [Visits 1A and 1B (Screening)]; Day 1 [Week 0, Visit 2 (Randomization/Baseline)]; Day 14 [(± 3days), Week2, Visit 3 (Interim)]; Day 42 [(± 3days), Week 6, Visit 4 (Interim)]; Day 56 [(± 3days), Week 8, Visit 5 (Interim); and Day 84 [(± 3days), Week 12, Visit 6 (End-of-Treatment/Early Termination)]. During Week 14 (approximately 15 days after the last dose of the investigational product), women received a telephone call and interview.

Efficacy information on vulvar and vaginal atrophy symptoms and signs was collected as follows:

- Vaginal cell maturation:
  Vaginal smears were collected from the lateral vaginal walls according to standard procedure at Screening 1B and Weeks 2, 5, 8, and 12 (or early termination) and sent to a central laboratory. The percentage of superficial, parabasal, and intermediate cells were determined. All on-therapy/early termination vaginal cytology results were blinded to the applicant, investigators and the trial participants. The mean change from Baseline to Week 12 (proportion of superficial and parabasal cells) was evaluated.
- Vaginal pH:
  A pH indicator strip was applied to the lateral vaginal wall at Screening 1B and Weeks 2, 5, 8, and 12 (or early termination) until it became wet, taking care to avoid cervical mucus known to affect vaginal pH. The color of the strip was immediately compared with a colorimetric scale and the measurement recorded. The mean change from Baseline to Week 12 was evaluated.
- Self-assessment of vaginal symptoms:
  The self-assessment of symptoms was evaluated by use of the VVA Symptom Self-Assessment Questionnaire at Screening Visit 1B and at Visit 3 (Week 2, Day 14 ± 3 days), Visit 4 (Week 6, Day 42 ± 3 days), Visit 5 (Week 8, Day 56 ± 3 days), and Visit 6 (Week 12, Day 84 ± 3 days). The mean change from Baseline (Screening Visit 1B, Day 1) to Week 12 in moderate to severe dyspareunia was evaluated as the primary efficacy endpoint.

All trial participants who were randomly assigned and had at least one dose of trial medication formed the intent to treat (ITT) population. The modified intent-to-treat (MITT) population was the primary efficacy population with supportive efficacy analyses conducted on the efficacy evaluable (EE) population. MITT population was defined as all ITT trial participants who received the treatment to which they were randomized, had baseline values for all co-primary variables, and had at least one post-baseline value for any of the following co-primary variables at any visit (superficial cells, parabasal cells, vaginal pH, or MBS of dyspareunia). Seven hundred sixty four (764) women were included in the mITT population.

For additional details of the design and conduct of Trial TXV14-01, including population definitions, evaluated primary and secondary endpoints and their analyses, the reader is referred to the reviews from Drs. van der Vlugt and Dwyer.

The disposition of the mITT population in 12-week, phase 3 Trial TXV14-01 is summarized in Table 9.

Table 9: Disposition of Enrolled Postmenopausal Women in Trial TXV14-01

Disposition	TX-004HR 4 mcg	TX-004HR 10 mcg	TX-004HR 25 mcg	Placebo
Number Randomized	191	191	190	192 (
Modified Intent-to-Treat (mITT) population	186 (100%)	188(100%)	86 (100%)	187 (100%)
Number and Percentage Completing Trial	175 (94.1)	174 (92.6)	177 (95.2)	177 (94.7)
Total Discontinued	11 (5.9%)	14 (7.4%)	9 (4.8)	10 (5.3%)
Reason Discontinued				
- Adverse Event	1 (0.5%)	3 (1.6%)	2 (1.1%)	3 (1.6%)
- Investigator Decision	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)
- Protocol Violation	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
- Withdrew Consent	5 (2.7%)	4 2.1%)	5 (2.7)	4 (2.1%)
- Lack of Efficacy	2 (1.1%)	2 (1.1%)	0 (0.0%)	0 (0.0%)
- Lost-to-follow-up	2 (1.1%)	3 (1.6%)	1 (0.5%)	3 (1.6%)

Source: Adapted from Statistical Review Table 3, page 10, Medical Officer Review Table 14, page 45 and NDA 208564, Trial ERC-231 Clinical Trial Report for TXV14-01, Table 10 Figure 8-1, page 69 of 3533

The primary efficacy analyses of all co-primary endpoints were performed on the modified Intent-to-Treat (ITT) population. The primary efficacy analysis was performed using analysis of covariance (ANCOVA), with the treatment group as the main factor and the baseline value as the covariate. The applicant performed primary efficacy analyses of the most bothersome symptom (MBS) of dyspareunia on the modified Intent-to-Treat (mITT) population utilizing the mixed model for repeated measures (MMRM) method (see Statistical Review Table. 5). Because women who 1) reported no sexual activity at Week 12 (n=68, 9.1% of women) or 2) were missing data on dyspareunia at Week 12 (n=52, 7.0% of women) were excluded from MMRM analysis of the MBS of dyspareunia, the Agency requested additional sensitivity analysis using LOCF to handle missing data.

To account for the multiple comparisons of testing placebo to each of the three doses of the estradiol vaginal insert (4 mcg, 10 mcg and 25 mcg) and the multiple testing of the four co-primary endpoints, the procedural testing started by examining the highest dose (25 mcg) for each of the co-primary endpoints in the following order:

1. vaginal superficial cells
2. vaginal parabasal cells
3. vaginal pH
4. severity of the MBS of dyspareunia

If all of the p-values for each of the four co-primaries were significant ($p \leq 0.05$) then the hypothesis testing continued on to the next lowest dose (10 mcg) for each of the co-primaries, as described above. If all of the four co-primary endpoints were significant

($p \leq 0.05$) for 10 mcg estradiol vaginal insert, then the hypothesis testing continued for the next lowest dose (4 mcg). If at any point the hypothesis testing yielded a non-significant result, the testing was stopped.

Efficacy results for these analyses of the MBS of dyspareunia along with the MMRM analyses of the signs of vaginal superficial and parabasal cells and vaginal pH from Trial TXV14-01 are provided in Table 10.

Table 10: Efficacy Summary of Trial TXV14-01, modified Intent-to-Treat Population (mITT)

