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May 1, 2020

Via Electronic Filing

Division of Docket Management
Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

TherapeuticsMD, Inc. ("TherapeuticsMD") submits this petition under 21 C.F.R. §§ 10.30 and 10.31 to request that the Food and Drug Administration ("FDA" or "Agency") refrain from receiving or approving any marketing application that references Imvexxy® (estradiol vaginal inserts), NDA #208564, unless (a) the application is submitted as an Abbreviated New Drug Application ("ANDA") under section 505(j) of the Food Drug and Cosmetic Act ("FDCA") and the ANDA product is manufactured qualitatively the same as Imvexxy, including the teardrop shape, for the reasons discussed herein (*i.e.*, has the same Q3 macro and microstructure as Imvexxy) or (b) the application is submitted under section 505(b)(2) of the FDCA. To that end, TherapeuticsMD requests that FDA issue product-specific guidance setting forth such requirements.

The macro and microstructure of Imvexxy's insert shell directly relate to the rate and extent of delivery of estradiol to the vaginal tissues. The factors below each impact the absorption characteristics, amount of estradiol available to be absorbed, and the ability of a woman to correctly place the Imvexxy insert in accordance with the product's Instructions for Use (IFU).

- Formulation: Gelatin composition, including Bloom strength, directly relates to rupture and dissolution of the gelatin shell, which affects the absorption characteristics, for example the rate of estradiol absorption and the amount of estradiol available to the vaginal tissue.
- Manufacturing: Manufacturing issues, such as ribbon thickness, seam width, and drying conditions directly relate to rupture and release of the insert, which affects the absorption characteristics.
- Polishing: The extent of polishing of the shell affects the tackiness of the insert, which directly relates to the ease of insertion and adherence to the vaginal wall, which can affect the absorption characteristics.
- Shape: The shape of the insert directly relates to its ease and correctness of insertion according to the IFU's, interacting with the compression forces imposed on the insert within the vagina, which also directly relate to rupture and release of the fill material.

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- Dissolution Time: Time to dissolution of the shell impacts the spreadability of the oil fill and its interaction with the vaginal mucosa, which affects the absorption characteristics.
- Microenvironment of Vagina: In addition to these compositional, configurational, and manufacturing issues, the vaginal environment also impacts the drug delivery. The vagina is a complex organ that is poorly studied in the literature as related to drug delivery, especially localized delivery. As shown herein, the vagina has a non-constant pressure along the length of its canal. Similarly, moisture distribution throughout the length of the vaginal canal is non-uniform. Both phenomena directly impact the shell and therefore its rupture and release of the fill material, which affects the absorption characteristics.
- IFU: Imvexxy's Instructions for Use (IFU) contains very specific instructions related to the use of the shaped insert that must be copied in the IFU for any ANDA.

These quality attributes of Imvexxy directly relate to efficacy (*i.e.*, the same amount of drug being delivered to the same target) and safety (*i.e.*, the prevention of estradiol reaching the uterus and causing proliferation of the endometrium and systemic side effects). Because Imvexxy does not show systemic absorption, these quality attributes are germane to FDA's review of a generic product because pharmacokinetics is not an adequate surrogate to establish bioequivalency to Imvexxy. Thus, to show therapeutic equivalence, we respectfully submit that FDA should address these quality attributes as part of the approval process of a generic by requiring the generic to submit through the 505(b)(2), or alternatively require the generic to be Q1Q2 and Q3 equivalent to Imvexxy.

This is the second Citizen Petition filed by TherapeuticsMD related to Imvexxy. On December 11, 2018, TherapeuticsMD filed a Citizen Petition requesting that FDA require certain data for an ANDA product that is Q1Q2 and Q3 to Imvexxy and that references Imvexxy as the reference listed drug.[1] The data requested in that Petition includes bioequivalence studies with pharmacokinetic and clinical endpoints as well as low surfactant dissolution testing since, TherapeuticsMD respectfully submits that bioequivalence for a product Q1Q2 and Q3 to Imvexxy cannot be established using existing test methodologies that do not incorporate at least those methods. The basis for this Citizen Petition is different although, as discussed fully herein, the fact that Imvexxy is absorbed locally into the vaginal tissue, and not systemically, is a significant factor in both Petitions. While this and the currently pending petition share some overlap and are complementary, the petitions are nonetheless independent, and the FDA should act on each accordingly.

[1] *See* Docket ID No. FDA-2018-P-4714. The focus of Petition FDA-2018-P-4714 was on the composition of the fill, whereas the present Petition focuses on the importance of the shell and its macro and microstructure in the delivery of the estradiol to the intended target tissues. Therefore, these Petitions necessarily raise different considerations.

During the preparation of this Citizen Petition, an ANDA was filed with respect to Imvexxy. The ANDA applicant has not yet produced a copy of its ANDA to TherapeuticsMD or its counsel. Therefore, TherapeuticsMD submitted this Citizen Petition before TherapeuticsMD or its counsel received the ANDA.

A. Action Requested

TherapeuticsMD requests that FDA refrain from receiving or approving any ANDA that references Imvexxy (estradiol vaginal inserts), NDA #208564, unless the shape of the vaginal insert is the same teardrop shape as that of Imvexxy and thus the labeling for the ANDA product, including the Instructions for Use ("IFU"), is "the same" as that of Imvexxy as required by 21 U.S.C. § 355(j)(2)(A)(v) and 21 C.F.R. § 314.94(a)(8)(iv). In addition, the ANDA product must satisfy FDA's Q3 criteria to Imvexxy because even subtle changes in manufacturing and processing, like changes in shape, can impact the product in ways that cannot be determined with the bioequivalence criteria available for a non-systemically absorbed product like Imvexxy. In the event a sponsor seeks to submit a marketing application for a product with different labeling than Imvexxy or manufactured qualitatively differently than Imvexxy such that the ANDA product's Q3 macro and microstructure is materially different from Imvexxy, TherapeuticsMD requests that FDA only consider such an application if submitted through the section 505(b)(2) pathway pursuant to 21 U.S.C. § 355(b)(2) and 21 CFR § 314.3(b).[2] Finally, TherapeuticsMD respectfully requests that FDA issue a product-specific guidance for Imvexxy to provide needed information and certainty for companies interested in developing a generic estradiol vaginal insert.

B. Background

1. Dyspareunia

a. Background on Menopause and Constellation of Symptoms

Menopause is a natural biological process that marks the end of a woman's menstrual cycles. It is diagnosed after the woman has gone twelve months without a menstrual period. The average age of onset of menopause in the U.S. is 51 years old. During menopause, the ovaries stop producing estrogen, which results in a variety of emotional and physical symptoms including irregular periods, hot flashes, chills night sweats, sleep disruption, mood changes, weight gain, thinning hair, dry skin, lower energy, and vulvar and vaginal atrophy (VVA), symptoms of which include dyspareunia, dryness, and others that result from estrogen deficiencies. Decreased estrogen causes a change in composition of vaginal tissue.[3] During menopause the vaginal tissue atrophies without estrogen. The superficial cells, which are a squamous layer of tissue designed to withstand

[2] See, *infra*, p. 19 for a discussion of FDA's Q3 criteria and the meaning of microstructure.

[3] *See* Maire MacBride *et al*., *Vulvovaginal Atrophy*, Mayo Clinical Proceedings 85:87-94 (2010) (attached hereto as Exhibit 1).

abrasion during sexual activity, and the intermediate layer decreases in thickness, and the parabasal layer increases in thickness. The changed vaginal tissue composition during menopause results in dryness, painful sex, bleeding during sex, and other similar symptoms. The decrease in estrogen also results in a less acidic, more basic vaginal environment, which can upset the balance of natural bacteria and fungi in the vagina, and ultimately can lead to infections, such as urinary tract infections due to the proximity of the urethra to the vagina.[4]

VVA is a chronic and progressive condition characterized by the thinning of vaginal tissue from decreased estrogen levels. Moderate to severe VVA is diagnosed in approximately 50% of postmenopausal women, and the most bothersome symptom for many women is painful intercourse or dyspareunia.[5] Other symptoms may include vaginal dryness, itching, irritation, bleeding with sexual activity, dysuria, recurrent urinary tract infections, and incontinence.[6] VVA and its constellation of symptoms can be extremely disruptive to the patient's lifestyle and well-being, and disruptive to women's relationships with their spouses or significant others.

b. Background on Treatments Approved Before Imvexxy

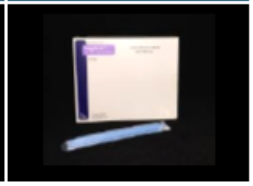
Estrogen therapy has been used for over a half-century for the management of menopausal symptoms, including VVA and vasomotor symptoms. Before Imvexxy, the FDA-approved estrogen VVA treatments included prescription vaginal creams, tablets, and a ring. Most of those products require the use of an applicator. Table 1 identifies and depicts the primary features of these products.

