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October 6, 2005

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BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Re: Submission of Citizen Petition on Behalf of Wyeth

Dear Sir or Madam:

Please accept for filing the attached citizen petition submitted on behalf of Wyeth in four copies pursuant to 21 C.F.R. §§ 10.20, 10.30.

Sincerely,



Sarah E. Botha

cc: Steven K. Galson, Acting Director, Center for Drug Evaluation and Research
David J. Horowitz, Director, Office of Compliance
Jane A. Axelrad, Director, Office of Regulatory Policy
Sheldon T. Bradshaw, Chief Counsel, Office of the Chief Counsel
Steven D. Silverman, Director, Division of New Drugs and Labeling Compliance
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Rockville, MD 20852

Re: Citizen Petition Seeking FDA Actions to Counter Flagrant Violations of the Law by Pharmacies Compounding Bio-Identical Hormone Replacement Therapy Drugs that Endanger Public Health

Dear Sir or Madam:

Pursuant to 21 C.F.R. §§ 10.20, 10.30, the undersigned, on behalf of Wyeth, submit this petition under sections 501, 502, and 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §§ 351, 352, and 355) (“FDCA or “the Act”) to request the Commissioner of Food and Drugs to take the actions specified below to address issues related to the growing, unlawful manufacture and marketing of so-called “bio-identical hormone replacement therapies” (“BHRT”),¹ which are available from numerous compounding pharmacies throughout the United States. It is important to note that this petition is not directed in any way at those pharmacies which satisfy legitimate patient needs by compounding individual products for individual needs that cannot be met by an FDA-approved product.

Wyeth is a leading manufacturer of FDA-approved estrogen-containing hormone therapy (“HT”) drug products and is a leader in women’s health. As such, Wyeth feels compelled to advise FDA of the following activities and the potential

¹ The term “bio-identical hormone replacement therapies” is used throughout this petition to refer to the unapproved hormone therapy products at issue because this is the term used within the compounding industry to describe the products. Although Wyeth has no knowledge of the specific ingredients that are actually being utilized in the preparation of these products, the compounding pharmacies represent that the products differ in composition from FDA-approved hormone therapies, such as Wyeth’s approved, conjugated estrogen hormone therapies.

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risks to which American women may be exposed due to insufficient information BHRT compounding pharmacies provide on the risks that accompany their products. Many of these pharmacies fail to inform consumers even of those risks that FDA requires be included in the labeling of estrogen-containing drug-products.² Specifically, FDA has indicated that in the absence of comparable data, the risks of all estrogens should be assumed to be similar.³ However, even though BHRT products contain estrogen, we are not aware that adequate and well-controlled clinical trials have been conducted that provide substantial evidence of the products' safety and efficacy, as required by the FDCA and FDA's regulations.⁴

During the past few years, the market for BHRT products has grown, spurred by publicity from such notable personalities as Suzanne Somers. By misrepresenting the reports of risks associated with all estrogen-containing hormone therapies and capitalizing on the publicity of "bio-identical" alternatives, compounding pharmacies have created a niche commercial market for BHRT drug products. The compounding pharmacies investigated that distribute these products have veered far away from traditional compounding activities; rather, they manufacture and market these products not as drugs compounded to address particularized patient needs in limited circumstances, but as safer and more effective wholesale substitutes for FDA-approved drug products for any woman wanting hormone therapy. And, they do this with misleading labeling and advertising

² See 21 C.F.R. § 310.515.

³ FDA, *Guidance for Industry, Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Prescribing Information for Health Care Providers and Patient Labeling* (draft) at 2 (Feb. 2004) ("Draft Estrogen Labeling Guidance").

⁴ 21 U.S.C. § 355(b)(1) and (d); 21 C.F.R. § 314.126.

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without the required evidence to substantiate their claims. *See* Metcalf Pharmacy website, <http://www.metcalfpharmacy.com/nhrt.htm> (Ex. A).

In short, these compounding pharmacies are engaging in the manufacture, sale, distribution and promotion of prescription drugs without complying with the requirements set forth in the FDCA and FDA's applicable regulations. Specifically, the pharmacies are manufacturing and marketing the drugs without the required FDA approval in violation of section 505; the products are also misbranded and adulterated under sections 501 and 502 of the Act. 21 U.S.C. §§ 351, 352 and 355. The public interest requires that this activity, which is putting women's health and safety at risk, be stopped.

I. Action Requested

The undersigned, on behalf of Wyeth, respectfully request the Commissioner of Food and Drugs to take the following actions with regard to pharmacies engaged in the compounding of so-called "bio-identical hormone replacement therapy" drugs:

A. Enforcement Actions

Initiate enforcement actions, in the form of seizures, injunctions and/or warning letters, against any BHRT compounding pharmacies whose facilities or whose manufacturing, labeling, advertising or dispensing practices FDA determines are in violation of the FDCA.

B. Labeling and Advertising Disclosures

1. Commence investigations to determine whether entities involved either in dispensing BHRT products or in promoting such products to patients or to health care professionals are providing proper patient

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package inserts for those drugs with each package that is intended to be dispensed to a patient, pursuant to 21 C.F.R. § 310.515, and are including material facts and risk information in all labeling and advertisements provided to patients and to health care professionals or directed to the consumer population at large, including the following:

- (a) That the BHRT product is a new drug and does not have FDA approval;
 - (b) That the BHRT product is/was compounded, or “prepared,” in a pharmacy that is not required to comply with FDA current good manufacturing requirements;
 - (c) That the BHRT product has not been demonstrated to be safe or effective for any use, or safer or more effective than FDA-approved HT products.
2. Require that all labeling and advertisements, whether directed to physicians or to patients and consumers, explain these material facts and all risk information, and require that consumer-directed materials be written in language that will be easily comprehensible to laypersons and that all comparative or superiority claims be appropriately supported by legitimate and sufficient data.
 3. Require, for those BHRT pharmacies that have failed to provide these material facts and/or risk information in labeling and in advertisements, that the pharmacies take the following actions:

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- (a) Where the pharmacy has failed to provide the aforementioned material facts and/or risk information in labeling or advertisements provided to health care professionals, FDA should require the pharmacy to notify each health care professional who submitted a prescription for a BHRT drug during the previous twelve months that the information was not provided; and
- (b) Where the pharmacy has failed to provide the aforementioned material facts and/or risk information in labeling or advertisements provided to patients or other potential consumers, FDA should require the pharmacy to post a correction at the pharmacy counter as well as provide individual notice to each patient to whom BHRT drugs were dispensed during the previous twelve months that the information was not provided.