Co-Primary Endpoint	**TX-004HR 4 mcg**	**TX-004HR 10 mcg**	**TX-004HR 25 mcg**	**Placebo**
Dyspareunia				
Baseline				
(n)	186	188	186	187
Mean (SD)	2.7 (0.48)	2.6 (0.48)	2.7 (0.44)	2.7 (0.46)
Week 12				
(n)	178	176	174	183
Mean (SD)	1.18 (0.97)	1.03 (0.95)	1.03 (0.97)	1.45 (1.03)
Change from Baseline*				
LS Mean (S.E.)**	-1.50 (0.07)	-1.64 (0.07)	-1.67 (0.07)	-1.25 (0.07)
Difference from. placebo***	-0.25	-0.38	-0.42	--
p-value vs. placebo***	0.0156	0.0002	<0.0001	--
%Superficial Cells				
Baseline				
(n)	186	188	186	187
Mean (SD)	1.3 (1.24)	1.2 (1.23)	1.3 (1.16)	1.3 (1.31)
Week 12				
(n)	170	171	174	172
Mean (SD)	18.7 (19.54	18.5 (19.95)	24.9 (24.23)	7.0 (14.7)
Change from Baseline (SD)				
Mean	-1.54 (1.04)	-1.68 (0.96)	-1.72 (0.94)	-1.28 (1.04)
LS Mean (SE)	17.50 (1.54)	16.72 (1.54)	23.20(1.53)	5.63 (1.54)
Difference vs. placebo****	11.87	11.09	17.57	--
p-value vs. placebo****	<0.0001	<0.0001	<0.0001	--
% Parabasal Cells				
Baseline				
(n)	186	188	186	187
Mean (SD)	52.3 (39.2)	51.3 (38.0)	53.5 (38.3	52.0 (39.2)
Week 12				
(n)	170	171	174	172
Mean (SD)	12.0 (22.3)	7.8 (18.5)	6.6 (16.6)	45.2 (40.3)
Change from Baseline				
Mean (SD)	-41.1 (41.6)	-43.8 (37.8)	-46.2 (40.0)	-6.3 (29.8)
LS Mean (SE)	-40.63 (1.75)	-44.07 (1.75)	-45.55 (1.74)	-6.73 (1.75)
Difference from. Placebo****	-33.90	-37.34	-38.82	--
p-value vs. placebo****	<0.0001	<0.0001	<0.0001	--

Co-Primary Endpoint	TX-004HR 4 mcg	TX-004HR 10 mcg	TX-004HR 25 mcg	Placebo
Vaginal pH				
Baseline				
(n)	186	188	186	187
Mean (SD)	6.3 (0.87)	6.3 (0.83)	6.3 (0.91)	6.3 (1.04)
Week 12				
(n)	170	171	174	174
Mean (SD)	1.1 (0.98)	0.9 (0.92)	1.0 (0.99)	1.4 (1.02)
Change from Baseline				
Mean	-1.33 (1.11)	-1.41 (1.03)	-1.37 (1.14)	-0.26 (1.05)
LS Mean (SE)	-1.32 (0.07)	-1.42 (0.07)	-1.34 (0.07)	-0.28 (0.07)
Difference vs. placebo	-1.03	-1.14	-1.06	--
p-value vs. placebo***	<0.0001	<0.0001	<0.0001	--

* Last Observation Carried Forward (LOCF)
**Difference vs. placebo is the (Week 12 mean for TX-004 minus baseline mean for TX-004) minus (Week 12 mean for placebo minus baseline mean for placebo).
*** ANCOVA: treatment as the main factor and baseline value as the covariate.
**** MMRM = Mixed Model Repeated Measures

Source: Adapted from Statistical Review Tables 6, 9, 10 and 11 page 10, 14 and 15; Medical Officer Review Tables 18 and 19, pages 57 and 58 and NDA 208564 Clinical Trial Report for TXV14-01, Table 25 page 84 of 3533

Abbreviations: mITT = modified Intent-to-Treat, LS = least square, SE = standard error, MMRM = mixed model repeated measures.

Each of the three doses of (b) (4) estrogen vaginal insert individually compared to placebo resulted in a statistically significant increase in the percentage of superficial vaginal cells and statistically significant decrease in the percentage of vaginal parabasal cells and statistically significant decrease in vaginal pH and statistically significant decrease in the mean change in severity from baseline; thus demonstrating efficacy.

8. Safety

The primary review of the safety information in NDA 208564 was performed by Dr.Theresa van der Vlugt.

The applicant submitted an Integrative Summary of Safety (ISS) pooling the results of phase 2 Trial TXV13-01 and phase 3 Trial TXV14-01 to explore adverse events, vital signs and other clinical findings from physical examinations of women exposed to (b) (4) estradiol vaginal insert up to 12 weeks of use. This reviewer holds that pooling of 14-day exposure data with 12-week exposure is not appropriate and serves only to distort (dilute) the findings (exposures and adverse outcomes) from exposures of 12 weeks. Presentation of safety data from TXV14-01 alone would have been a more appropriate representation of the safety findings correlating with the 12-week evaluation of efficacy. The applicant provided no information on long term chronic exposure to estradiol vaginal insert.

The overall mean (SD) duration of exposure in Trial TXV14-01 was 78.8 days (17). The mean (SD) duration of exposure was similar across all treatment groups [4 mcg – 78.5

(15.29) days, 10 mcg – 78.0 (19) days, 25 mcg – 79.5 (16) days, and placebo 79.2 (17.4) days.

No deaths occurred in any of the clinical trials during the (b) (4) estradiol vaginal insert development program.

No serious adverse events (SAEs) were reported in the three phase 1 and the single phase 2 clinical Trial TXV13-01. Overall, a small percentage of women in the estradiol vaginal insert development program experienced serious adverse events, 1 % (8 of 814 trial participants). All of the SAEs occurred in 12-week Trial TXV14-01.

In 12 week Trial TXV14-01, eight women experienced a total of nine (9) treatment-emergent SAEs. One woman in the 10 mcg estradiol vaginal insert treatment group experienced two SAEs (ankle fracture and sinus node dysfunction); all others experienced only one SAE. SAEs are presented in Table 11.

Table 11: Serious Adverse Events by System Organ Class and Preferred Term (Safety Population in 12-Week Trial TXV14-01

System Organ Class Preferred Term	TX-004HR 4 mcg (N=191)	TX-004HR 10 mcg (N=215)	TX-004HR 25 mcg (N=190)	Placebo (N=218)
Participating women with at least one SAE	0 (0)	3 (1.4)	4 (2.1)	1 (0.5)
Cardiac disorder - Atrial fibrillation - Sinus node dysfunction	 0 (0) 0 (0)	 0 (0) 1 (0.5)	 1 (0.5) 0 (0)	 0 (0) 0 (0)
Gastrointestinal disorders - Appendicitis	 0 (0)	 0 (0)	 1 (0.5)	 0 (0)
Infections and infestations - Endophthalmitis	 0 (0)	 0 (0)	 1 (0.5)	 0 (0)
Injury, poisoning, and procedural disorders - Ankle fracture	 0 (0)	 1 (0.5)	 0 (0)	 0 (0)
Musculoskeletal and connective tissue disorders - Arthralgia	 0 (0)	 1 (0.5)	 0 (0)	 0 (0)
Neoplasms benign, malignant and unspecified - Malignant melanoma	 0 (0)	 1 (0.5)	 0 90)	 0 (0)
Nervous system disorders - Cervical myelopathy	 0 (0)	 0 (0)	 0 (0)	 1 (0.5)
Respiratory, thoracic and mediastinal disorders - Chronic obstructive pulmonary disease	 0 (0)	 0 (0)	 1 (0.5)	 0 (0)

Source: Medical Officer Table 29, page 77; adapted from NDA 208564, Integrated Summary of Safety, Table 11 on page 19 of 80.

Abbreviation: SAE = serious adverse event.

Note: If a woman had more than one treatment-emergent AE that coded to the same preferred term she was counted only once for that preferred term.