[4] *See id.*

[5] James A. Simon *et al.*, *Visual Improvements in Vaginal Mucosa Correlate with Symptoms of VVA: Data from a Double-Blind, Placebo-Controlled Trial,* Menopause 24:1003-10 (2017) (Attached hereto as Exhibit 2).

[6] *See* MacBride, *supra* note 3.

Table 1. FDA-Approved Estrogen VVA Products Before Imvexxy

Products	Estrace Cream®	Premarin Cream®	Vagifem®	Estring®
				
	Allergan	Pfizer	novo nordisk	Pfizer
FDA Approval	1984	1978	1999	1996
Method of Admin	Vaginal Cream	Vaginal Cream	Vaginal Tablet	Ring
Application	Reusable Vaginal Applicator	Reusable Vaginal Applicator	Vaginal Applicator	90-day Ring
Active Ingredient	100 mcg Estradiol	625 mcg/g Conjugated Equine Estrogens	10 mcg Estradiol	2,000 mcg Estradiol
Average Maintenance Dose	100 mcg 2x/week	312.5 mcg 2x/week	10 mcg 2x/week	7.5 mcg daily

Facing these choices (and before the approval of Imvexxy), a significant number of women did not seek treatment for VVA or did not maintain treatment after starting. Of the approximately 32 million women suffering from VVA symptoms,[7] only about 50% sought treatment.[8] Only 7% were treated with prescription hormone therapy,[9] citing long-term safety concerns, efficacy,

[7] The North American Menopause Society, *Management of Symptomatic Vulvovaginal Atrophy: 2013 Position Statement of The North American Menopause Society*, Menopause 20:888-902 (2013) (Attached hereto as Exhibit 3); Margery L.S. Gass *et al*., *Patterns and Predictions of Sexual Activity Among Women in the Hormone Trials of the Women's Health Initiative*, Menopause 19:1160-1171 (2011) (Attached hereto as Exhibit 4).

[8] *See* Sheryl A. Kingsberg *et al*., *The Women's EMPOWER Survey: Identifying Women's Perceptions on Vulvar and Vaginal Atrophy and its Treatment*, J. Sexual Med. 14:413-24 (2017) (Attached hereto as Exhibit 5).

[9] *See* TherapeuticsMD, TXMD Overview (March 2018), https://ir.therapeuticsmd.com/static-files/ f628f762-04c4-43f3-9c93-d974d2626c25 (Attached hereto as Exhibit 6).

messiness, and the need for an applicator as reasons for not receiving treatment.[10] Moreover, 8% were past users of prescription hormone therapy but stopped because they were unsatisfied or unsuccessful with treatment, and 25% were users of over the counter products, such as lubricants that do not treat the underlying pathology of VVA.[11] Thus a major portion of a large patient population was not receiving effective treatment, due at least in part to perceived deficiencies in the available treatments.

2. Imvexxy

a. The Imvexxy Softgel Insert

Imvexxy is a teardrop-shaped gelatin insert with the active pharmaceutical ingredient ("API") solubilized in a liquid fill. Imvexxy's fill formula contains a nonirritating oil that readily disperses estradiol throughout the vaginal cavity. TherapeuticsMD designed the fill formulation to substantially remain in the vaginal cavity.[12] Due to Imvexxy being a liquid-fill formulation for delivery to the vaginal cavity, TherapeuticsMD has observed that a small volume of the delivered product can leak from the vaginal cavity.[13]

Figure 2 depicts the Imvexxy teardrop-shaped softgel insert.

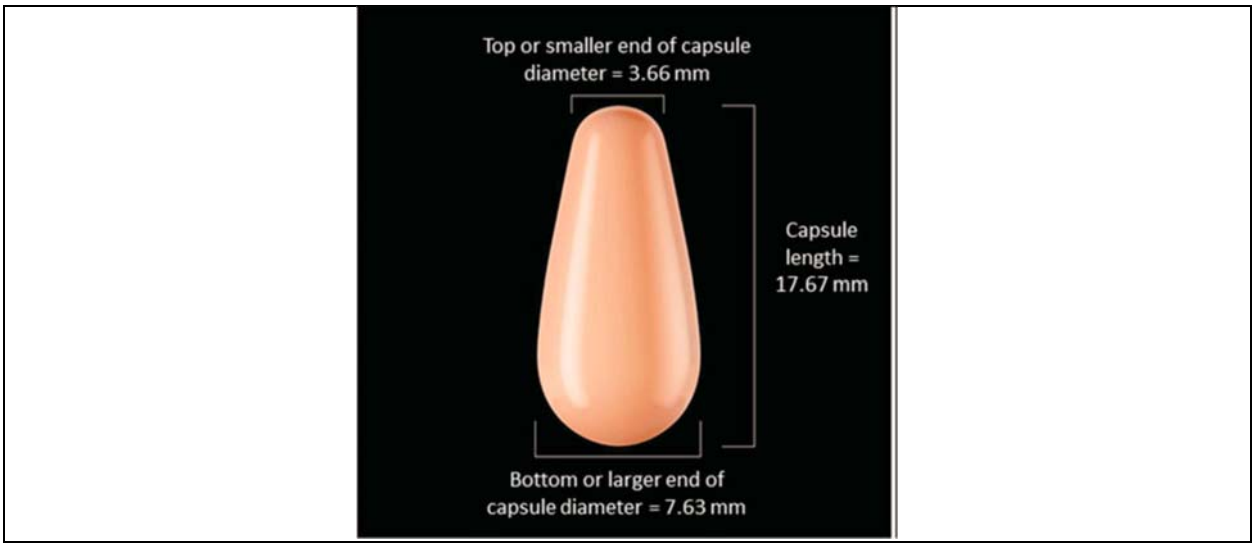
[10] Susan Wysocki *et al.*, *Management of Vaginal Atrophy: Implications from the REVIVE Survey*, Clinical Medicine Insights: Reproductive Health 8:23-30 (2014) (Attached hereto as Exhibit 7).

[11] *See* Kingsberg *et al.*, *supra* note 8.

[12] *See* James Pickar *et al.*, *Pharmacokinetic Studies of Solubilized Estradiol Given Vaginally in a Novel Softgel Capsule*, Climateric 19:181, 181 (2016) (Attached hereto as Exhibit 12) ("The novel capsule was designed to provide local efficacy (*i.e.* estrogenic effect on the vaginal tissue) without increasing systemic exposure of estradiol. In addition, it was designed for convenience; it is easily inserted without the need for an applicator and is not as messy as creams"); Sheryl A. Kingsberg *et al.*, *Patient Acceptability and Satisfaction with a Low-Dose Solubilized Vaginal Estradiol Softgel Capsule, TX-004HR*, Menopause 24:894, 898 (2017) (Attached hereto as Exhibit 13) ("TX-004HR [Imvexxy] has been designed to rapidly dissolve, with no vaginal secretions required for activation, and therefore, should minimize vaginal discharge, resulting in less messiness").

[13] *See* Ginger D. Constantine *et al.*, *The REJOICE Trial: A Phase 3 Randomized, Controlled Trial Evaluating the Safety and Efficacy of a Novel Vaginal Estradiol Soft-Gel Capsule for Symptomatic Vulvar and Vaginal Atrophy*, Menopause 24:409-415 (2017) (Attached hereto as Exhibit 10) at 410, 415.

Figure 2. Imvexxy Teardrop-Shaped Softgel Insert[14]



During manufacture, the fill material with the estradiol and liquid excipients is heated and mixed to create a homogenous solution. Separately the gelatin shell is prepared by heating the gelatin excipients to create two gelatin ribbons of uniform thickness. These ribbons are then fed into an encapsulating apparatus where a first seam is created linking the two ribbons together. The liquid fill is then added to the well created by the ribbons and, as the final step, the insert is sealed along the seam. The insert is then further processed with drying and polishing steps. The drying step reduces the tackiness of the insert and allows for a more uniform rupture upon insertion in a woman. The polishing steps help remove lubricants used in manufacture, reducing the potential for clumping or bricking, and further reducing the tackiness of the product. In designing the thickness of the ribbon, TherapeuticsMD selected a thickness that facilitated ease of rupture within the vagina. Rupture is activated by the native vaginal moisture as well as pressure by the vaginal walls against the surface of the insert. Ribbons that are too thick would undergo delayed rupture and hence release, while a thinner ribbon would lead to leaking inserts and loss of drug during manufacturing and storage. That is, ribbons that are too thin are fragile, and are associated with manufacturing and storage defects.