C. FDA Alert or Talk Paper

Issue an Alert or Talk Paper directed to consumers, health care providers and the compounding industry that:

1. Advises pharmacies of their obligations under the Act and FDA regulations when compounding, dispensing, and promoting so-called “bio-identical hormone replacement therapy” drugs.
2. Notifies consumers, health care providers, and pharmacies that FDA has neither approved compounded BHRT products as safe and effective, nor determined that they are safer or more effective than FDA-approved HT products.

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3. States that there are inherent risks in such products and describe the risks, with particular reference to the Agency's 1977 regulation requiring patient package inserts for non-contraceptive estrogen products and the 2004 Draft Estrogen Labeling Guidance, as well as the boxed warning and other risk information deemed necessary by the Agency following the reports of the Women's Health Initiative ("WHI") study.
4. Forcefully reminds health care professionals and pharmacies that BHRT drugs can be compounded lawfully only to meet the individualized needs of individual patients that cannot be met by FDA-approved hormone therapies and cannot be marketed or advertised without including all material facts and risk information.
5. Confirms that:
 - (a) Any labeling or advertising contrary to these principles is false, misleading and unlawful;
 - (b) Any compounding or distribution of BHRT drugs beyond traditional compounding practices as described in the FDA's Compliance Policy Guide for pharmacy compounding ("CPG") is also unlawful; and
 - (c) Any such unlawful promotion or compounding will subject the BHRT products and pharmacies involved to seizure and injunction.

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II. Statement of Grounds

A. **Background**

1. Estrogen-Containing Hormone Therapies

Estrogen and combination estrogen/progestin prescription drug therapies are widely used for the treatment of post-menopausal symptoms in women. Wyeth is the manufacturer of the FDA-approved HT drugs Prempro® (conjugated estrogens/medroxyprogesterone acetate tablets) and Premphase® (conjugated estrogens/medroxyprogesterone acetate tablets) (containing estrogens with a progestin), and Premarin® (conjugated estrogens tablets, USP) (containing estrogens only).

FDA has mandated patient labeling for all non-contraceptive prescription estrogens since 1977, in an effort to ensure safe and effective use of the drugs. The Agency determined that patients must be advised of the risks of endometrial cancer and other adverse health effects that are associated with the products so that patients can properly assess the advantages and risks of taking them. *See* Requirement for Labeling Directed to the Patient, 42 Fed. Reg. 37636, 37637 (July 22, 1977) (codified at 21 C.F.R. § 310.515) (Ex. B). Prompting the requirement was FDA's express concern that physicians might not otherwise adequately provide their patients with full information on the risks and benefits of these drugs, and that patients might forget or misinterpret any information that was provided. *Id.*

More recently, the National Institute for Health supported a study as part of the Women's Health Initiative ("WHI") that was designed to evaluate the long-term benefits and risks of estrogen or combination HT products in post-menopausal women. The study received a huge amount of publicity in the lay press, leaving many women with questions and concerns. To warn and alert physicians and

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patients to these findings and their implications for women's health, FDA stated that all HT products should add a boxed warning as well as updated relevant information. Wyeth's Prempro®, Premphase® and Premarin® HT products, among others, have updated, FDA-approved labeling incorporating both the boxed warning and the information from the WHI studies. As discussed below, labeling of BHRT products usually does not incorporate either the boxed warning or other important risk information – a failing that sparks serious safety concerns.

2. “Compounded” Bio-Identical Hormone Replacement Therapy Drugs

Pharmacies have traditionally engaged in drug compounding to provide variations of commercially-marketed drugs in order to accommodate the particular medical needs of specific individuals. For example, upon receipt of a valid prescription from a licensed practitioner, a pharmacist might prepare an FDA-approved prescription drug in a different dosage form or without a particular ingredient in response to the needs of an individually identified patient.

In the wake of the WHI findings, women with concerns about HT have become targets for vendors offering unproven alternatives as a false remedy. In that regard, many pharmacies are manufacturing and marketing “bio-identical” hormone therapies, which they are promoting as risk-free alternatives to FDA-approved HT products, under the false guise of “compounding.” The pharmacies use the terms “bio-identical” and “natural” to describe their products because they utilize hormones purporting to have the same molecular structure as those present in humans. In reality, though, these products are plant derived (*see* handouts on bio-identical hormones, provided by Mary M. Morton, FNP-C (Ex. C)) and further processed to resemble human hormones; they are not “natural” to humans.

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Moreover, rather than compounding to meet the specific individualized needs of a particular person, these pharmacies are capitalizing on the confusion raised by the WHI study by falsely trumpeting their own “bio-identical” products to all women as a no-risk alternative to FDA-approved HT products, some even going so far as to provide CME programs that misrepresent the safety profiles of both FDA-approved HT and BHRT. *See* Brochure for Health Max Pharmacy Regional Symposium on Bio-Identical Hormone Replacement Therapy (N.Y., Apr. 30, 2005) (Ex. D). This practice goes far beyond traditional compounding: the pharmacies are selling and marketing their products as wholesale substitutes for the FDA-approved hormones for use by all women.

Thus, “bio-identical” HT products are being dispensed to thousands of patients across the county without adequate data to demonstrate safety or efficacy, not merely to a few patients to meet their individual needs which cannot be met by FDA-approved therapies.⁵ The “compounded” BHRT products contain estrogen ingredients to which specific risks have been attributed by FDA and the WHI study, but patients using these products receive little or no information about the potential risks of these drugs. In addition, some of the products being advertised contain an active ingredient (Estriol) that is not a component of any FDA-approved drug, raising additional public health and safety concerns for any women taking these products. Intensifying this problem is the fact that some compounding pharmacies substitute compounded BHRT products when filling prescriptions for prescribed

⁵ Some of the pharmacies at issue encourage patients to submit a saliva sample for hormone testing, claiming that the BHRT product may then be tailored to the individual needs of the patient. Saliva cannot, however, be used to accurately measure an individual’s hormone levels, as the hormones in saliva fluctuate considerably during the course of a single day. Instead, hormone levels may only be accurately measured by drawing a blood sample. The use of this inaccurate measure in formulating the compounded drug is an added risk related to these pharmacies’ sale of BHRT products.