The low numbers and percentages of SAEs are not unexpected in a 12 week vulvar and vaginal symptom trial. SAEs were similarly distributed in the 10 mcg (3 women, 4 events) and 25 mcg dosage groups of estradiol vaginal insert (4 women, 4 events). As previously stated, one woman in the 10 mcg estradiol vaginal insert treatment group experienced two SAEs (ankle fracture and sinus node dysfunction); all others experienced only one SAE. One (1) woman in the placebo vaginal insert treatment group experienced a SAE. The investigator and applicant concluded that none of these reported SAEs were considered related to trial medication. Dr. van der Vlugt agreed with the applicant's conclusions.

No long-term (at least 12-month) clinical trial was conducted during the estradiol vaginal insert clinical development program to allow for an evaluation of possible AEs occurring over time with chronic use of (b) (4) estradiol vaginal insert..

In the single phase 3 Trial TXV14-01, 14 women discontinued due to a treat-emergent adverse event (TEAE; nine women treated with estradiol vagina inserts and five women treated with placebo vaginal insert). The most TEAs leading to discontinuations occurred in the placebo group of Trial TXV14-01and was caused by vulvar/vaginal burning. One woman in the placebo treatment group in phase 2 Trial TXV13-01 discontinued due to a TEAE in the placebo vaginal insert treatment groups.

Seven (7) women in the Integrative Summary of Safety (ISS) experienced vaginal "spotting" and/or "bleeding". The instances of spotting and/or bleeding occurred similarly across all dosage strengths of the estradiol vaginal insert [4 mcg (2 cases), 10 mcg (1 case), and 25 mcg (1 case)] as well as in the placebo vaginal insert treatment group (3 cases). All were self-limiting and resolved. Each of these women received endometrial biopsy assessment with histological findings of: endometrial tissue "Other", no endometrial polyp; or no endometrial tissue identified, no endometrial polyp. No cases of endometrial hyperplasia or carcinoma were reported. These cases of vaginal spotting/bleeding are not associated with concerning endometrial histology findings and alone do not raise safety concerns for the treatment groups in this 12-week clinical trial.

The sponsor reported common TEAEs based on the ISS of Trials TXV14-01 and TXV13-01. Refer to Dr. van der Vlugt's review for a listing of ISS common TEAEs. The applicant did not present a table of common TEAEs in the trial report for pivotal Trial TXV14-01.

Serious adverse effects of the reproductive track, in particular breast and endometrium, are of particular interest for any product intended to impact the reproductive track. The applicant did not submit clinical trials of sufficient duration to be able to adequately and appropriately assess the effect of long-term exposure to estradiol vaginal insert on the breast and the endometrium. Though very low serum estradiol levels suggest, but do not prove, that systemic effects of (b) (4) estradiol vaginal inserts are expected to be minimal. Such comments cannot be made regarding expectations for effects on the endometrium. The estrogen concentrations in local tissues are expected to have a greater influence on the safety of the endometrium.

In phase 3 Trial TXV14-01, endometrial biopsies were performed at Screening 1B and at Week 12/End-of-Treatment (at least 10 weeks of trial drug exposure). An endometrial safety

population (ES) was *a priori* defined for the evaluation of potential endometrial changes. To be included in the ES population, the trial participant had to have:

- Had a pretreatment endometrial biopsy and an endometrial biopsy performed within 30 days of her last dose of trial medication with no exclusionary protocol violations.
- Taken at least 80% of the assigned trial medication over the 12-week dosing period.
- Not taken any prohibited concomitant medication that may impact endometrial safety.

To ensure uniformity in interpretation, TherapeuticsMD established a chartered Pathology Committee (TXV14-01 Pathology Committee Charter) consisting of three independent primary pathologists to assess the endometrial biopsy samples in a blinded fashion. A fourth independent, blinded pathologist was added as a permanent alternate to cover in the absence of one of the three primary pathologists in case of illness or other absence.

Endometrial biopsies collected at Screening were read centrally by two blinded pathologists. A woman was excluded for trial participation if one of these two pathologists assessed her Screening endometrial biopsy sample as endometrial hyperplasia, endometrial cancer, proliferative endometrium, weakly proliferative endometrium, or disordered proliferative pattern, or if one of these two pathologist identified an endometrial polyp with hyperplasia, glandular atypia of any degree (atypical nuclei), or cancer.

Additionally, for consideration of the woman's study eligibility, at least one pathologist had to identify sufficient tissue to evaluate the biopsy. If both Screening pathologists reported endometrial tissue insufficient for diagnosis, no endometrium identified, or no tissue identified, and if the woman met all other protocol-specified eligibility criteria, a single repeat of the Screening endometrial biopsy was allowed with the approval of the Medical Monitor.

At Week 12 (or Early Termination) endometrial biopsies and on-treatment unscheduled biopsies were assessed by three independent, blinded pathologists. Each pathologist's report was classified into one of the following three categories:

- *Category 1*: non hyperplasia / non malignancy: proliferative endometrium, weakly proliferative endometrium, disordered proliferative pattern, secretory endometrium, endometrial tissue other [benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma, etc.], endometrial tissue insufficient for diagnosis, no endometrium identified, no tissue identified.
- *Category 2*: hyperplasia: simple hyperplasia with or without atypia and complex hyperplasia with or without atypia.
- *Category 3*: malignancy endometrial malignancy.

The final diagnosis was based on agreement of two of the three pathologists. If all three pathologists reported a different category, the final diagnosis was based on the most severe category identified.

The protocol allowed for a single repeat of the end-of-treatment endometrial biopsy if all three pathologists reported one of the following: 1) endometrial tissue insufficient for diagnosis, 2) no endometrium identified, or 3) no tissue identified. If the same histology findings were reported on the repeat endometrial biopsy, a TVU was performed. If the endometrial thickness was ≤ to 4 mm, no further evaluation was required. If the endometrial thickness was > 4 mm, hysteroscopy with endometrial sampling was performed.

The Clinical Review Team notes that TherapeuticsMD did not follow the Agency's 2003 draft Guidance for Industry, entitled "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" (henceforth, referred to as the Agency's Draft 2003 Clinical Evaluation Guidance) recommendations for histological diagnoses [(0) No tissue; (1) Tissue insufficient for diagnosis; (2) Atrophic; (3) Inactive; (4) Proliferative: a-Weekly proliferative, b-Active proliferative, and c-Disordered proliferative; (5) Secretory: a-Cyclic type and b-Progestational type (including stromal decidualization); (6) Menstrual type; (7) Simple hyperplasia without atypia; 8) Simple hyperplasia with atypia; (9) Complex hyperplasia without atypia; (10) Complex hyperplasia with atypia; and (11) Carcinoma (specify type)]. As indicated for Trial TXV14-01, the applicant presented categorical diagnoses of biopsied samples. The Applicant's Category 2 and Category 3 are consistent with the Agency's Draft 2003 Clinical Evaluation Guidance recommendations. However, the applicant's Category 1 classification does not fully comply with the Agency's Draft 2003 Clinical Evaluation Guidance; Category 1 classification does not clearly identify the presence of secretory endometrium or menstrual type endometrium which is included in "endometrial tissue "other" [that is, benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma, etc.]. That said, we do not anticipate that the applicant's categorical classification of endometrial histology would have interfered with an appropriate classification of endometrial hyperplasia or endometrial cancer.