Users of Imvexxy are instructed to manually insert each softgel insert by grasping the wider end and inserting with the narrower end leading. This enhances ease of use and may reduce the

[14] *See* Ginger D. Constantine et al., *Estradiol Vaginal Inserts (4 mg and 10 mg) for Treating Moderate to Sever Vulvar and Vaginal Atrophy: A Review of Phase 3 Safety, Efficacy and Pharmacokinetic Data,* Current Med. Res. & Op. 1-6 (Attached hereto as Exhibit 31).

risk of vaginal abrasions.[15] The patient is also instructed to insert Imvexxy approximately two inches into the vagina. The shape and finish of the insert were designed to ease insertion, particularly for women whose vaginal openings have significantly atrophied, making insertion of vaginal suppositories very difficult to achieve.[16] Further, to minimize vaginal discharge, Imvexxy is designed to completely and rapidly dissolve upon exposure to the vaginal mucosa; vaginal secretions are not required to activate dissolution.[17] One study indicated that while women may experience vaginal discharge with Imvexxy use, most women reported the severity of vaginal discharge as being mild to moderate, i.e., reports of vaginal discharge with women using Imvexxy were fewer than those with women administering placebo.[18]

b. FDA Approval of Imvexxy

On May 29, 2018, FDA approved Imvexxy (NDA #208564) for the treatment of moderate-to-severe dyspareunia due to menopause in women.[19] Imvexxy is a locally acting estradiol softgel vaginal insert available in 4 mcg and 10 mcg strengths. The 4 mcg strength represents the lowest approved strength of vaginal estradiol. Imvexxy is designed to be manually inserted (without an applicator) approximately two inches into the vagina daily for two weeks and then twice weekly thereafter.[20]

FDA approved Imvexxy based on the results of a Phase 3, 12-week, randomized, double-blind, placebo-controlled study that evaluated the safety and efficacy of Imvexxy (4 mcg and 10 mcg) compared to a placebo from baseline to week 12. The study showed that both strengths of Imvexxy provided relief of moderate-to-severe dyspareunia due to menopause.

As shown in Table 2 below, the 4 mcg and 10 mcg strengths achieved statistically significant improvement to both the primary and co-primary endpoints as early as two weeks.[21] Importantly, after six weeks of treatment, patient response to Imvexxy stabilized. Although both

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[15] *See* TherapeuticsMD, *Imvexxy Prescribing Information*, at 4 (Nov. 2019) (Attached hereto as Exhibit 9).

[16] *See* Constantine, *supra* note 13.

[17] *See id*.

[18] *See* Constantine, *supra* note 13, at 415.

[19] *See* Letter from Christine P. Nguyen, M.D., Deputy Director for Safety, Division of Bone, Reproductive, and Urologic Products, Office of Drug Evaluation III, Center for Drug Evaluation and Research, FDA, to Christine Miller, Pharm.D., Chief Regulatory and Quality Officer, TherapeuticsMD, re: *NDA Approval* (May 29, 2019), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/208564Orig1s000ltr.pdf (Attached hereto as Exhibit 8)

[20] TherapeuticsMD, *Imvexxy Prescribing Information*, *supra* note 15 at Fig. 1.

[21] *See* Constantine *et al*., *supra* note 13.

the 4 mcg and 10 mcg dosage strengths showed statistical improvements relative to placebo, the 4 mcg and 10 mcg strengths showed comparable changes from baseline relative to each other.

Table 2. Change from Baseline (LS Means SE) at Weeks 2, 6, 8, and 12 for the 4 Co-Primary Endpoints (MITT Population).[22]

		% Superficial cells			% Parabasal cells			Vaginal pH			Dyspareunia (score)		
TX-004HR	Week	n	LS mean ± SE	P[a]	n	LS mean ± SE	P[a]	n	LS mean ± SE	P[a]	n	LS mean ± SE	P[a]
4 µg	2	186	31.4 ± 1.50	<0.0001	186	−40.2 ± 1.72	<0.0001	186	−1.23 ± 0.06	<0.0001	145	−0.99 ± 0.07	0.0260
	6	172	18.4 ± 1.54	<0.0001	172	−39.4 ± 1.75	<0.0001	172	−1.32 ± 0.07	<0.0001	148	−1.30 ± 0.07	0.0069
	8	164	19.0 ± 1.56	<0.0001	164	−41.9 ± 1.77	<0.0001	164	−1.35 ± 0.07	<0.0001	140	−1.52 ± 0.07	0.0003
	12	170	17.5 ± 1.54	<0.0001	170	−40.6 ± 1.76	<0.0001	170	−1.32 ± 0.07	<0.0001	151	−1.52 ± 0.07	0.0149
10 µg	2	188	31.9 ± 1.50	<0.0001	188	−44.4 ± 1.71	<0.0001	188	−1.37 ± 0.06	<0.0001	147	−1.08 ± 0.07	0.0019
	6	170	16.9 ± 1.54	<0.0001	170	−43.6 ± 1.75	<0.0001	170	−1.40 ± 0.07	<0.0001	150	−1.37 ± 0.07	0.0009
	8	165	17.4 ± 1.56	<0.0001	165	−43.8 ± 1.76	<0.0001	165	−1.46 ± 0.07	<0.0001	136	−1.64 ± 0.07	<0.0001
	12	171	16.7 ± 1.54	<0.0001	171	−44.1 ± 1.75	<0.0001	171	−1.42 ± 0.07	<0.0001	154	−1.69 ± 0.07	<0.0001
25 µg	2	184	38.9 ± 1.50	<0.0001	184	−45.6 ± 1.72	<0.0001	184	−1.30 ± 0.07	<0.0001	140	−1.02 ± 0.07	0.0105
	6	173	22.7 ± 1.53	<0.0001	173	−45.6 ± 1.75	<0.0001	173	−1.48 ± 0.07	<0.0001	150	−1.48 ± 0.07	<0.0001
	8	166	23.9 ± 1.55	<0.0001	166	−45.1 ± 1.76	<0.0001	166	−1.45 ± 0.07	<0.0001	129	−1.62 ± 0.08	<0.0001
	12	174	23.2 ± 1.53	<0.0001	174	−45.6 ± 1.75	<0.0001	174	−1.34 ± 0.07	<0.0001	159	−1.69 ± 0.07	<0.0001
Placebo	2	185	6.1 ± 1.50	—	185	−7.0 ± 1.72	—	186	−0.28 ± 0.06	—	141	−0.76 ± 0.07	—
	6	176	5.4 ± 1.53	—	176	−9.2 ± 1.74	—	176	−0.30 ± 0.07	—	159	−1.03 ± 0.07	—
	8	167	6.0 ± 1.55	—	167	−7.9 ± 1.76	—	167	−0.38 ± 0.07	—	143	−1.15 ± 0.07	—
	12	172	5.6 ± 1.54	—	172	−6.7 ± 1.75	—	174	−0.28 ± 0.07	—	163	−1.28 ± 0.07	—

LS, least square; MITT, modified intent-to-treat.
[a]TX-004HR versus placebo, based on mixed-effects model repeated measures.

Importantly, "the ultra-low-dose E2 softgel vaginal insert was found to be safe and well tolerated."[23] "[N]o cases of endometrial hyperplasia or malignancy were reported with 12 weeks of the E2 vaginal insert use."[24] As shown in Table 3 below, the most common Treatment-Emergent Adverse Event across all treatment arms was headache.[25]

Preferred Term	4 µg E2 (*n* = 191)	10 µg E2 (*n* = 191)	Placebo (*n* = 192)
Any subject with reported TEAE	97 (50.8)	94 (49.2)	111 (57.8)
Headache	12 (6.3)	14 (7.3)	15 (7.8)
Vaginal discharge	5 (2.6)	6 (3.1)	13 (6.8)
Nasopharyngitis	5 (2.6)	6 (3.1)	10 (5.2)
Vulvovaginal pruritus	4 (2.1)	3 (1.6)	10 (5.2)
Back pain	9 (4.7)	1 (0.5)	8 (4.2)
Urinary tract infection	5 (2.6)	5 (2.6)	4 (2.1)
Upper respiratory tract infection	5 (2.6)	6 (3.1)	5 (2.6)
Oropharyngeal pain	1 (0.5)	0 (0)	1 (0.5)