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FDA-approved HT products, creating potential medical concerns, liability issues for doctors and manufacturers, and a threat to the integrity of FDA's whole system of drug approval. *See* Scarbrough Medical Arts Pharmacy's "Dear Doctor" letter (Ex. E). In a sense, these pharmacies are improperly treating compounded BHRT products as though they were approved, generic equivalents of FDA-approved hormone products – but this is not the case.

The BHRT "compounding" industry is growing rapidly in light of media attention and promotion through talk shows and publications such as Suzanne Somers' books, *The Sexy Years* and *Slim and Sexy Forever*, as well as advertising in the lay press and on numerous websites. *See, e.g.* Women's Health America, <http://www.womenshealth.com> (last visited Oct. 5, 2005). Under FDA's standards, these pharmacies are clearly "manufacturing" rather than engaging in traditional compounding to meet individualized needs. They are taking advantage of the lack of information about these products to offer them in a way that presents potentially serious health risks to a large patient population. FDA's response to this abuse and threat to public health must be visible and far-reaching.

Labeling and advertising materials distributed by the following compounding pharmacies in association with their BHRT drugs provide additional examples of the unlawful conduct in which a great many BHRT compounding pharmacies are engaged:

- Silverbow Rx Compounding Pharmacy, Butte, Montana. (*See* promotional materials in Ex. F).
- PenCol Medisave Pharmacy, Denver, Colorado. (*See* promotional materials in Ex. G).
- The Medicine Shoppe, Bountiful, Utah. (*See* "Dear Doctor" letter in Ex. H).

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- Rancho Park Compounding Pharmacy, Los Angeles, California. (*See* promotional materials in Ex. I).
- Red River Pharmacy Services, Texarkana, Texas. (*See* “Dear Doctor” letters in Ex. J).
- Women’s Health America/Madison Pharmacy Associates, Madison, Wisconsin. (*See* promotional materials in Ex. K).

Pharmacies such as these are acting as manufacturers based on their practices of compounding drugs using bulk active ingredients that are not components of FDA-approved drugs, promoting BHRT products as wholesale substitutes for FDA-approved hormones, making comparative safety and efficacy claims without substantiation meeting FDA requirements, and compounding drug products that are essentially copies of FDA-approved drugs. In addition, these labeling and advertising materials being distributed in association with BHRT drugs violate FDCA requirements and render the products misbranded.

However, these pharmacies are just a sampling; many other pharmacies across the country compounding BHRT products are engaging in similar practices that exceed traditional, legitimate compounding activities and pose substantial risks to public health and safety.

B. FDA’s Legal Authority over Compounded Pharmaceuticals and the Pharmacies Engaged in Compounding

1. FDA Authority to Regulate Compounded Drugs

Retail pharmacies that engage in drug compounding are generally subject to the new drug, adulteration, and misbranding provisions of the FDCA. *See, e.g., In re Wedgewood Vill. Pharmacy, Inc.*, 270 F. Supp. 2d 525, 543-44 (D.N.J. 2003) (holding that the FDCA provisions regarding new drugs, misbranding and

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adulteration are applicable to the relevant pharmacy practices), *aff'd on other grounds*, 421 F.3d 263 (3d Cir. 2005).⁶ FDA has long recognized that compounded drugs typically cannot meet the Act's new drug application ("NDA") pre-market approval requirements because they are made in such small amounts, based on the needs of individual patients, that testing for safety and efficacy would not be feasible. Due to this fact and to the legitimate benefits compounded drugs can provide to individual patients with conditions or individualized variations of conditions that cannot be treated with FDA-approved drugs, FDA has exercised its discretion to refrain from enforcing these requirements with respect to pharmacies engaged in legitimate compounding to meet the individualized needs of these patients.

However, at the same time, FDA has also recognized the public health issues that can arise when pharmacies compound drugs in a manner resembling manufacturing. Therefore, the Agency's enforcement discretion has been contingent on a pharmacy limiting its compounding to only those practices that are recognized as traditional compounding activities. FDA has advised the industry of specific types of activities that it will consider to be illegal drug manufacturing, as

⁶ Retail pharmacies that compound drug products are exempt only from the registration requirements of the FDCA and from certain inspection provisions of the Act, provided they comply with local laws regulating the practice of pharmacy. *See* 21 U.S.C. § 360(g)(1); 21 U.S.C. § 374(a)(2). However, compliance with local laws does not exempt compounding pharmacies from any other provisions of the FDCA. If FDA determines that a pharmacy's practices fall outside of traditional compounding activities, the pharmacy will be subject to all the registration and inspection provisions, as well as the other provisions applicable to prescription drugs. *See* FDA, Compliance Policy Guides Manual, Section 460.200 Pharmacy Compounding at 4 (posted June 7, 2002) (the "2002 CPG" or "current CPG"), http://www.fda.gov/OHRMS/DOCKETS/98fr/02D-0242_gdl0001.pdf (explaining that such pharmacies will be subject to misbranding actions under 21 U.S.C. § 352(o), which renders drugs misbranded if they are manufactured, prepared, propagated, compounded, or processed in an establishment not duly registered under 21 U.S.C. § 360).

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opposed to permissible drug compounding, in a Compliance Policy Guide (“CPG”) for pharmacy compounding.⁷ The current CPG was issued in June 2002, subsequent to the Supreme Court’s decision in *Thompson v. Western States Medical Center*.⁸ The guidance lists factors the Agency considers in determining whether a pharmacy’s compounding activities constitute drug manufacturing, thereby prompting the need for regulatory action.⁹ These include:

- “Compounding finished drugs from bulk active ingredients that are not components of FDA approved drugs without an FDA sanctioned investigational new drug application;”
- “Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available, FDA-approved drug products;”
- “Compounding [] drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions;”

⁷ The original CPG, issued in 1992, was prompted by concern over the manufacture and distribution of “commercial amounts” of unapproved new drug products by pharmacies, which often lacked “adequate recordkeeping” practices to trace and recall harmful products, or lacked “proper labeling or adequate manufacturing controls to assure the drugs’ quality.” See Press Release, FDA, Compliance Policy Guide Addresses Prescription Drug Compounding (Apr. 14, 1992) <http://www.fda.gov/bbs/topics/ANSWERS/ANS00394.html>.