Four-hundred twenty five (425) non-hysterectomized women participated in 12-week Trial TXV14-01. Of these women, 390 had end-of-trial/follow-up endometrial biopsies performed. Eleven (11) women were not included in the ES population for the following reasons (because the Clinical Team that the results of these biopsies should be considered, the histological diagnoses are included):

- Four (4) women were non-compliant per protocol [Numbers (b) (6) (25 mcg, endometrial tissue benign), (b) (6) (placebo, endometrial tissue benign), (b) (6) (25 mcg, endometrial tissue benign), and (b) (6) (25 mcg, endometrial tissue benign)].
- Three (3) women were excluded because they took prohibited medications [Numbers (b) (6) (4 mcg, endometrial tissue benign), (b) (6) (10 mcg, endometrial tissue benign), and (b) (6) (4 mcg, endometrial tissue benign)].
- Two (2) women were excluded because they did not have an end-of-trial biopsy performed within 30 days of last dose of trial medication [Numbers 495-003 (10 mcg, endometrial tissue benign) and 459-039 (placebo, endometrial tissue "Other", benign endometrial polyp)]:

  - Number (b) (6) in the placebo treatment group had an endometrial biopsy performed post-trial Day 155. Her post-trial biopsy was reported as follows:
    - First pathologist = endometrial tissue "Other", benign endometrial polyp
    - Second pathologist = endometrial tissue "Other", polyp with hyperplasia without atypia (1 mm polyp)
    - Third pathologist = endometrial tissue "Other", benign endometrial polyp

- One (1) woman [Number (b) (6), (4 mcg, no endometrium identified]) had no tissue identified on three endometrial biopsy reads. She refused a repeat biopsy, therefore, a TVU was performed with a reported double-wall thickness of 3.1 mm.
- One woman [Number (b) (6), (25 mcg)] with a prior hysterectomy had a "biopsy" performed in error with the result "no endometrium identified" captured.

A total 379 non-hysterectomized women in TXV14-01, had endometrial biopsies performed and were included in the ES population:

- 4 mcg estradiol vaginal insert - 87
- 10 mcg estradiol vaginal insert - 91
- 25 mcg estradiol vaginal insert - 94
- Placebo vaginal insert - 107

Reported biopsy results by the protocol-specified categories: Category 1 (non-hyperplastic/non-malignant), Category 2 (hyperplasia – simple and complex), and Category 3 (endometrial malignancy), are shown in Table 12.

Table 12: Endometrial Biopsy Results by Applicant Defined Category in Trial TXV14-01

Category, n (%)	TX-004HR 4 mcg (N=87)	TX-004HR 10 mcg (N=91)	TX-004HR 25 mcg (N=94)	Placebo (N=107)	Total (N-379)
Baseline - Non-hyperplasia/ Non-malignant	87 (100)	91 (100)	94 (100)	107(100)	379 (100)
Week 12/End-of-Trial* - Non-hyperplasia/ Non-malignant	87 (100)	91 (100)	94 (100)	107(100)	379 (100)
- Hyperplasia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
- Malignancy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

* For inclusion trial participants have taken at least 10 weeks of trial medication.

Source: Adapted from Medical Officer Review Table 32, page 93 and NDA 208564, Integrated Summary of Safety, Table 17 on page 30 of 80.

Three women included in Category 1 (non-hyperplasia/non-malignant) had histologic findings at Week 12 that demonstrate estrogenic effects on the endometrium in Trial TXV14-01. Table 13 presents a description of these findings.

Table 13: Summary of Trial Participants with a Diagnosis of Endometrial Proliferation on Endometrial Biopsy in 12-Week Trial TXV14-01

Trial Participant Number	Treatment	Histology Findings Dr. Felix	Histology Findings Dr. Wheeler	Histology Findings Dr. Yeh	Histology Findings Dr. Brooks (Alternate)	Final Histology Findings in the Application
(b) (6)	10 mcg estradiol vaginal insert	Proliferative endometrium	Disordered Proliferative pattern	Endometrial tissue (Other)	N/A	Non-hyperplasia/Non-malignant
	25 mcg estradiol vaginal insert	N/A	Weakly proliferative endometrium	Weakly proliferative endometrium	Complex hyperplasia without atypia	Non-hyperplasia/Non-malignant
	25 mcg estradiol vaginal insert	Endometrial tissue (Other)	Weakly proliferative endometrium	Proliferative endometrium	N/A	Non-hyperplasia/Non-malignant

Source: Adapted from Medical Officer Review Table 33, page 94 and NDA 208564, Integrated Summary of Safety, Table 18 0n page 30 of 80.
Abbreviation: N/A = not applicable.

Additional discussions for these three women are provided below:

1. Number (b) (6) – A woman 52 years of age, randomized to the 10 mcg estradiol vaginal insert treatment group, experienced vaginal bleeding that started on post-trial Day 92 and resolved on post-trial Day103. Her Screening endometrial biopsy was reported as endometrial tissue "Other" (benign, inactive, or atrophic fragments of glands, stroma, etc.).

   Her end-of-trial endometrial biopsy on trial Day 92 was reported as follows:

   - First pathologist - proliferative endometrium, no endometrial polyp, benign endocervical polyp identified.
   - Second pathologist - Disordered proliferative pattern, no endometrial polyp.
   - Third pathologist - endometrial tissue "Other", no endometrial polyp.

   Each of the three pathologists reported a different histologic finding, because of this non agreement, the specific final diagnosis per the Agency's Draft 2003 Clinical Evaluation Guidance would be adjudicated as the most severe diagnosis of disordered proliferative endometrium.

   Disordered proliferative endometrium is thought to be a precursor for endometrial hyperplasia. No investigator assessment of this TEAE is provided in the application. This woman completed the clinical trial.

2. Number (b) (6) – A woman 52 years of age, randomized to the 25 mcg estradiol vaginal insert treatment group, whose end-of-trial endometrial biopsy revealed endometrial proliferation. Her Screening endometrial biopsy was reported as endometrial tissue "Other". She had no reported vaginal bleeding or spotting. Her end-of-trial endometrial biopsy on trial Day 90 was reported as follows:

   - First pathologist - weakly proliferative endometrium, no endometrial polyp, benign endocervical polyp identified.

- Second pathologist - weakly proliferative endometrium, no endometrial polyp.
- Third pathologist - complex hyperplasia without atypia, no endometrial polyp.

The specific final diagnosis per the Agency's Draft 2003 Clinical Evaluation Guidance would be that of two out of the three pathologists; in this instance weakly proliferative. However, it is further concerning that one of the pathologists made a final diagnosis of complex hyperplasia without atypia for this woman's 12-week endometrial sample.

No investigator assessment of this TEAE is provided in the application. This woman completed the clinical trial.

3. Number (b) (6) – A woman 54 years of age, randomized to the 25 mcg estradiol vaginal insert treatment group, whose end-of-trial endometrial biopsy revealed endometrial proliferation. Her Screening endometrial biopsy was reported as endometrial tissue "Other". She had no reported vaginal bleeding or spotting. Her end-of-trial endometrial biopsy on trial Day 83 was reported as follows:

   - First pathologist = endometrial tissue "Other", no endometrial polyp.
   - Second pathologist = weakly proliferative endometrium, no endometrial polyp.
   - Third pathologist = proliferative endometrium, no endometrial polyp.