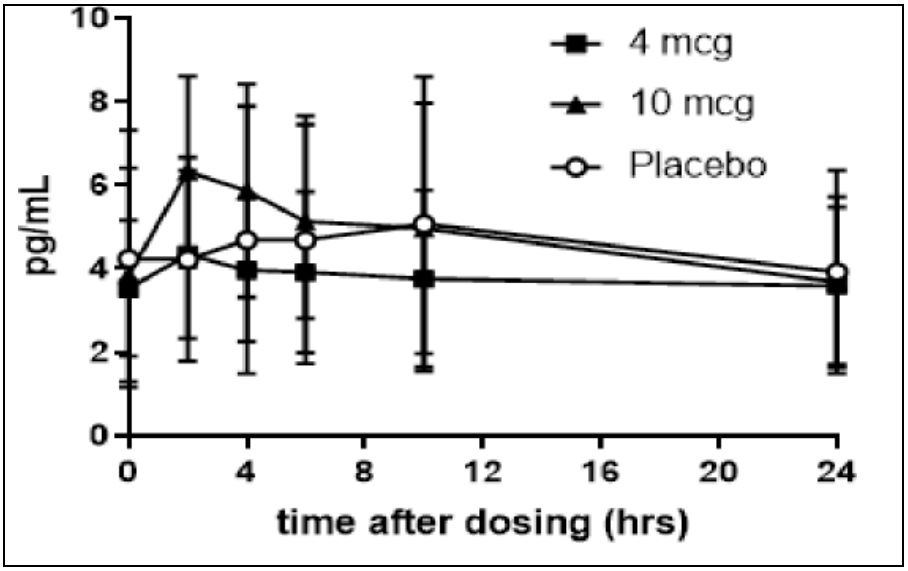
Data reported as *n* (%).
Abbreviation. TEAE, treatment-emergent adverse event.

[22] *Id.* at 413.
[23] Constantine, *supra* note 14, at 3.
[24] *Id.* at 5.
[25] *Id.* at 4.

c. The Estradiol in Imvexxy Is Not Systemically Absorbed

Imvexxy is unlike all other estrogen drug products because while most "[e]strogen drug products are well absorbed through the skin, mucous membranes, and the gastrointestinal tract,"[26] Imvexxy does not show systemic absorption and acts only locally. As shown in Figure 1 below, with both the 4 mcg and 10 mcg strengths, the mean concentration of systemic estradiol measured in the blood remained within the average postmenopausal range after administration of Imvexxy. At steady state, the 4 mcg and 10 mcg dosage strengths had p-values versus placebo of 0.3829 and 0.7724, respectively, for the area under the curve ("AUC") values on day 14.[23] The 4 mcg and 10 mcg dosage strengths thus could not be differentiated statistically from placebo in pharmacokinetic studies, which means that there is no statistically significant evidence that the 4 mcg and 10 mcg dosage strengths are systemically absorbed.

Figure 1. Mean (±SD) Serum Concentration of Estradiol and Estrone on Day 14 Following Daily Administration of IMVEXXY 4 mcg, IMVEXXY 10 mcg and Placebo.[27]



[26] TherapeuticsMD, *Imvexxy Prescribing Information*, *supra* note 13 at 14-15.

[27] *See* TherapeuticsMD, *Imvexxy Prescribing Information*, *supra* note 13 at Fig. 1; *see also* James A. Simon, *A Vaginal Estradiol Softgel Capsule, TX-004HR, Has Negligible to Very Low Systemic Absorption of Estradiol: Efficacy and Pharmacokinetic Data Review,* Maturitas 99:51, 56-57 (2017) (Attached hereto as Exhibit 11).

3. Considerations Unique to Vaginal Drug Delivery

Localized drug delivery to the vagina presents several unique considerations and challenges when compared to the delivery of drugs to other locations in the body. For the reasons explained more fully below, drug formulations and their manufacturing steps, in general, interact with vaginal physiology and anatomy to govern the rate and extent of drug absorption.[28] Thus, in the context of a drug product that cannot be systemically measured, such as Imvexxy, it is difficult, if not impossible, to systematically analyze the effects of the multivariate relationships of product design and manufacturing factors on the rate and extent of drug absorption.

a. The Vaginal Cavity, its Native Moisture Levels, and its Pressure Profile

The vagina is a closed canal approximately 10 cm in length.[29] While the vagina does not secrete fluid *per se*, it may contain upwards of approximately 1-2 mL of ambient vaginal fluid.[30] This fluid includes mucus from the cervix that flows down through the external cervical os into the floor of the fornix in the innermost region of the canal.[31] This fluid also includes exudate that percolates out through the epithelial layer of the mucosa. The distribution of vaginal fluid varies along the length of the canal. The vagina may discharge excess vaginal fluid. Formulators seeking to develop vaginal liquid formulations must account for vaginal discharge, and how the formulation and drug itself will interact with, and be affected by, the ambient vaginal fluid and its flow. Small increases in the vagina's discharge process can result in drug leakage, thereby altering the dose absorbed. That is, as fluid is discharged from the vagina, it can remove the drug with it and consequently reduce net drug absorption.[32]

Further confronting vaginal drug delivery design is the non-constant intravaginal pressure along the length of the vaginal canal. Vaginal pressure ranges from about or under 5kPa at the region of the vaginal opening, to peak values of about 15-20 kPa at locations about 3.5-4 cm into

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[28] *See* Alamdar Hussain & Fakhrul Ahsan, *The Vagina as a Route for Systemic Drug Delivery*, J. of Controlled Release 103:301, 301, 303-04 (2005) (Attached hereto as Exhibit 14).

[29] *See* Noelani M. Guaderrama *et al.*, *The Vaginal Pressure Profile*, Neurourology and Urodynamics 24:243-47 (2005) (Attached hereto as Exhibit 15).

[30] *See* David F. Katz *et al.*, *Vaginal Drug Distribution Modeling*, Adv. Drug Delivery Rev. 92:2-13 (2015) (Attached hereto as Exhibit 16); *see generally* Derek H. Owen & David F. Katz, *A Vaginal Fluid Simulant*, Contraception 59:91, 92 (1999) (Attached hereto as Exhibit 17) (discussing the quantity of vaginal fluid in the vagina).

[31] *See* Hussain & Ahsan, *supra* note 28, at 303; *see also* Owen & Katz, *supra* note 30, at 91.

[32] *See id.*; *see generally* Chinmaya Keshari Sahoo *et al.*, *Intra Vaginal Drug Delivery System: An Overview*, Am. J. Advanced Drug Delivery (2013), *available at* http://www.imedpub.com/articles/intra-vaginal-drug-delivery-systeman-overview.pdf (Attached hereto as Exhibit 18).

the vagina, and drops to about 10 kPa about 7 cm into the vagina.[33] Therefore, it appears that about two inches (i.e., 5 cm) into the vagina is within or just past the zone of maximal intravaginal pressure.[34] As a result, small changes in depth of placement, even a quarter-inch difference, could potentially double intravaginal pressure on an insert, as measured in the Cacciari study. The pressure within the vagina is germane to Imvexxy as discussed below.

b. The Rate of Drug Absorption for Products Like Imvexxy Is Influenced by Release and Spreading of the Liquid Fill Upon Release

The therapeutic benefit of a locally acting vaginal drug product is dependent on the drug product's ability to coat the vaginal wall and be absorbed into the vaginal epithelium all along the canal. The composition of the gelatin shell, as well as the composition and amount of the liquid fill, interactively affect the spreading of the drug product, and are discussed further below.[35]

To be absorbed locally, an estradiol vaginal insert must rupture and release the liquid fill so that it can spread throughout the vagina, reach the vaginal estrogen receptors on cells within the vaginal tissue, and thence bind to those estrogen receptors. These receptors are located throughout the vagina.[36] The degree to which the liquid fill spreads over the vaginal tissue influences the rate of absorption and therapeutic effect.[37] Therefore, Imvexxy's therapeutic effect depends on the tissue surface area directly exposed to Imvexxy. The total surface area is relatively large (over 100 cm^2). This presents a significant challenge to a formulation that must spread and coat this large area, but not leak out from the vaginal canal.[38]

Rupture of a softgel within the low moisture vaginal environment depends in part on the composition and configuration of the product and its method of manufacture. Process and quality control of the manufacturing steps are thus critical. For a product such as Imvexxy, these factors are subtle and significantly interrelated; collectively, they influence the extent of rupture and formulation spreading.

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[33] *See* Licia P. Cacciari *et al.*, *Novel Instrumented Probe for Measuring 3D Pressure Distribution Along the Vaginal Canal*, J. Biomech. 58:139-46 (2017) (Attached hereto as Exhibit 19), at Figure 4.

[34] *See id.*; *see also* Guaderrama, *supra* note 29, at 247 explaining that "the level of the bell-shaped curve of the high-pressure zone [is] at least 5cm within the vagina."