⁸ *Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002).

⁹ In *Western States*, the Supreme Court held that the mere act of advertising or engaging in promotional activities could not establish that a pharmacy was operating as a manufacturer. *Id.* at 376-77. As a result, FDA omitted from the 2002 CPG the act of soliciting compounding of specific drugs or classes of drugs, which had been included in the 1992 CPG as an action indicative of manufacturing activity. However, as discussed *infra* at n. 22, the *Western States* opinion and other First Amendment precedent make clear that FDA can regulate advertising for compounded prescription drugs to prevent false and misleading advertisements.

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- “Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale;” and
- “Using commercial scale manufacturing or testing equipment for compounding drug products.”

2002 CPG at 3-4.

Using these factors, among others, if FDA determines that compounding pharmacies are engaged in the manufacture and distribution of unapproved new drugs in a manner that is “clearly outside the bounds of traditional pharmacy practice,” FDA will treat those pharmacies as manufacturers and require compliance with the new drug, adulteration and misbranding provisions of the Act. *Id.* at 3.

2. FDA’s Recent Enforcement Activities Against Compounding Pharmacies

Since issuing the 2002 CPG, FDA has uncovered numerous instances of compounding pharmacies engaging in unauthorized manufacturing activities. FDA has sent warning letters to compounding pharmacies in the following circumstances:¹⁰

- Pharmacies were using active ingredients in their compounded products that were not components of any FDA-approved drug product (*See, e.g.*, Warning Letter No. 2004-DAL-WL-16 to Peoples Pharmacy, Inc. (June 7, 2004); Warning Letter No. 04-NWJ-14 to Drugs Are Us, Inc. DBA Hopewell Pharmacy (June 7, 2004); Warning Letter No. FLA-04-34 to Axium Healthcare Pharmacy (June 7, 2004); Warning Letter No. DEN-05-08 to Palace Pharmacy (Mar. 23, 2005));
- There was no evidence of particular patients having a medical need for specific variation between a commercially-available drug and the pharmacy’s compounded drug product (*See, e.g.*, Warning Letter No.

¹⁰ FDA warning letters can be found generally at <http://www.fda.gov/foi/warning.htm>.

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CIN-04-4746 to Gentere, Inc. DBA Teregen Labs (July 13, 2004);
Warning Letter No. NWE-18-03W to Carneys Drug (May 27, 2003);
Warning Letter No. 2004-NOL-36 to Delta Pharma, Inc. (Sept. 17,
2004));

- Pharmacies were making products that were essentially copies of commercially-available products (*See, e.g.*, Warning Letter No. CIN-04-4746; Warning Letter No. FLA-04-34; Warning Letter No. NWE-18-03W; Warning Letter No. 2004-NOL-36; Warning Letter No. SJN-05-02 to Respi Care Group (Dec. 20, 2004); Warning Letter No. 2005-NOL-06 to Lincare, Inc., and Reliant Pharmacy Services, Inc. (Dec. 9, 2004));
- Pharmacies were selling compounded products without a prescription or manufacturing them in anticipation of receiving a prescription (*See, e.g.*, Warning Letter No. CIN-04-4746; Warning Letter No. 2004-NOL-36; Warning Letter No. 2004-DT-03 to White Lake Pharmacy (Jan. 16, 2004); Warning Letter No. CBER-04-003 to Custom Compounding Centers (Dec. 23, 2003); Warning Letter No. 3003528540 to Med-Mart Pulmonary Services (Sept. 30, 2002));
- Pharmacies were making and distributing products in large quantities, including drugs for general sale as “office stock” to physicians and clinics (*See, e.g.*, Warning Letter No. CIN-04-4746; Warning Letter No. 3003528540; Warning Letter No. SJN-05-02; Warning Letter No. 2005-NOL-06; Warning Letter No. 2004-NOL-36);
- Pharmacies were manufacturing products in such large quantities that use of commercial scale equipment was required (*See, e.g.*, Warning Letter No. 3003528540);
- Pharmacies were furnishing products to prescribers as samples (*See, e.g.*, Warning Letter No. 3003528540).

In each of these instances, FDA stated that engaging in such practices subjects compounding pharmacies and the products they produce to the new drug, adulteration, and misbranding provisions of the FDCA. FDA has advised these pharmacies that their actions are in violation of the Act unless they (1) submit

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NDA's or ANDA's; (2) ensure that their products bear adequate directions for use and, in some cases, adequate warnings against use by children; and (3) ensure that their products are manufactured in a duly registered establishment and in accordance with current good manufacturing practices regulations.¹¹

To our knowledge, FDA has not yet initiated enforcement action against any BHRT compounding pharmacy. It is past time for the agency to do so.

C. Factual, Legal and Policy Bases for FDA to Initiate Enforcement and Regulatory Action

1. Many Pharmacies Compounding Bio-Identical Hormone Replacement Therapy Drugs Are Engaged in Unlawful Manufacturing Under FDA's CPG

Based on the examples provided with this petition, it is clear that numerous compounding pharmacies are exposing women to potential health risks by engaging in the manufacture of BHRT products in violation of the FDCA. As discussed below, these pharmacies are using unapproved ingredients to compound their products and are promoting their own BHRT formulations as wholesale substitutes for FDA-approved estrogen-containing hormone therapies. These pharmacies undoubtedly engage in additional as yet undetermined practices indicative of manufacturing activities rather than legitimate compounding under FDA's CPG.

By manufacturing prescription drug products without meeting the approval, labeling and manufacturing requirements of the FDCA and FDA regulations, BHRT

¹¹ FDA generally based these warnings letters on inspections of purported compounding pharmacies that the Agency reasonably suspected of engaging in manufacturing activities in violation of the FDCA. FDA's authority to inspect a pharmacy in order to determine whether it is acting as a drug manufacturer has been upheld in court. *See In re Wedgewood Vill. Pharmacy, Inc.*, 270 F. Supp. 2d 525, 551-52 (D.N.J. 2003), *aff'd*, 421 F.3d 263, 273-74 (3d Cir. 2005).