   Because of the non-agreement of the three pathologists, the specific final diagnosis per the Agency's Draft 2003 Clinical Evaluation Guidance would be adjudicated as the most severe diagnosis of proliferative endometrium. No investigator assessment of this TEAE is provided in the application. This woman completed the clinical trial.

Although the numbers are small, the findings of proliferative endometrium ranging from weakly to disordered proliferative endometrium in the estradiol vaginal insert treatment groups (10 mcg and 25 mcg) and the presence of benign endometrial polyps in the 25 mcg treatment group need to be further investigated with a long-term endometrial and safety trial.

At Baseline in Trial TXV14-01, a total of 13 endometrial polyps were identified which were all reported as benign (4 in participating women randomized to the 4 mcg estradiol vaginal insert treatment group, 4 in participating women randomized to the 10 mcg estradiol vaginal insert treatment group, 2 in participating women randomized to the 25 mcg estradiol vaginal insert treatment group, and 3 in trial participants randomized to the placebo estradiol vaginal insert treatment group). Per protocol, endometrial polyps were categorized as benign, hyperplasia with atypia, hyperplasia without atypia, carcinomatous, or other. As such, women with diagnoses of benign endometrial polyp, were enrolled into Trial TXV14-01. The Clinical Review Team disagrees with this decision. As endometrial polyps are estrogen-sensitive and can be stimulated by estrogen therapy, these women should have been excluded from participation.

At Week 12 in Trial TXV14-01, the following benign polyps were identified by at least two of the pathologists: one (1) in the 4 mcg estradiol vaginal insert treatment group [her polyp was present at screening (Number (b) (6))], and three (3) in the 25 mcg estradiol vaginal

insert treatment group. The Clinical Team holds that the individual with a polyp at baseline should not have been allowed to continue in the trial, as estrogen exposure can stimulate polyps. The three polyps confirmed at the 25 mcg estradiol vaginal insert treatment group versus no polyps identified in the placebo vaginal insert treatment group in 12-week Trial TXV14-01 appears to suggest proliferative effect.

In Trial TXV14-01, one instance of a breast mass was seen in a woman 69 years of age with a normal screening mammogram. The breast mass was discovered on post-trial Day 90. A diagnostic mammogram with computer aided detection and an ultrasound of the left breast performed on post-trial Day 93 were negative - BIRADS category 1. The investigator assessed this TEAE as mild in severity and not related to trial medication. This woman completed the clinical trial. No clinical trial in the development of (b) (4) estradiol vaginal insert was of sufficient duration to adequately assess the risk of breast cancer.

The Clinical Team does not consider that NDA 208564 provides sufficient information on the endometrium. No long-term endometrial assessment, as would be generally requested to assess the effects of a chronically-administered estrogen product, was conducted and presented in the (b) (4) NDA.

Additionally, in the absence of long-term general and endometrial safety trial, the NDA lacked sufficient long term exposure data to meet ICH E1 requirements for drug products intended for chronic administration. The ICH E1 guidelines recommend exposure in 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures should occur at the dose or dose range believed to be efficacious. The mean duration of exposure in the single, 12-week, phase 3 Trial TXV14-01 is 78.8 (SD 16.97). Therefore insufficient numbers of women were exposed for six months or one year durations.

As previously stated, the September 16, 2016 74-day Filing Review Issues Identified letter to Therapeutics MD, advised the applicant that:

1. NDA 208564 does not provide long-term (12 months or more) general and endometrial safety data for the 4, 10, (b) (4) mcg estradiol vaginal inserts.
2. Endometrial histology evaluation obtained at or greater than 12 months of use is critical to the safety evaluation of unopposed estrogen:
    - Unopposed estrogen use in a postmenopausal women with a uterus increases the risk of endometrial hyperplasia/cancer.
    - 12-week safety data from Trial TXV 4-01 are inadequate to assess long-term general and endometrial safety of your estradiol vaginal insert.
3. Your application does not provide data on chronic exposure at 6 months and 1 year for the 4, 10, (b) (4) mcg estradiol vaginal inserts.
    - Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause is a chronic use indication in postmenopausal women.
    - The International Council for Harmonisation (ICH) guidelines for exposure for chronically administered drugs recommends exposure of 500 women

exposed overall, 300-600 women for 6 months, and 100 women for 1 year at the dose or dose range believed to be efficacious.

On October 10, 2016, TherapeuticsMD responded:

1. **"The Sponsor's rationale for originally proposing, performing, and now relying on a 12-week Phase 3 pivotal trial includes:**
   - **Estradiol has a well-established safety profile through a long history of human use in marketed, FDA-approved, oral, topical, and vaginal drug products at higher Estradiol has a well-established safety profile through a long history of human use in marketed, FDA-approved, oral, topical, and vaginal drug products at higher doses than those proposed for TX-004HR (proposed doses are 4, 10 (b) (4) mcg twice weekly).**
   - **Precedents of approvals of several other estrogen products that relied on a 12-week efficacy and safety study.**
   - **TX-004HR data from the clinical development program, including the Phase 3 trial, that are consistent with general and endometrial safety.**
   - **Reliance on the 1999 FDA Guidance for Industry for Applications Covered by Section 505(b)(2) encouraging innovation and drug development by utilizing information already known about a drug."**

While the applicant is correct that the effect of the use of unopposed estrogens on the endometrium has been known for some long time, the potential effect is deleterious. Evidence has existed since the early 1970's[3,4] that use of unopposed estrogens is associated with an increase in the risk of endometrial cancer. In 1975, the FDA Obstetrics and Gynecology Advisory Committee recommended that estrogen labeling be revised to include a specific warning for an increased risk of endometrial cancer in postmenopausal women with a uterus and unopposed estrogen use.[5]

Subsequent evidence demonstrated that the addition of a progestin to estrogen therapy could mitigate the risk of estrogen-induced endometrial changes.[6,7] The risk of endometrial cancer increases substantially with long duration of unopposed estrogen use, and the increased risk persists for several years after discontinuation of estrogen. Treatment with progestins was demonstrated to reduce the risk in a duration dependent fashion.[8] In 1976, FDA proposed a Boxed Warning that endometrial cancer is associated with long-term unopposed estrogen use.[9]

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[3] Antunes CM. Endometrial cancer and estrogen use. Report fo a large case-control study. 1979;300(1):9-13
[4] Gardan J etal. Oestrogen and endometrial carcinoma, an independent pathology review supporting original size estimate. 1977;297:570
[5] 1975 FDA Obstetrics and Gynecology Advisory Committee - Transcripts
[6] Whitehead MI et al. Effects of various types and dosages of progestogens on the postmenopausal endometrium. J Reprod Med 1982;27:539-548
[7] Gelfand MM and Ferencczy. A prospective 1-year study of estrogen and progestin in postmenopaus women: Effects on the endometrium. 1989;74:398-402
[8] Grady D. Hormone replacement therapy and endometrial cancer risk: A meta-analysis. Ostet Gynceol 1995;85:304-313
[9] Federal Register. Wednesday September 29, 1976;41(190):43117