[35] *See* Citizen Petition, Docket ID No. FDA-2018-P-4714 (December 11, 2018).

[36] *See* Michael F. Press *et al*., *Estrogen Receptor Localization in the Female Genital Tract*, Am. J. Pathology 123:280, 283-87 (1986) (attached hereto as Exhibit 20).

[37] *See generally* Katz, *supra* note 30, at 2-8, 16-17.

[38] Imvexxy was designed to balance the desire to provide local efficacy, but also to minimize the amount of drug product leaked from the vagina. *See* James H. Pickar *et al*., *A Randomized, Double-Blind, Placebo-Controlled Phase 2 Pilot Trial Evaluating a Novel, Vaginal Softgel Capsule Containing Solubilized Estradiol*, Menopause 23:506-10 (2016).

The gelatin impacts release: Gelatin comes in a variety of Bloom strengths. The selection of Bloom strength influences the rigidity of the insert and time of rupture. Rigidity can also impact ease of product insertion and likelihood of expulsion. The rate of absorption of vaginal moisture impacts the hardness of the shell, softening it and enabling the release of the liquid fill active.[39] But even for a product that is Q1Q2 to Imvexxy, method of manufacture and quality issues will also impact the microstructure of the product and therefore rupture. A Q1Q2 product but with a shape other than Imvexxy's teardrop shape will necessarily have a different ribbon thickness because it will utilize the same quantity of shell material as Imvexxy but be molded to different geometrical shape. In the low moisture environment of an atrophic vagina, increased ribbon thickness will slow rupture (as will residual moisture amounts of the shell post drying).[40] Decreased ribbon thickness will impact product shelf life and will likely affect the patient's ability to properly administer the product. Drying times and rate also impact product quality attributes and rupture time.[41]

Shell manufacturing quality issues impact rupture: Imvexxy's seam runs vertically along the long axis between the wider and narrower portions of the insert. As Imvexxy is exposed to the vaginal moisture, it is believed that the seam is the location of product release because, as the weakest part of the Imvexxy gelatin shell, this is where the shell first ruptures. The liquid fill is then released along this point of rupture. The liquid flow is influenced by surface tension and capillary action, and spreads about the residual shell of the insert before the shell becomes fully dissolved. Different manufacturing methods can create the weak point of the shell at different locations. For example, prolonged processing could minimize the weakness of the seam creating a tendency for rupture to occur elsewhere on the shell. This could change the character of release. Different mold designs can create a wider or narrower seam, depending on manufacturing design considerations. Such design issues impact rupture and release and yet are completely independent of whether the ANDA product is Q1Q2 to Imvexxy.[42] Yet these subtle differences further highlight

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[39] *See* Margareth R.C. Marques et al., *Liquid-Filled Gelatin Capsules*, Pharmacopeial Forum 35:1029-1041 (2009) (attached hereto as Exhibit 22).

[40] USP >711 includes dissolution testing for oral softgel products. However, dissolution is a poor surrogate test for vaginal products such as Imvexxy that are introduced and released in a low moisture environment. *See, e.g.,* Om Anand et al., *Dissolution Testing for Generic Drugs: An FDA Perspective*, AAPS Journal 13:328-335 (2011) (attached hereto as Exhibit 23) (noting that "[f]or ophthalmic suspensions, generic liposome formulations, and rectal and vaginal suppositories, if there is no USP or FDA recommended method then the DBE [Division of Bioequivalence] encourages the firms to develop a method to characterize the *in vitro* release.")

[41] Marques, *supra* note 39, at 1035 ("The rate and extent of capsule drying probably is the most important processing parameter.").

[42] In its previously filed Citizen Petition, TherapeuticsMD explained why a generic drug product needed to be Q1Q2 and Q3 to Imvexxy. *See* Docket ID No. FDA-2018-P-4714. Q3 was

the importance for establishing a Q3 criteria for Imvexxy, especially as it is not shown to be systemically absorbed and therefore pharmacokinetics cannot demonstrate the bioequivalence of the two products.

Impact of manufacturing quality issues on release: Imvexxy is polished as a final finishing step. This polishing step serves many functions, several of which are related to the issues in this Petition. By polishing the insert, shell defects are removed. By removing such artifacts from the shell wall, a more uniform time of rupture is obtained across lots and within each lot. In addition, gelatin is tacky. This is initially minimized by the drying of the product post-release from the mold.[43] But further minimization by this polishing step is necessary.[44] As in other aspects of Imvexxy, these nuances of product quality and consequent uniformity of time of rupture are not addressed by a product that is merely Q1Q2 to Imvexxy. To match the release of Imvexxy *in situ*, and thereby the rate and extent of absorption, Imvexxy's Q3 quality attributes must also otherwise be matched.

Impact of shape on release: The physical shape of the vaginal insert also affects release of its fill, interacting with the other factors mentioned above. For example, after vaginal insertion, the forces distributed over the surface of a product shaped like a perfect sphere are different than those occurring on a teardrop shape like Imvexxy. Mechanically, these act as "stresses" (defined as local forces per unit surface area). In the example of the sphere, the stresses are much more uniformly distributed over the surface that they are for a teardrop shape, which has localized regions of elevated stress (stress risers). The presence and details of these stress risers contribute to the rapid rupture and drug release of Imvexxy. The uniform distribution of stresses acting on the surface of a spherical insert would act to slow rupture and release by it, in contrast to Imvexxy.

The rate and volumetric amount of liquid fill release are functions of several interacting properties: its shape and volume; the thickness of the shell; the physical properties of the shell and of the fill (as influenced by vaginal moisture); and the intravaginal pressure exerted upon the insert by the walls of the vagina. The vaginal cavity tends to close upon itself after distension (*e.g.*, by an inserted product). It does not exert constant pressure along its length; together with the above,

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broadly explained, in that Petition, as relating to certain rheological properties of an insert, such as viscosity. Yet for the reasons presented in this Petition, the Q3 criteria should more broadly include non-formulation issues, such as those discussed herein, that affect the rupture, release, and spreading of the active.

[43] Marques, *supra* note 39, at 1035 ("Not enough drying results in capsules that are too soft and that may weep, become tacky, and/or tightly stick to each other.").

[44] To the extent that an ANDA product eliminated polishing or reduced the extent of polishing, while that product could have the same Q1Q2 formulation to Imvexxy, these changes in processing conditions could still affect the product in significant ways that cannot be ascertained for these products because of its non-systemic absorption.

this, too, impacts the rupture process and rate and amount of fill release.[45] Inserts that are shaped differently from Imvexxy are in principle expected to have different release rates. This is due, in part, to a different combination of rupture and liquid fill release dynamics, which then are believed to affect the rate of absorption due to different liquid fill release dynamics. For example, a product that is spherical in shape would have the smallest surface-area-to-volume ratio compared to any other shape.[46] As a sphere is elongated, for example, into an ovoid shape, the surface area to volume ratio increases.[47] Shapes, like Imvexxy, which have a wider base and a narrower top than a sphere, have an even greater surface-area-to-volume ratio than does a sphere.[48]

The above factors impact an intravaginal insert in several ways. For example, inserts with a higher surface-to-volume area should rupture sooner, in part because the shell is thinner and in part these products have relatively more surface area for the limited vaginal moisture to affect. More rapid (or slower) release rates may result in differential drug absorption due to a variety of factors including: (i) greater vaginal discharge of the API contained in the liquid fill; (ii) more rapid absorption into the vaginal tissues causing the estradiol to diffuse out of the local tissues resulting in a systemic impact; and (iii) more or less spreading, which can impact the local pharmacokinetics of the drug product.[49]

c. Vaginal Insert Placement in Relation to Estradiol's Effect on Vaginal Tissues

A study of vaginal estradiol tablets has "demonstrate[d] dramatic difference in the preferential distribution of estrogens that are administered vaginally, depending on whether the E_2 tablets were placed proximally in the outer one third of the vagina or distally in the inner one third

[45] *See* Cacciari, *supra* note 33. The region in the vagina the insert ruptures will affect the compressing force of the vagina on the insert. Closer to the vaginal opening, the intravaginal pressure was measured to be less than bout 5 kPa. Whereas approximately 1.5 inches (or 3.5-4 cm) into the vagina, which is the region of maximal intravaginal pressure, the vagina's internal pressure is 15 kPa. At or about two inches (i.e., 5 cm) into the vagina, the pressure begins to drop until it becomes that of the pressure of the abdominal region (i.e., about 5-8 kPa).

[46] *See* https://en.wikipedia.org/wiki/Surface-area-to-volume_ratio, reporting that a sphere has a surface area to volume ratio of 4.83598 per unit of volume.