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compounding pharmacies are introducing drug products into the market that have not been tested appropriately for safety and efficacy, lack appropriate labeling information and have been manufactured under conditions that do not meet current good manufacturing practices (“cGMPs”). This problem is exacerbated by the fact that the products contain estrogens, drugs for which FDA requires that particular labeling and warnings be provided directly to patients. Thus, important public health interests and the law combine to strongly impel FDA to initiate regulatory action against BHRT compounding pharmacies that are failing to comply with the new drug, adulteration, and misbranding provisions of the FDCA and to prevent further violations.

- a. Pharmacies Using Unapproved Bulk Active Ingredients Are Engaged in Manufacture of Drug Products and Their Compounded BHRT Products are Unapproved New Drugs

FDA has expressly stated that a pharmacy is not operating as a traditional compounding pharmacy if its products are compounded from bulk active ingredients that are not components of FDA-approved drugs. 2002 CPG at 4. Pharmacies that use unapproved ingredients in compounding drug products are deemed to be acting as manufacturers in violation of the FDCA. As evidenced by the attached materials, BHRT compounding pharmacies are manufacturing, promoting and dispensing products that contain the hormone Estriol, which is not a component of any FDA-approved drug.¹² By using the unapproved ingredient

¹² See, e.g., Silverbow Rx Compounding Pharmacy’s promotional materials Bio-Identical Hormones: Customized Replacement Therapy to Meet the Needs of Each Woman & Man (Ex. F); PenCol Medisave Pharmacy promotional materials Beginning or Conversion to Bio-Identical Hormone Replacement Therapy (BHRT) (Ex. G); The Medicine Shoppe’s Oct. 10, 2001, “Dear Doctor” letter (Ex. H); Rancho Park Compounding Pharmacy’s promotional materials Bio-Identical Hormone Replacement Therapy for Women (Ex. I); Red River Pharmacy Services’ “Dear Doctor” letter (Ex. J); Women’s Health

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Estriol in their “compounded” BHRT products, BHRT compounding pharmacies are engaging in manufacturing new, unapproved drug products rather than in traditional compounding activities.

The use of Estriol in compounded BHRT drugs parallels the activities of pharmacies that recently received FDA warning letters based on their practice of compounding finished drugs from the bulk active ingredient domperidone, which is also not a component of any FDA-approved drug. *See, e.g.*, Warning Letter No. FLA-04-34; Warning Letter No. 04-NWJ-14; Warning Letter No. 2004-DAL-WL-16; Warning Letter No. DEN-05-0. FDA stated that compounded products containing the unapproved substance domperidone are “drugs” under section 201(g). *See, e.g.*, Warning Letter No. FLA-04-34, at 2. FDA further noted that because domperidone is “not generally recognized by qualified experts as safe and effective for [its] labeled use, the products are new drugs, as defined by section 201(p) of the Act.” *Id.* The introduction of these products into interstate commerce without a new drug application violated section 505(a) and the failure of the products to bear adequate directions for use rendered the products misbranded under section 502(f)(1). *Id.*

FDA’s position regarding the use of the unapproved ingredient Estriol in compounded BHRT products can be no different. FDA should therefore initiate enforcement action against compounded BHRT products containing Estriol and the pharmacies manufacturing them on the grounds that the products are adulterated and

(Continued . . .)

America/Madison Pharmacy Associates website,
http://www.womenshealth.com/estrogen_therapy.html (Ex. K).

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misbranded and that their sale without prior FDA approval of an NDA violates the new drug provisions of the Act and poses a serious threat to public health.

b. Promotional Claims Made by BHRT Compounding Pharmacies Demonstrate That They Are Engaged in Manufacturing Activities

The attached materials are examples of common unlawful practices by BHRT compounding pharmacies that promote compounded BHRT products as wholesale substitutes for FDA-approved hormones, urge doctors to rely on BHRT as an alternative method of treatment and make comparative claims regarding the safety and effectiveness of “bio-identical” and synthetic hormones.¹³

By marketing their products as wholesale substitutes for FDA-approved HT products, it is apparent that BHRT compounding pharmacies intend their BHRT drugs to be competitive products in the market rather than traditional compounded drugs, which are substitutes for approved drugs in limited cases based on an individual patient’s particular medical circumstance. For example, one pharmacy

¹³ See PenCol Medisave Pharmacy, *supra* (offering to help patients “make the conversion to bio-identical from synthetic hormones” and promoting the “benefits of BHRT” over synthetic products) (Ex. G); The Medicine Shoppe’s Oct. 10, 2001, “Dear Doctor” letter (advising doctors to consider “switch[ing]” their patients currently on products like Premarin® and Prempro® to BHRT products, due to a purported shortage of animal-derived conjugated estrogen needed to produce the commercial products) (Ex. H); Rancho Park Compounding Pharmacy, *supra* (stating that data from the “large studies on HRT” are not applicable to BHRT products, and comparing the risks of non-bio-identical hormones to the benefits of BHRT products) (Ex. I); Red River Pharmacy Services’ “Dear Doctor” letter (promoting the use of BHRT products “as an alternative to synthetic hormone replacement therapy” in light of the WHI study findings) (Ex. J); Women’s Health America/Madison Pharmacy Associates Website, <http://www.womenshealth.com/hrtregimen.html> (comparing FDA-approved progestin products, termed “synthetic,” with compounded “natural” progesterone products), http://www.womenshealth.com/library/hrt_conf.html (discussing “downside” of synthetic hormones and the “natural alternative” of compounded hormone products) (Ex. K).