The exact risk of unopposed estrogen was not evaluated in the Women's Health Initiative, Estrogen -alone arm, as women assigned to this arm of the WHI were hysterectomized at enrollment. However, risk of endometrial cancer in women treated with a combination estrogen plus progestin product was evaluated. After 5.6 years' median intervention and 13 years' median cumulative follow-up in the estrogen plus progestin arm, there were fewer endometrial cancers in the combined hormone therapy compared with the placebo group [66 vs 95 case patients, yearly incidence, 0.06% versus 0.10%; hazard ratio (HR) = 0.65, 95% confidence interval [CI] = 0.48 to 0.89, p = 0.007]. While there were somewhat fewer endometrial cancers during intervention (25 vs 30, respectively; HR = 0.77, 95% CI = 0.45 to 1.31), the difference became statistically significant post-intervention (41 vs 65, respectively; HR = 0.59, 95% CI = 0.40 to 0.88, p = .008), but hazard ratios did not differ between phases (p difference = .46). There was a statistically non-significant reduction in deaths from endometrial cancer in the estrogen plus progestin group (5 vs 11 deaths, HR = 0.42, 95% CI = 0.15 to 1.22).[10]

Recently members of a working group associated with the North American Menopause Society (NAMS) have advocated in an editorial that the Boxed Warning of certain low dose vaginally-administered estrogen-alone products (similar to estradiol vaginal insert) be eliminated based on the fact that the Boxed Warning of such products is "based on extrapolations of data from trials of systemic estrogen or combination estrogen-progestin hormone therapy, which involve substantially higher levels of exposure. It is noteworthy that there are dramatic differences in estrogen blood levels achieved with low-dose vaginal estrogen therapies compared with systemic estrogen administration. Our view is that the highly visible boxed warning on low-dose vaginal estrogen is unsubstantiated and not evidence-based."[11] *The labeling initially-submitted with the NDA was consistent with the view in the NAMS editorial.*

The signs and individual symptoms of vulvar and vaginal atrophy result from the absence of estrogen stimulation to the respective tissues as a result of menopause. In the absence of treatment, signs and symptoms return. Therefore, treatment, once begun, is expected to be life-long (or in the case of dyspareunia, as long as the woman engages in vaginal intercourse). The data to support the known risk of unopposed estrogen on the endometrium as well as the data from the Women's Health Initiative and previous smaller clinical trials and observational trials were indeed obtained from higher dosed products. However, our position is that the only way to know if lower-dosed and lower serum-exposure products are associated with risks for endometrial cancers is to conduct long-term clinical trials of sufficient duration to allow a true determination of the risk for endometrial cancer. One cannot appropriately conclude that vaginal administration eliminates the risk of endometrial cancer. As noted in my discussion of the estrogen concentrations and

[10] Chlebowski RT, Anderson GL et al. Continuous combined estrogen plus progestin and endometrial cancer: The Women's Health Initiative randomized trial. J. Natl Cancer Inst 2016;108(3):1-10

[11] Manson JE. Editorial-Why the product labeling for low-dose vaginal estrogen should be changed. Menopause; The Journal of the North American Menopause Society 2014;21(9);911-916

effect (refer to Clinical Pharmacology/Biopharmaceutics - Sections 5 and Clinical/Statistical Efficacy – Section 7 of this review), low serum concentrations did not correlate with findings of efficacy. It is obvious that there are sufficient tissue concentrations of estrogens to mitigate signs and symptoms of dyspareunia. Such tissue concentrations may be sufficient to stimulate metaplastic changes in contiguous/adjacent local reproductive tissues (i.e. endometrial, tubal and ovarian tissues). Importantly, we note that 12 week exposures to (b) (4) *estradiol vaginal insert were associated with proliferative changes to the endometrium including disordered endometrium; this may be a signal. A mean 78.8 days (17) exposure is not sufficient to fully delineate the risk of endometrial hyperplasia/cancer with chronic use.*

The applicant represents that the Agency has approved some higher dose products without long-term safety data. The products noted are Elestrin [estradiol gel, (0.87 gram per day (estimated mean systemic delivery rate 0.0125 mg per day), 1.7 gram per day (estimated mean systemic delivery 0.0375 mg per day), and 2.6 gram per day (estimated mean systemic delivery rate 0.05 mg per day), approved December 15, 2006 for the treatment of vasomotor symptoms], Divigel [estradiol gel 0.1% (0.25, 0.5 and 1 gram of gel per day), approved June 4, 2007 for the treatment of vasomotor symptoms], and Evamist [estradiol transdermal spray, (1-spray, 2-spray and 3-spray), approved July 27, 2007) for the treatment of vasomotor symptoms]. Each of these products was approved for the treatment of vasomotor symptoms at a time when the Division was handling treatment of vasomotor symptoms as a time-limited and not a chronic indication. At the time, the Division considered the risk of endometrial cancer for these products to be the same as that of other previously approved estradiol products. If an application for any of these products were to be submitted contemporaneously, applicant's would be advised to provide long-term (12 months or greater, dependent on the dosage strength) endometrial safety evaluation. That said, FAERS data has not supported that these previously-approved products should be removed from marketing.

The Clinical Review Team holds that previous approval of an estrogen-alone product for which the risk of endometrial hyperplasia/cancer was considered known and thus new long term safety studies were not required, should not preclude collection of long term safety data on products with routes of administration and product strengths, for which we do not have such information.

2. **"The Sponsor has communicated the clinical development plan for TX-004HR from submission of the initial IND through the preNDA meeting and has complied with the Agency's recommendations."**

The Clinical Review Team acknowledges that it was not proactively diligent in the developmental stage to remind the applicant that its estrogen-alone product in addition to its estrogen plus progestin product would also need to be evaluated in a long-term clinical trial.

The Clinical Team concludes that the applicant needs to conduct a long-term clinical trial of sufficient duration to determine a true risk of endometrial cancer and other long-term safety effects associated with chronic use of (b) (4)

The reader is encouraged to review the Medical Officer Review of Dr. Theresa van der Vlugt for a more detailed discussion of the safety data presented in the NDA.

Overall, the long-term safety profiles of 4 mcg, 10 mcg (b) (4) mcg of (b) (4) estradiol vaginal insert are not well supported in the NDA. This reviewer believes that lack of long-term safety data precludes approval of the product.

9. Advisory Committee Meeting

Advice of the Reproductive Health Advisory Committee was not sought during the period of consideration and recommendation for this product. The primary review concern is the absence of data to support long-term safety for this chronically-administered product. The Clinical Team did not think that an Advisory Committee input would add much to the consideration of this issue.

10. Pediatrics

A full pediatric waiver for ages 0 to 18 was requested by TherapeuticsMD with the rationale that the condition (treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause) does not apply to children. DBRUP concurs with the Applicant's assessment that the product would not be indicated in children. TherapeuticsMD's request for a full pediatric waiver for (b) (4) (estradiol vaginal insert) was discussed at the March 23, 2015 meeting of the Pediatric Review Committee (PeRC). The committee determined that (b) (4) would be granted a full waiver based on the fact that vulvar and vaginal atrophy due to menopause is a condition that qualifies for waiver because studies would be impossible or highly impractical. On March 29, 2017, PeRC confirmed its agreement for full waiver of Pediatric Research Equity Act (PREA) requirements based on the consideration that studies are impossible or highly impractical. DBRUP concurs that a full pediatric waiver be granted from the study requirements of PREA.