[47] *See* https://en.wikipedia.org/wiki/Surface-area-to-volume_ratio, reporting that a capsule has a surface area to volume ratio of 5.251 per unit of volume.

[48] *See* https://en.wikipedia.org/wiki/Surface-area-to-volume_ratio, reporting that a tetrahedron has a surface area to volume ratio of 7.21 per unit of volume.

[49] To the extent an ANDA product had systemically measurable PK values of estradiol, such a product could not be a generic to Imvexxy, as Imvexxy does not have statistically measurable PK values for estradiol.

of the vagina."[50] The study concluded that the "findings lead us to recommend the placement of E_2 tablets in the outer one third of the vagina to optimize the direct effects where they are desired."[51] The study found that placement of estrogen products lower in the vagina resulted in a higher increase in blood flow in the urethrovaginal septum arteries, compared to a higher placement of the estradiol tablet in the vagina (i.e., closer to the cervix), which resulted in higher blood flow in the ipsilateral uterine artery and the contralateral uterine artery, which could result in transport of estradiol to the endometrium.[52] The author concluded that "vaginal E2 [tablets] should be placed in the outer one third of the vagina for best results on local symptoms of menopause (vaginal and periurethral atrophy), which will minimize the risk of endometrial proliferation."[53] Thus, distribution of estradiol through the lower portion of the vaginal (i.e., where Imvexxy is delivered) versus the upper portion of the vagina (i.e., where estradiol tablets are delivered) can lead to different physiological responses.[54]

Related to the placement of the insert is the possibility that the insert will be expelled from the vagina before rupture. It is axiomatic that insert expelled before rupture would not deliver the active to the intended target tissues. A change in shape, or other Q3 attributes relative to Imvexxy, could increase the expulsion frequency of the insert. This would materially alter the rate and extent of delivery of the estradiol to the intended target tissues in a manner which would not be measured through the existing surrogate assays of dissolution, pharmacokinetics, and the like. A well-designed, powered patient comparability study could address the question of expulsion rate differences, but not the other questions presented in this Petition.

4. Imvexxy Is Uniquely Configured to Deliver Estradiol to the Vaginal Tissues

Users of Imvexxy are instructed to manually insert each Imvexxy softgel insert by grasping the wider end and inserting with the narrower end, which enhances ease of use and may reduce the risk of vaginal abrasions. Because Imvexxy is a polished softgel insert, with a tapered shape,

[50] *See* Ettore Cicinelli, et al., *Placement of the Vaginal 17/3-Estradiol Tablets in the Inner or Outer One Third of the Vagina Affects the Preferential Delivery of 17/3-Estradiol Toward the Uterus or Periurethral Areas, thereby Modifying Efficacy and Endometrial Safety*, Am. J. Obstet. Gynecol. 18:57 (2003) (Attached hereto as Exhibit 24).

[51] *Id.* at 57.

[52] *See id.*

[53] *Id.*

[54] *See generally* Kelly Isbill, *Thoughts on Sexuality*, Perm. J. 22:17-188 (2018) (Attached as Exhibit 25) ("[Vaginal estradiol tablets and vaginal estradiol rings] tend to only improve lubrication in the upper two-thirds of the vagina. If penetration is painful, it's not enough for the upper two-thirds to be lubricated when the lower one-third remains dry and painful.").

women find the product easy to insert to the instructed depth of two inches into the vagina.[55] The shape was designed, in part, to ease insertion, particularly for women with the vaginal shortening and narrowing which tend to occur in VVA.[56] Those render insertion of vaginal suppositories difficult or otherwise impracticable. In comparison to Imvexxy, it is expected that not all shapes will be as easy to insert.[57]

Imvexxy contains approximately 300 mg of fill, which is liquid at body temperature. A dosage of Imvexxy can therefore increase the mass of vaginal fluids by over 50%, depending on the amount of ambient vaginal fluid. While vaginal discharge was not noted in the use of Imvexxy during its clinical evaluation, TherapeuticsMD received post-commercialization feedback from patients concerning vaginal discharge. This led TherapeuticsMD to add vaginal discharge as a "Postmarketing Experience" to the label.[58] While the modalities for these discharge reports are not fully known for all reports, many of the reports are likely due to incomplete insertion of the insert by the patient. Therefore, a change in shape that makes insertion less easy will likely lead to more patient adverse experiences of discharge caused by the inadequate insertion.

If a patient does not place the insert to the instructed depth, the insert is more likely to lead to leakage of the fill material the closer the insert is to the vaginal opening. As noted above, as related to the study by Cacciari *et al*., when a product is inserted two inches into the vagina, such as Imvexxy being inserted by a woman in compliance with the label, it would be positioned just past a zone of maximal intravaginal pressure.[59] Therefore, it can be expected that the zone of maximal pressure would have a tendency to retain Imvexxy once it has liquified. Yet an insert delivered short of the instructed depth could be in front of this zone of maximal intravaginal pressure and could be postulated to leak to a far greater degree than Imvexxy.[60]

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[55] Kingsberg, *supra* note 8. In contrast, an unpolished or less polished insert would tend to be tackier than Imvexxy, which could impede a woman's ability to insert the product to the indicated depth of two inches.

[56] *See* MacBride *supra* note 3.

[57] *See* Bangde Li *et al*., *Shape of Vaginal Suppositories Affects Willingness-to-Try and Preference*, Antiviral Res. 97:280-84 (2013) (Attached as Exhibit 26) (which provides evidence that women do not prefer spherical vaginal inserts, presumably due to concerns over grasping and insertion).

[58] *See* TherapeuticsMD, *Imvexxy Prescribing Information*, *supra* note 15, at Sec. 6.2.

[59] *See* Cacciari *supra* note 33.; *see also* Guaderrama *supra* note 29, at 247, explaining that "the level of the bell-shaped curve of the high-pressure zone [is] at least 5cm within the vagina."

[60] *See* Guadarrama *supra* note 29, explaining that (at p. 247) "[t]he vagina does not have any sphincter of its own" and that (at p. 244) the vaginal pressure at the region of the vaginal opening is essentially atmospheric pressure ("The pressure in the distal zone [i.e., the vaginal opening region] is the same as the atmospheric pressure").

C. Statement of Grounds

1. Legal Standard

In exchange for an abbreviated pathway for obtaining drug approval, the generic drug product that is the subject of an ANDA must contain the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with limited permissible differences) labeling as the reference listed drug ("RLD").[61] An ANDA applicant also has the burden of demonstrating that its proposed generic drug product is bioequivalent to the RLD.[62] Generally, a generic drug is bioequivalent to the RLD if the rate and extent of absorption of the drug does not show a significant difference from the rate and extent of absorption of the RLD when the same therapeutic ingredient is administered at the same molar dose.[63]

In addition, an applicant must conduct bioavailability and BE testing using the most accurate, sensitive, and reproducible approach available.[64] FDA regulations provide a list of preferred BE methods in descending order of accuracy, sensitivity, and reproducibility.[65] FDA "may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect."[66]

For drug products that are systemically absorbed, an ANDA applicant often can show bioequivalence by comparing the drug and/or metabolite concentrations in biological fluid (e.g., blood) after administration of a dose of the test product and of the reference drug product. In a locally acting, non-systemically absorbed drug product, however, the rate and extent of absorption in biological fluid has limited utility due to the lack of correlation between blood levels of the

[61] *See* 21 U.S.C. § 355(j)(2)(A)(i)-(iii), (v); 21 C.F.R. § 314.94(a).

[62] *See* 21 U.S.C. § 355(j)(2)(A)(iv); 21 C.F.R. § 314.94(a).

[63] 21 U.S.C. § 355(j)(8)(B)(i); *see also* 21 C.F.R. § 314.3 ("Bioequivalence is the *absence of a significant difference* in the rate and extent to which the active ingredient . . . becomes available *at the site of drug action* when administered *at the same molar dose* under similar conditions in an appropriately designed study").

[64] *See* 21 C.F.R. § 320.24.

[65] *See id.*

[66] 21 U.S.C. § 355(j)(8)(c).

active moiety and dosing or efficacy.[67] Comparable blood levels for such products therefore are not sufficient to provide an assurance that the generic version is bioequivalent to the RLD.[68]

Where a product candidate is not appropriate for an ANDA, a sponsor may submit a New Drug Application under section 505(b)(2) of the FDCA.[69] The scientific premise underlying these provisions of the Hatch-Waxman Amendments is that a drug product approved in an ANDA under section 505(j) of the FD&C Act is presumed to be therapeutically equivalent to the reference listed drug, and thus can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the reference product. In contrast, a 505(b)(2) application allows greater flexibility as to the characteristics of the proposed product.