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boasts “over 5,000 patients,” whom it claims are “correctly and safely using these products with few side effects, alleviating uncomfortable symptoms, and decreasing the potential long-term risks that come along with synthetic hormone replacement.” PenCol Medisave Pharmacy, *supra* (Ex. G). These and similar claims establish that such compounded BHRT products are new drugs; the compounding pharmacists are therefore manufacturers seeking to market to an uniformed patient population and are subject to the new drug, adulteration and misbranding provisions of the FDCA. *See* 21 U.S.C. § 321(g)(1)(B)-(C); 21 C.F.R § 201.128.

c. The Compounded BHRT Products That Pharmacies Are Producing Are Copies of Commercially-Available Drugs and Therefore Production of Those Products Constitutes Manufacturing

Under FDA’s 2002 CPG, compounding of products that are “essentially copies of commercially available FDA-approved drug products” is an indicator that a pharmacy is engaged in manufacturing activities rather than traditional compounding in violation of the Act. 2002 CPG at 4. The legislative history of the 1997 FDAMA amendments to the FDCA indicates that a compound should be considered a “copy” if, among other things, the product does not “produce a ‘significant difference’ for the particular patient” that uses it. H.R Conf. Rep. No. 105-399, at 94 (1997), *as reprinted in*, 1997 U.S.C.C.A.N. 2880, 2884 (Ex. L). However, while a “significant difference” can result where an ingredient that would have a particular health effect is removed or substituted, it cannot occur in situations “where it is readily apparent, based on the circumstances, the ‘significant difference’ is a mere pretext to allow compounding of products that are essentially copies of commercially available products.” *Id.*

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Pursuant to this policy, FDA has issued warning letters to pharmacies engaged in such practices. *See, e.g.*, Warning Letter No. CIN-04-4746 at 2 (noting pharmacy's products were "copies," because the pharmacy could not "document a medical need for particular patients for these versions of otherwise commercially-available products"); Warning Letter No. NWE-18-03W at 2 (pharmacy was "copying a commercially-available drug" by producing the product in different strengths without being able to document a medical need for particular patients for particular variations); Warning Letter No. SJN-05-02 at 2 (use of a different dosage form did not create a "meaningful distinction," especially absent a documented, "patient-specific, medical need for the compounded product"); Warning Letter No. 2005-NOL-06 at 2 (pharmacy's offering of the products in a different dosage form did not produce a "meaningful distinction" from the commercially-available product).

Here, FDA has already expressly recognized that "natural" hormone therapies have the same risk profile as commercially-available hormone products.¹⁴ Thus, the change from manufactured hormone ingredients to "natural" ingredients via "compounding" does not create a significant difference for a patient using the BHRT products. In addition, many BHRT pharmacies are not compounding variations of FDA-approved hormone products based on the specific medical needs of particular patients. For these reasons, BHRT pharmacies are compounding copies of FDA-approved hormone products, and their practices constitute manufacturing under the 2002 CPG.

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¹⁴ *See* discussion *infra* Parts II.C.2.a.ii-iii.

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In sum, many BHRT pharmacies are engaged in drug manufacturing rather than traditional compounding. As a result, there is no basis for FDA to continue to exercise its enforcement discretion to exempt these pharmacies from all the relevant requirements of the FDCA, including the adulteration and misbranding provisions, and the requirement to obtain approved NDAs prior to marketing these drug products. Rather, because of the serious public health interests implicated by these activities, the Agency should act promptly, forcefully and comprehensively to end these practices.

2. BHRT Compounding Pharmacies Are Violating FDCA Requirements for the Labeling and Promotion of Drugs
 - a. BHRT Pharmacies Are Violating the Labeling Requirements of the FDCA and FDA Regulations

Numerous BHRT compounding pharmacies are distributing brochures, letters to doctors, and other literature that constitute labeling subject to section 502 of the Act.¹⁵ *See, e.g.*, Exs. H (Medicine Shoppe's Oct. 10, 2001 "Dear Doctor" letter) and J (Red River Pharmacy Services' "Dear Doctor" letter). Others are distributing such messages via the Internet. *See, e.g.*, Ex. K (Women's Health America/Madison Pharmacy Associates Website, <http://www.womenshealth.com>). As discussed below, in addition to never having been approved by FDA, much of this labeling fails to meet the minimum statutory and regulatory requirements for drug labeling.¹⁶

¹⁵ Labeling is defined as "all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers or accompanying such article." 21 U.S.C. § 321(m). Labeling includes brochures, booklets, mailing pieces, detailing pieces, bulletins and letters. 21 C.F.R. §202.1(1)(2).

¹⁶ Many of the other materials attached to this petition as examples, including the pamphlets and other literature that describe the products to a consumer-audience, are also labeling to

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i. BHRT Pharmacies' Labeling Materials
Violate FDA's Regulations on their Face and
Render the Products Misbranded

Under the FDCA, a drug is misbranded unless its labeling bears adequate directions for use. 21 U.S.C. § 352(f)(1). As permitted by the FDCA, FDA regulations provide an exemption for prescription drugs from the adequate directions for use requirement, but only if certain conditions are met. 21 C.F.R. § 201.100. One of these conditions is that labeling for the prescription drug must bear the following information:

[a]dequate information for such use, including indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to administer the drug can use the drug safely and for the purpose for which it is intended, including all conditions for which it is advertised or represented.

21 C.F.R. § 201.100(d)(1). This requirement applies to “any labeling . . . whether or not it is on or within a package from which the drug is to be dispensed, distributed by or on behalf of the manufacturer, packer, or distributor of the drug, that furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for the use of the drug.” *Id.* § 201.100(d).

(Continued . . .)

the extent the compounding pharmacies distribute these materials in the pharmacy, with the dispensed products, or directly to physicians and other medical practitioners by detailers. Any promotional materials that are distributed completely separately from the BHRT products constitute “advertising” under the FDCA and FDA regulations. Because it is unclear into which category some of the materials at issue would fall, the petition addresses both the FDCA labeling and advertising violations that are evident in the promotional materials at issue.

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None of the BHRT pharmacies' promotional labeling Wyeth has collected provides the information required by section 201.100(d); it is unlikely that many, if any, BHRT compounding pharmacies provide this information on their BHRT product labeling, depriving users of information about proper use and risks that FDA deems vital. Accordingly, BHRT drug products marketed and sold using labeling that lacks this important information – *i.e.*, virtually all BHRT products – are not exempt from FDA's adequate directions for use requirements, and are therefore misbranded.

ii. BHRT Pharmacies' Labeling Materials are also Misleading Under the Act, Rendering the Products Misbranded

Retail pharmacies that dispense prescription drugs are not exempt from the FDCA prohibition on false and misleading labeling.¹⁷ In determining whether a drug is misbranded as a result of misleading labeling, FDA considers

not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling ... fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling ... relates under the conditions of use prescribed in the labeling ... thereof or under such conditions of use as are customary or usual.