11. Other Relevant Regulatory Issues

Clearance by 505(b)(2) Committee

NDA 208564 was discussed at the April 24, 2017 505(b)(2) clearance meeting. DBRUP represented that literature was required to support in part the approval of (b) (4) estradiol vaginal insert (refer to Nonclinical Pharmacology/Toxicology – Section 4 of this review), Further, none of the published literature identified a specific brand name. Additionally, DBRUP noted that the application does not rely on the findings of safety and effectiveness for one or more listed (approved drugs) to support approval.

The application was cleared for action from a 505(b)(2) perspective.

Good Clinical Practices and Office of Scientific Investigations (OSI) Findings

Investigator site audits were performed by external auditors under the supervision of TherapeuticsMD's Quality Assurance and independently of the site monitors. The dates and locations of these audits were as follows:

- Site 431: Visions Clinical Research, Tucson, AZ; Cynthia Goldberg, MD; Date of Audit: June 22-23, 2015.
- Site 484 – Ideal Clinical Research, North Miami Beach, FL; Christ-Ann Magloire, MD; Date of Audit: August 11-12, 2015.
- Site 478 – Clinical Research Center, Eastern Virginia Medical School, Norfolk, VA; David F. Archer, MD; Date of Audit: March 31, 2015 – April 1, 2015.
- Site 434 – Wake Research Associates, LLC, Raleigh, NC; Pouru Bhiwandi, MD; Date of Audit: May 28-29, 2015.
- Site 498 – Diex Research Montreal Inc., Montreal, Quebec Canada; Manon Gelinas, MD, Date of Audit: July 23-14, 2015.
- Site 435 – Seattle Women's: Health, Research, and Gynecology, Seattle, WA; Robin Kroll, MD; Date of Audit: April 9-10, 2015.
- Site 433 – Affiliated Clinical Research, Inc., Las Vegas, NV; Garn Mabey, MD; Date of Audit: June 25-26, 2015.
- Site 436 – Radiant Research, Chicago, IL; Phyllis Marx, MD; Date of Audit: March 17-18, 2015.
- Site 400 – Women's Health Research a Subsidiary of Aventiv Research, Columbus, OH; David F. Portman, MD; Date of Audit: May 18-19, 2015.
- Site 401 – Downtown Women's Health Care, Denver, CO; Arthur Waldbaum, MD; Date of Audit: May 12-13, 2015.
- Site 454 – Medical Center for Clinical Research, San Diego, CA; William Koltun, MD; Date of Audit: March 23-24, 2015.

No corrective action appears to have been taken based on findings from these internal audits. Per the applicant, their audit program helped to provide reassurance that valid procedures for data management and analysis were adhered to, and that the TherapeuticsMD's clinical trial program was carried out in accordance with GCP guidelines.

On September 21, 2016, DBRUP requested clinical site inspection by OSI, Division of Clinical Compliance Evaluation (DCCE) for the following clinical sites in the U.S.:

- Priority 1: Site 454; William Koltun, MD, Medical Center for Clinical Research, 9040 Friars Road, Suite540, San Diego, CA 92108. Site 454 enrolled 33 postmenopausal women. Two (2) of the eight (8) women in the 10 mcg estradiol vaginal insert treatment group had major protocol deviations. Participating woman Number (b) (6) used Boron (trace mineral) for the entire trial duration. Boron is reported to help arthritis and osteoporosis, and help to reduce postmenopausal symptoms. Participating woman Number (b) (6) used Prempro® on Days 36 to 45 of trial duration. Prempro® is used to treat moderate to severe vulvar and vaginal atrophy symptoms due to menopause. The effects of use of these prohibited medications, on the efficacy of the 10 mcg estradiol vaginal insert, are not known.

  On March 20, 2017, OSI/DCCE provided an evaluation of the clinical inspection for Site 454; William Koltun, MD, conducted between January 25, 2017 and January 30, 2017. Dr. Kolton received a letter indicating "…we conclude you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and protection of human subjects." A form FDA 483 was not issued at the conclusion of the inspection. Site 454 received a no action indicated (NAI) classification.

- Priority 2: Site 435; Robin Kroll, MD, Seattle Women's: Health, Research, Gynecology, 3216 NE 45th Place, Suite 100, Seattle, WA 98105. Site 435 enrolled 18 postmenopausal women.

  On February 15, 2017, OSI/DCCE provided an evaluation of the clinical inspection for Site 435; Robin Kroll, MD. Dr. Kroll received a letter indicating "…we conclude you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and protection of human subjects." A form FDA 483 was not issued at the conclusion of the inspection. Site 435 received a NAI classification.

- Priority 3: Site 484; Christ-Ann Magloire, MD, Ideal Clinical Research, 1880 NE 163rd Street, Suite 102, North Miami Beach, FL 33162. Site 484 enrolled 41 postmenopausal women. Four (4) major protocol deviations are reported for Site 484. These four protocol deviations involved not collecting Pap smears, per protocol procedure, at Week 12 on the following postmenopausal women: 1) Number (b) (6) in the 4 mcg estradiol vaginal insert treatment group, 2) Number (b) (6) in the 25 mcg estradiol vaginal insert treatment group, 3) Number (b) (6) in the placebo vaginal insert treatment group, and 4) Number (b) (6) in the placebo vaginal insert treatment group. These four protocol deviations demonstrate inconsistency in following established and end-of-trial procedures.

  On March 20, 2017, OSI/DCCE provided an evaluation of the clinical inspection for Site 484; Christ-Ann Magloire, MD, conducted between January 19, 2017 and January 26, 2017. Dr. Magloire received a letter indicating "…we conclude you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and protection of human subjects." A form FDA 483 was not issued at the conclusion of the inspection. Site 484 received a NAI classification.

- Priority 4: Site 400; David Portman, MD, Women's Health Research a Subsidiary of Aventiv Research, 99 North Brice Road, Suite 120, Columbus, OH 43213. Site 400 enrolled 27 postmenopausal women. The Statistical reviewer determined that Site 400 was critical to the efficacy evaluation of the 4 mcg estradiol vaginal insert due to significant variability.

  On February 15, 2017, OSI/DCCE provided an evaluation of the clinical inspection for Site 400. Dr. Portman received a letter indicating "…we conclude you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and protection of human subjects." A form FDA 483 was not issued at the conclusion of the inspection. Site 400 received NAI classification.

The Division concurs with OSI's recommendations and general conclusions the quality of the data generated in the NDA appear acceptable.

Division of Medication Error Prevention and Analysis (DMEPA)

As note in Background and Regulatory History – Section 2 of this review, at the pre-NDA meeting with the applicant on December 15, 2015, the Agency recommended that the application include a comprehensive use-related risk analysis and identification of use-related risks or failure to perform required tasks on the part of users and the potential negative clinical consequences of such error.