2. FDA's "Shape Guidance" Cautions for the Inclusion of Consumer Preferences and Comparative Ease of Administration in Reviewing ANDAs

FDA has issued guidance addressing the importance of "size, shape, and other physical attributes" of tablets and capsules ("Shape Guidance") that has a compelling connection to the issues presented by this Citizen Petition.[70] Specifically, the Shape Guidance goes beyond traditional bioequivalence criteria used in assessing an ANDA, and explains the critical importance of assessing consumer preferences and comparative ease of administration in reviewing ANDAs.[71]

The Shape Guidance begins with the proposition that "[t]ablets and capsules . . . may provide a number of advantages over other dosage forms," and concludes that "[w]hile generic formulations of [tablets and capsules] are required to be both pharmaceutically and therapeutically equivalent to a reference listed drug (RLD), we are concerned that differences in physical

[67] *See generally* FDA, *Approved Drug Products with Therapeutic Equivalents* viii (38th ed. 2018) ("Where these above methods are not applicable (e.g., for drug products that are not intended to be absorbed into the bloodstream), other scientifically valid in vivo or in vitro test methods to demonstrate bioequivalence may be appropriate.").

[68] *See* Letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, to Edward F. Hanover, Corporate Counsel, Novo Nordisk Inc., re: *Docket Nos. FDA-2009-P-0089 and FDA-2011-P-0482* (May 22, 2015), at 8 (stating that, with regard to vaginal estradiol tablets, "[w]e agree with the contention that PK data alone would be insufficient to support the approval of an ANDA for estradiol vaginal tablet relying on Vagifem as the RLD and that a clinical endpoint study will be required") (Attached hereto as Exhibit 27).

[69] *See* 21 U.S.C. § 355(b)(2); 21 CFR § 314.3(b).

[70] *See* FDA, Guidance for Industry, *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* (June 2015) (the "Shape Guidance"). While largely addressing oral routes of administration, the principles discussed in the Shape Guidance would apply to other dosage forms, especially vaginal inserts.

[71] *Id.* at 1. *See also* Li, *supra* note 57, discussing consumer preferences of women for vaginal drug product suppository shapes.

characteristics (e.g., size and shape of the tablet or capsule) may affect patient compliance and acceptability of medication regimens or could lead to medication errors." The Shape Guidance notes that dysphagia, or difficulty swallowing, can lead to a significant level of patient noncompliance, and recognizes that "[s]ize and shape of tablets and capsules affect the transit of the product through the pharynx and esophagus and may directly affect a patient's ability to swallow a particular drug product" and thus "[p]atient compliance with medication regimes may be influenced by the size and shape of a tablet or capsule.[72] Indeed, the Shape Guidance specifically states that age and "the presence of certain medical conditions" can cause dysphagia.[73] While the Shape Guidance discusses tablets and capsules in the context of oral administration, the principles and considerations identified by FDA are also applicable to the issues of shape presented by this Citizen Petition. Indeed, dysphagia due to age and/or medical conditions may be considered analogous to the postmenopausal vagina and presence of dyspareunia, which could similarly cause problems in placement of the vaginal insert and patient compliance.

Thus, in discussing compliance and acceptability of medications regimens as factors in generic drug development and ANDA approval, FDA recognizes that pharmaceutical and therapeutic equivalence are not solely determinative. Rather, comparable patient compliance aspects can be a significant factor for FDA to consider in developing generic drug guidance.[74]

3. FDA and Q3 Criteria for Locally Acting Drugs

FDA has recognized the difficulty in establishing guidance for certain locally-acting drug products, which applies to the context of Imvexxy.[75] Therefore, for certain drugs, FDA has imposed Q3 criteria in addition to Q1 and Q2 criteria for a product to be submitted through the ANDA pathway. Briefly, Q3 criteria are explained as having the "[s]ame components in same concentration with the same arrangement of matter (microstructure)." In relevant part, "Q3 is [a] characterization based determination" and "Q3 differences [can] come from manufacturing or excipient sourcing."[76] At issue for locally-acting, topical drugs is the role that manufacturing and the related macro and microstructure of the product imparts on the bioavailability of drugs when the typical pharmacokinetic surrogate assays lack the precision to demonstrate bioequivalence. For

[72] *See* Shape Guidance, *supra* note 70, at 2.

[73] *Id.* at 4.

[74] *See id*. at 3 ("Patient compliance with medication regimens may be influenced by the size and shape of a tablet or capsule.")

[75] *See* U.S. Food & Drug Administration, *Equivalence of Locally-Acting Drug Products*, Markham C. Luke, GDUFA Research Public Workshop, May 3, 2017 (Attached hereto as Exhibit 28).

[76] *See id.; see also* Rong-Kun Chang *et al*., *Generic Development of Topical Dermatologic Products: Formulation Development, Process Development, and Testing of Topical Dermatologic Products*, AAPS Journal 15:41-52 (2013) (Attached hereto as Exhibit 29) (discussing testing and establishing Q3 criteria for topical products during ANDA drug development).

such products, FDA has asked the ANDA applicant to demonstrate with additional testing requirements that the macro and microstructure of the generic product are equivalent to that of the RLD such that it can be reasonably inferred that the products are interchangeable in their rate and extent of delivery of the active ingredient to the target tissues.

4. Labeling Requirements Do Not Permit a Change in Shape for a Product like Imvexxy

The FDCA and FDA regulations promulgated thereunder expressly require that the labeling of an ANDA-approved drug must be "the same" as that of the RLD which the ANDA references, with certain enumerated exceptions. These requirements are set forth in detail in both the FDCA section applicable to New Drugs, as well as the accompanying CFR section addressing ANDAs.

a. 21 U.S. Code § 355. New Drugs

The FDCA section on New Drugs expressly provides that an ANDA and the RLD drug which it references must have "the same" labeling, with certain limited exceptions.

> An abbreviated application for a new drug shall contain . . . information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers . . . .[77]

b. 21 C.F.R. § 314.94 – Content and format of an ANDA

Similarly, the FDA regulations on ANDAs also expressly provides the proposed labeling for the ANDA must be "the same" as the approved labeling for the RLD, again with certain limited exceptions.

> Labeling (including the container label, package insert, and, if applicable, Medication Guide) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers.[78]

[77] 21 U.S.C. § 355(j)(2)(A)(v).
[78] 21 C.F.R. § 314.94(a)(8)(iv).

c. Permissible Differences in Labeling

As the foregoing statutory and regulatory provisions demonstrate, there are only two permissible differences in labeling between the ANDA and the RLD it references.

1. Differences approved under a petition
2. Drug product produced and/or distributed by different manufacturers

Neither of these categories allows for a difference in the IFUs. First, the bases on which a petition for a difference in labeling may be submitted are specific and limited. They include stating a different active ingredient, route of administration, strength, or dosage form.[79] It is axiomatic that none of the former three categories applies here. The latter, dosage form, would not apply either since a capsule is a dosage form, as is a tablet.[80] A difference in the label from a capsule to a tablet might afford a basis for a petition as a difference in dosage form, but not a difference in the label resulting from the manufacture of a different shape of the same dosage form. Ultimately, even if such a petition were allowed, it would require evidence establishing that the product that is labeled differently is a bioequivalent and therapeutically interchangeable ANDA product relative to the RLD. In the context of a product that has systemically measurable pharmacokinetics, such a showing might be done. However, for Imvexxy, which has no measurable systemic pharmacokinetics, such a showing cannot be made, and thus FDA should not grant such a petition should.[81]

Second, as for differences in manufacturers, the permissibility of that difference in labeling is grounded in the reality that the ANDA product necessarily would be manufactured by a different entity than the RLD, and so if the ANDA is approved its label would necessarily differ from the RLD label in that regard. That permissible difference has no application here.

Other than these two categories of labeling differences, the labeling of the ANDA product, including the IFUs, must be the same as that of the RLD.[82] Thus, the ANDA applicant cannot use

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[79] 21 U.S.C. § 355(j)(2)(C).

[80] *See* 21 C.F.R. §206.3 ("Drug product means a finished dosage form, e.g., a tablet or capsule...."); 21 C.F.R. §210.3(b)(4) ("Drug product means a finished dosage form for example, tablet capsule, solution...."); FDA, Drugs@FDA Glossary, *available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page* ("A dosage form is the physical form in which a drug is produced and dispensed, such as a tablet, a capsule, or an injectable.").

[81] 21 U.S.C. § 355(j)(2)(C)(i) ("The Secretary shall approve such a petition unless the Secretary finds (i) that investigations must be conducted to show the safety and effectiveness of … the dosage form….").