¹⁷ See 21 U.S.C. § 352(a); *Pharm. Mfrs. Ass'n v. FDA*, 484 F. Supp. 1179, 1184-86 (D. Del. 1980), *aff'd per curiam*, 634 F.2d 106, 108 (3d Cir. 1980) (noting that section 503(b)(2) exempts dispensed prescription drugs from the labeling requirements of sections 502(b), relating to quantity of contents, 502(e), relating to common names, and 502(f), relating to "adequate directions for use," but explicitly does not exempt prescriptions drugs from the requirement of section 502(a) that their labels not be misleading).

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21 U.S.C. § 321(n) (emphasis added).

Many of the representations and omissions in the BHRT compounding pharmacy materials are misleading under this standard. For example, as discussed further below, many BHRT compounding pharmacies' promotional materials contain safety and efficacy claims, both explicit and implied, but contain no information on the side effects or contraindications of the BHRT products they promote. *See, e.g.*, PenCol Medisave Pharmacy pamphlet (Ex. G), Silverbow Rx Compounding Pharmacy pamphlet (Ex. F), and Rancho Park Compounding Pharmacy brochure (Ex. I).¹⁸ The omission of such material information renders these materials misleading under 21 U.S.C. § 321(n). As a result, the products being promoted are misbranded.

Moreover, clinical data on "bio-identical hormone replacement therapies" are insufficient to support express and implied claims of either safety, efficacy or superiority that are often contained in promotional materials for BHRT products. Specifically,

- We are unaware of any well-controlled clinical investigations meeting FDA's standards demonstrating efficacy and safety of any BHRT product(s).
- We are unaware of data meeting FDA's standard for superiority claims – *i.e.*, well-controlled, head-to-head clinical studies comparing any BHRT product(s) with FDA-approved HT products – that demonstrate superiority or even comparable efficacy (*see* 21 C.F.R. §§ 202.1(e)(4)(ii)(B), 202.1(e)(6)(i)-(ii)).
- FDA's recent Guidance to the industry regarding labeling requirements for noncontraceptive estrogen drug products confirms that "there is no

¹⁸ *See infra* Part II.C.2.b.ii.

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evidence that the use of ‘natural’ estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.” Draft Estrogen Labeling Guidance at 2.

- In a fact-sheet for consumers on hormone therapy, FDA states that “at this time, we do not know if herbs or other ‘natural’ products are helpful or safe. Studies are being done to learn about the benefits and risks.” FDA, Menopause & Hormones (Fact Sheet) (July 2005), *available at* <http://www.fda.gov/womens/menopause/mht-FS.html> (emphasis added).

Thus, the compounding pharmacies’ claims that their “bio-identical” hormone products are safe and effective – or that they have superior safety profiles to FDA-approved HT products – lack clinical support. Under FDA’s own Guidance and Fact Sheet, such claims are false and misleading. Significantly, at least one pharmacy has even admitted that little clinical testing has been conducted for these products, even though that pharmacy makes express safety and efficacy claims for its products in its promotional pamphlet. *See* Ex. F. Because FDA has determined that there is no evidence that “natural” hormones contain fewer potential risks than other hormone products, and promotional materials distributed by BHRT pharmacies cite no studies establishing that the products being promoted are safe and effective, claims of safety and efficacy for BHRT compounded products – superiority, comparative, or otherwise – lack adequate substantiation. Such unsubstantiated claims mislead users about the safety and efficacy of these products, creating a serious public health concern and violating the Act. *See United States v. Sene X Eleemosynary Corp.*, 479 F. Supp. 970, 980 (S.D. Fla. 1979) (determining that promotional literature distributed regarding a compounded product was misleading “labeling” due to the lack of clinical proof, in the form of adequately controlled clinical studies, that the compounded products were effective for any indicated use). As a result, the BHRT drugs promoted using such claims are misbranded.

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iii. Any Failure by BHRT Pharmacies to Distribute Patient Package Inserts with their Compounded Drug Products Violates the Act and Renders the Products Misbranded

FDA regulations obligate all pharmacies to distribute patient package inserts (“PPI’s”) when dispensing prescription estrogen products. 21 C.F.R.

§ 310.515(b)(1); Requirement for Labeling Directed to the Patient, 42 Fed. Reg. at 37638 (Ex. B) (stating that in the overwhelming majority of cases the pharmacist will dispense the patient labeling along with the drug).¹⁹ This requirement applies to pharmacies that dispense compounded drug products containing estrogens because the regulation covers “drug products containing estrogens” and is not limited to synthetic estrogens, conjugated estrogens or FDA-approved estrogen products. 21 C.F.R. § 301.515(a). As a result, any BHRT pharmacy that is not including the required PPIs with its compounded estrogen products is dispensing misbranded products under section 502(a) of the Act. 21 C.F.R. § 310.515.

In furtherance of these requirements, FDA’s recent Draft Estrogen Labeling Guidance sets forth in detail the information PPIs should include to comply with the regulation. *See* Draft Estrogen Labeling Guidance. Among the information that must be presented in the PPI is a statement of the benefits and proper uses of estrogens, as well as a description of the contraindications, most serious risks and other side effects related to estrogen use. The Draft Guidance explicitly confirms that drugs produced from “natural” estrogens are subject to the same labeling requirements as FDA-approved hormone products. Specifically, the Draft Guidance

¹⁹ Indeed, in upholding the PPI requirement as a valid exercise of FDA’s authority under the FDCA, one court acknowledged that “physicians *as well as pharmacists* are required to provide the labeling when they act as dispensers of the medication.” *Pharm. Mfrs. Ass’n*, 484 F. Supp. at 1181 (emphasis added).

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provides that labeling for health care providers include a statement that no evidence exists indicating that the use of “natural” estrogens “results in a different endometrial risk profile than synthetic estrogens at equivalent doses.” *Id.* at 2, 10. It is highly unlikely that many BHRT compounding pharmacies provide such a statement.

The extent to which BHRT compounding pharmacies are violating these requirements is impossible for Wyeth to ascertain. Frankly, however, the fact that other labeling prepared by these pharmacies fails to comply with FDA regulations suggests strongly that many of these pharmacies are not providing PPIs and that any PPIs that are provided do not meet the requirements set forth in the FDA Draft Guidance.