The applicant submitted a URRA, which identifies and evaluates all critical use tasks involved with the use of their product, the use errors that might occur, and the potential negative clinical consequences of those use errors. According to the applicant, the use-related risk analysis did not reveal a safety concern for oral or other incorrect routes of administration.

Their applicant's risk analysis included an evaluation of all the steps involved in using the product. In addition, the applicant considered the risk that the user would ingest the medication orally. The applicant's risk analysis states if such an event occurs, the product is 'non-toxic' and would not cause patient harm if a single dose is ingested. The applicant's plans to mitigate any risk for oral ingestion of the vaginal insert with labeling. Specifically, the applicant plans to emphasize the vaginal route in their labeling. The route 'vaginal' is included in the established name, is included in the net quantity statement, and is clearly stated in the usual dosage statement. Additionally, the statement "For Vaginal Use Only" is presented in all capital letters on the principal display panel of the carton labeling and on the blister label (See Appendix F). Furthermore, the applicant states that the results of the use risk analysis indicate that no mitigations are necessary and that a label comprehension study is not needed.

DMEPA reviewed the Instructions for Use (IFU) and the Use Failure Mode Affects and Analysis Report and agreed that the applicant evaluated all critical use tasks required for the safe and effective use of the product. Per DMEPA, "Additionally, we note that this proposed product is similar to another marketed product, Vagifem (estradiol vaginal inserts), NDA 020908, approved March 26, 1999. Both Vagifem and this vaginal insert share the same

patient population (e.g., menopausal women), are inserted vaginally, share critical use tasks, and are given with the same frequency. However, Vagifem is inserted using an applicator and the proposed product will be inserted manually. Given that the presence of an applicator suggests that this product is not for oral administration, DMEPA is concerned that the absence of an applicator for vaginal insert, may suggest otherwise (e.g., to give the medication orally)."

"Additionally, the dosage form 'insert' does not trigger a specific route of administration for the user, which may pose a risk of wrong route errors. DMEPA finds the proposed labeling mitigation strategy to be adequate in that it prominently emphasizes the route of administration in several locations in the labeling and increases the opportunity for the user to see this important information. DMEPA concludes that no further Human Factors testing is necessary at this time."

DMEPA had the following labeling comments:

- The carton labeling trade dress contains colors that overlap with colors used for expressions of strength and also the individual strengths can be better differentiated. We are concerned the overlap of colors decreases the differentiation between the strengths and may contribute to strength selection errors.

- The carton labeling and container label and the PI use the dosage form designation (b) (4) This is not an acceptable dosage form for this product.

- The established name on the carton labeling lacks prominence commensurate with the proprietary name. We are concerned the lack of prominence may contribute to product selection error.

- The strength statement on the carton labeling is located away from the established name and dosage form. This presentation may contribute to strength selection errors.

- There is lack of drug-identifying information on the blister label. Specifically, the blister label lacks important product information (e.g. proprietary and established name; product strength; lot or control number; expiration date [per USP]; and the name of the manufacturer, packer, or distributer) in accordance with 21 CFR 201.10(i) and 21 CFR 201.17.

As the recommendation is for complete response, DMEPA's labeling comments were not shared with the applicant before an application decision was made.

The Office of Prescription Drug Promotion (OPDP)

As a complete response is recommended for this application, OPDP will defer their labeling comment to a subsequent review cycle. OPDP requests that a new consult request be made by DBRUP once the applicant resubmits their NDA.

Office of Medical Policy/Division of Medical Policy Programs (DMPP)

As a complete response is recommended for this application, DMPP will defer their patient labeling comment to a subsequent review cycle. DMPP requests that a new consult request be made by DBRUP once the applicant resubmits their NDA.

Financial Disclosure

Form FDA 3454 (3/16) dated May 3, 2016 states: "As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study where by the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payment of other sorts (as defined in 21 CFR 54.2(f)).

A Form FDA 3454 in the application provides a tabular listing of investigators/sub-investigators who participated in clinical Trial TXV14-01 certifying no disclosable interests.

(b) (6), a sub-investigator at (b) (6), reported a significant equity interest that met the criteria for disclosure. Dr. Cohen has stock options that would potentially exceed $50,000 US in aggregate. He disclosed ownership of a total of 216,000 options in TherapeuticsMD stock. Of these, the first 108,000 options are at $0.10 per option and the second 108,000 options are at $0.25 per option. Per the applicant, the circumstances which prevent potential bias are:

- (b) (6) was a subinvestigator at site (b) (6) and not directly responsible for conduct of the trial at the site.
- Trial TXV14-01 was a multicenter, randomized, placebo-controlled study. A total of 100 sites consented participating women during screening, with 89 sites randomizing 764 women to the study. (b) (6) screened (b) (6) and randomized (b) (6) women. These (b) (6) women represent less than (b) (6) of the randomized patient population. A Form FDA 3455 for Dr. Cohen is available in the application.

The second bullet was considered of greater significance in support that the sub-investigator's financial interest would not have exerted a substantial influence on the outcome of the pivotal trial. The Clinical Team concluded that the applicant's financial disclosure was appropriate.

Tradename Review

On April 9, 2015, TherapeuticsMD submitted a proprietary name/request for review for the proposed name (b) (4)™. On September 9, 2015, a Proprietary Name Request Unacceptable letter was sent to the applicant indicating this name is unacceptable.

On October 20, 2015, Yuvvexy™ (hereafter referred to as Yuvvexy) was submitted for review under IND 118439. On February 3, 2016, a Proprietary Name Request Conditionally

Acceptable letter was sent to the applicant with instruction that a request for proprietary name review should be submitted with the NDA. A proprietary name request for Yuvvexy is included in the NDA application.

On February 2, 2017, Therapeutics withdrew the proposed proprietary Yuvvexy and submitted the proposed proprietary name (b) (4) y™. On February 17, 2017 TherapeuticsMD received a Proprietary Name Request unacceptable letter from the Agency stating: "The proposed proprietary name, (b) (4) is vulnerable to medication errors due to confusion with another product that is also under review. Therefore, the ultimate acceptability of your proposed name, (b) (4) is dependent upon which underlying application is approved first. If another product is approved prior to your product, with a name that would be confused with your proposed name of (b) (4) you will be requested to submit another name."

On February 24, 2017, TherapeuticsMD submitted a Request for Alternative Proprietary Name Review for the name (b) (4) ™. This submission includes a Drug Safety Institute, Inc. (DSI) Failure Mode and Effect Analysis (FEMA) report in support of the proposed alternative proprietary name. TherapeuticsMD indicated that the previously proposed proprietary name (b) (4) remains their first choice.

12. Labeling

Based on the absence of long term endometrial and general safety, the recommendation is to not approve. On April 06, 2017, FDA provided to TherapeuticsMD, an Advice Letter, Deficiencies Preclude Discussion, with the following advice, "As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time. This notification does not reflect a final decision on the information under review."

13. Conclusions/Recommendations/Risk Benefit Assessment

I concur with the recommendation of the Primary Clinical Reviewer, Dr. van der Vlugt, that NDA 208564 for (b) (4) estradiol vaginal insert not receive Approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHELLEY R SLAUGHTER
05/04/2017