[82] *Id.* at 355(j)(2)(a)(v) ("information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug….")

a different IFU than the RLD, including a modified IFU as it relates to the shape of the vaginal insert.

5. Imvexxy's Labeling, its Unique Non-Systemic Mechanism of Action, and the Nuances of Vaginal Drug Delivery Necessitate Guidance that Does Not Permit a Shape Change or the Marco and Microstructure (*i.e.*, Q3 Quality Attributes) of the ANDA Product

TherapeuticsMD respectfully submits that Imvexxy is unique and that due to its uniqueness product specific guidance is required. More specifically, for the reasons set forth in this Petition, the FDA cannot permit a change in the shape of a product referencing Imvexxy submitted through the ANDA pathway because there are significant technical issues associated with intravaginal drug delivery of Imvexxy that cannot be addressed through normal surrogate tests conducted in support of an ANDA. Moreover, because subtle manufacturing changes in a generic product can affect the microstructure of the product and therefore the ability to release the same amount active in the same way as the RLD, FDA should impose Q3 criteria on any ANDA product.

The approved labeling for Imvexxy contains Instructions for Use (IFU) that are highly specific as to how a woman inserts the vaginal insert so that it is properly placed. The shape of the insert is an important feature of the instructions. The IFU specifically states that the insert has a "larger end" and a "smaller end" consistent with the teardrop shape of the insert. The IFU instructs the patient to perform a specific set of steps in a prescribed sequence, based on the shape of the insert and requiring the specific positioning of the patient's fingers with relative to the two different ends of the teardrop-shaped insert and the patient's anatomy. Figure 4 depicts the IFUs in the approved labeling.

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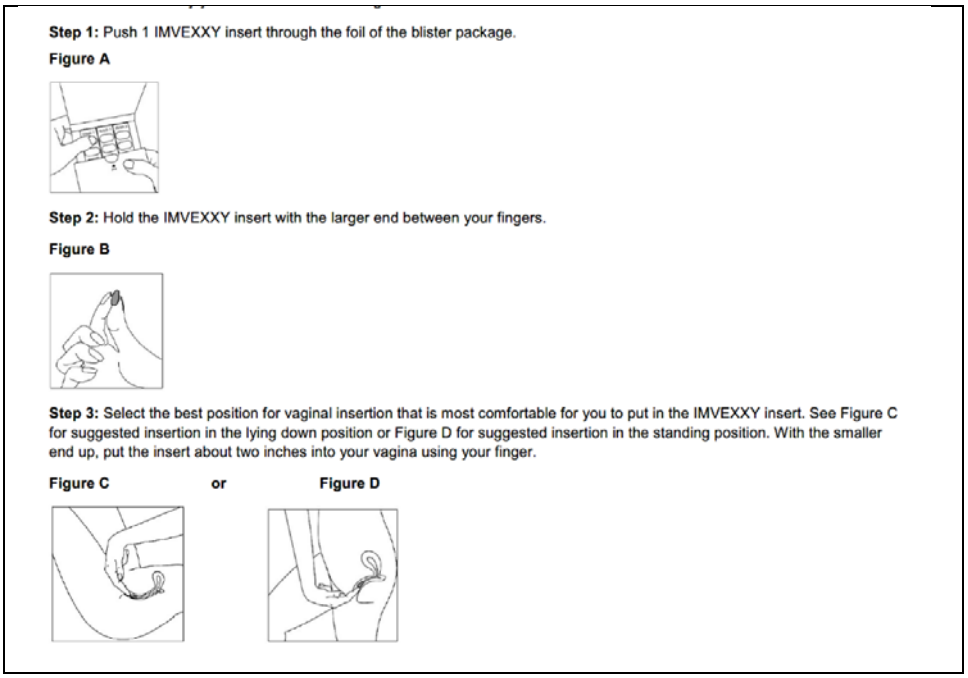
Figure 4. Imvexxy Instructions for Use



The IFU is highly specific about the shape of the insert and its manner of administration. Indeed, the IFU cannot be followed unless the insert is teardrop shaped as referenced in the approval labeling. For an ANDA product to be capable of meeting the regulatory requirement for its labeling to be "the same" as that of the RLD, in addition to other applicable regulatory approval requirements, the ANDA product must be a softgel insert in the teardrop shape of Imvexxy. Otherwise, the ANDA applicant would be requesting impermissible changes to the IFU.

As noted above, Imvexxy is not systemically absorbed. As such, surrogate measures under existing testing methodologies typically used for systemic drugs are inadequate to demonstrate therapeutic equivalence by itself unless the composition of the product is Q1, Q2, and Q3 identical to Imvexxy. Notwithstanding Q1 and Q2 equivalence, a change to the shape of the soft gelatin shell may nonetheless impact the rate and extent of absorption of the ANDA product, and there is no surrogate, such as blood levels of drug, to measure the effect of such a change.

Because Imvexxy is absorbed locally only, if an ANDA were to be filed for an estradiol vaginal insert with a differently shaped insert than Imvexxy, it would therefore require a labeling change to the IFU. Data would be needed to verify that the different shape results in a clinically effective and safe product based on the placement along the vagina relative to vaginal pressure, rupture characteristics, discharge rates, and other characteristics unique to vaginally administered liquid filled products. TherapeuticsMD respectfully submits that such an application would be

inappropriate under the ANDA process, and instead should be approved through the 505(b)(2) process.

A change in shape could affect the patient's ability to insert the drug product two inches as required by the labeled instruction and that incomplete insertion of the drug product can lead to excess leakage. Moreover, a change in the cross-sectional width of the generic drug product could affect the manner and force by which the drug product is released from the insert. This could affect drug distribution and further exacerbate leakage of the drug product from the vagina. For the reasons discussed above, because Imvexxy is locally acting with no measurable impact on systemic pharmacokinetics, it cannot be ascertained through a surrogate test whether a change in shape affected the rate and extent of absorption of estradiol.[83] Absent the ability to make such a showing, an ANDA product must be submitted as a 505(b)(2) application or satisfy the Q1Q2 and Q3 quality attributes including shape and other criteria discussed throughout this petition.

Notably, because Imvexxy is not systemically absorbed, such testing would merely demonstrate that the test product was efficacious like Imvexxy. This testing would not establish whether it is equally safe because it would not establish that the rate and extent of release and absorption of the estradiol are bioequivalent to that of Imvexxy.

Similarly, even for a Q1Q2 product, subtle changes in manufacturing can impact the rate and extent of absorption of the active ingredient.[84] It has been shown in this Petition that changes to a product that prevent insertion of the product to the labeled depth can significantly alter the local environment experienced by the insert.[85] These changes can impact the rupture and thereby release of the fill as well as the tendency of the vagina to retain or leak the liquified fill material. Time to rupture, which implicate formulation as well as manufacturing steps, can impact the rate and extent of bioavailability of the estradiol. Notably, however, without the ability to measure relevant local pharmacokinetics for the estradiol, these changes cannot be evaluated when reviewing whether an ANDA has demonstrated bioequivalence. For these reasons, TherapeuticsMD respectfully submits that an ANDA must be Q1Q2 as well as satisfy the shape requirements and other Q3 criteria mentioned herein that relate to the microstructure of the insert and therefore its

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[83] *See* 21 C.F.R. § 320.23(b)(1) ("Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions….").

[84] *See* Chang, *supra* note 76, at 47 (explaining that "the manufacturing process can have a profound impact upon the formulation microstructure.")

[85] See, e.g., U.S. Food and Drug Administration, Markham C. Luke, *Topical Dermatologic Generic Drug Products: Overcoming Barriers and Improving Patient Access to Topical Dermatologic Drugs, Division of Therapeutic Performance and Office of Research and Standard,* GDUFA Research Workshop (Oct. 20, 2017) (in discussing Q3 criteria noting that "'[l]ook and feel' can affect how the product sticks to the diseased skin.") (Attached hereto as Exhibit 30).

release and bioavailability of the estradiol. Absent the ability to adequately demonstrate the bioequivalence of the test product across all these parameters, the product must be submitted through the 505(b)(2) pathway.

D. Environmental Impact

An environmental assessment report on the action requested in this petition is not required under 21 C.F.R. § 25.31(g).

E. Economic Impact

An economic impact statement will be submitted at the request of the Commissioner.

F. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner that are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: May 29, 2018 (the date on which FDA approved NDA #208564 for Imvexxy (estradiol vaginal inserts)). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: my employer, TherapeuticsMD, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Sincerely,

DocuSigned by:
Kevin McCabe
[illegible]

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Enclosures (Exhibits 1-30)