These are not minor, technical omissions. They go straight to the heart of informing women taking estrogen products. These pharmacies’ failure to provide this legally-required information demonstrates forcefully that they are simply trying to dupe an unsuspecting patient population. In light of the substantial public health concern, FDA must take prompt action to ensure that BHRT compounding pharmacies are complying with their obligation to dispense PPIs with their compounded products.

iv. BHRT Promotional Materials are Misleading Under the Compounding Pharmacy Industry’s Own Guidelines

In addition to misleading patients in violation of FDA regulations, BHRT promotional materials of the kind discussed above also violate the compounding pharmacy industry’s own standards regarding appropriate content for advertising and other promotional materials. In its Legal and Ethical Advertising of Compounded Medications statement, the International Academy of Compounding

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Pharmacists (“IACP”)²⁰ advises that pharmacists “should not make claims as to safety and effectiveness of compounded medications [and should] [a]void statements, including performance claims that would be false or misleading.” The IACP further advises pharmacists to “avoid referring to manufacturer’s products, or trade names in promotional materials,” and notes:

Such references, or claims that a compounded product is similar to a manufactured product, could be viewed as misleading, suggesting that the compounded product is as safe and effective as the commercially available product. Such a drug may be considered “misbranded” under the FD&C Act and subject to FDA enforcement action.

IACP, Legal and Ethical Advertising of Compounded Medications, http://www.iacprx.org/pdf/legal_and_ethical.pdf (Ex. M).

The IACP has also developed a Code of Ethics for compounding pharmacists. The Code provides that pharmacists have a responsibility not to “engage in marketing or promotional practices that: a) utilize manufacturers’ names or the names of patented products; b) create misinformation with claims of therapeutic equivalence; c) create misinformation by perception that compounded products are generic products, and d) base such promotion and advertising solely on price.” IACP, Code of Ethics, <http://www.iacprx.org/pdf/ethics.pdf> (Ex. N).

Despite these industry guidelines, many BHRT compounding pharmacies’ promotional materials not only make reference to the brand names of commercially-available estrogen-containing hormone therapies, such as Premarin®, Provera® and Prempro®, but also compare the safety and efficacy of the BHRT products to that of

²⁰ The IACP describes itself as an international non-profit organization that represents and serves over 1,300 compounding pharmacists. *See* <http://www.iacprx.org>.

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the commercial products. *See, e.g.*, PenCol Medisave Pharmacy, *supra* (Ex. G); Rancho Park Compounding Pharmacy, *supra* (Ex. I); Red River Pharmacy Services' "Dear Doctor" letter (Ex. J). Moreover, as noted above, there is anecdotal evidence that some BHRT compounding pharmacies are substituting BHRT compounded products as equivalents for FDA-approved hormone products that have been prescribed by doctors, thus, in effect, treating them as generics (*supra*, at 9-10).

In short, even the compounding pharmacy industry representatives consider the advertising claims being made by many BHRT compounding pharmacies to be misleading and inconsistent with the industry's ethics, which poses a grave public health concern and renders the products "'misbranded' under the FD&C Act and subject to FDA enforcement action." IACP, Legal and Ethical Advertising of Compounded Medications (Ex. M).

b. BHRT Compounding Pharmacies' Advertising Violates the FDCA by Improperly Omitting the Brief Summary

The brief summary requirement in section 502(n) of the FDCA applies to "all advertisements for any prescription drug" (21 C.F.R. § 202.1(e)(1) (emphasis added)), and the responsibility for inclusion of the brief summary lies with the manufacturer, packer, or distributor of the advertised drug who issued the advertisement or otherwise caused the ad to be issued. 21 U.S.C. § 352(n). No exemption is provided to advertising for compounded prescription drugs,²¹ and

²¹ Section 503(b)(2) of the FDCA does not exempt pharmacies from complying with the brief summary requirement in advertisements that are published prior to the pharmacies' receipt of a prescription and distribution of a compounded drug product. Instead, the FDCA only provides an exemption from certain labeling requirements at the time a prescribed prescription drug is dispensed. *See* 21 U.S.C. 353(b)(2); S. Rep. No. 82-946 (1951), *as reprinted in*, 1951 U.S.C.C.A.N. 2454, 2462-63 (Ex. O); H.R. Rep. No. 82-700, at 16 (1951) (Ex. P); *see also United States v. Articles of Drug*, 625 F.2d 665, 670 (5th Cir.

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public health would be endangered if a brief summary were not required. No basis exists for distinguishing compounded drugs from other drugs in this regard and, thus, failure to comply with the brief summary requirements renders the compounded drug products being advertised misbranded. 21 U.S.C. § 352(n).

i. BHRT Compounding Pharmacies Must Comply With the Brief Summary Requirement

BHRT compounding pharmacies are certainly “distributors” to whom the brief summary requirement applies. Under FDA’s regulations, to “distribute means to sell, offer to sell, deliver, or offer to deliver a drug to a recipient.” 21 C.F.R. § 203.3(h). Because BHRT compounding pharmacies sell, offer to sell, deliver and offer to deliver the compounded drug products that they dispense, they are “distributors,” and their advertisements for compounding BHRT products must contain a “brief summary.”

Moreover, these pharmacies are also “manufacturers” of the compounded BHRT products they dispense for the purposes of the brief summary requirement, even if FDA finds that a particular pharmacy’s activities do not rise to the level of “manufacturing” under the 2002 CPG. This is because the factors considered in determining whether an entity is a “manufacturer” under the drug marketing

(Continued . . .)

1980) (noting that “Prior to being dispensed a prescription drug must meet the misbranding requirements of section 352 After a prescription drug has been lawfully prescribed, it is exempt from most of the requirements of section 352 but must meet the labeling requirements of section 353(b)(2).”). In addition, while FDA regulations provide an exemption from the brief summary requirement for advertisements directed toward compounding pharmacies by manufacturers of prescription drug components, this exemption does not apply to pharmacies’ own consumer- and physician-directed advertisements for finished compounded products. *See* 21 C.F.R. § 202.1(e)(2)(iii). Nothing in *Western States* exempts compounding pharmacies from the brief summary requirement.

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regulations are different from the factors considered under the 2002 CPG on pharmacy compounding. *Compare* 2002 CPG with 21 C.F.R. § 201.1(b). The factors applicable to marketing are mixing, granulating, milling, molding, lyophilizing, tableting, encapsulating, coating, sterilizing, and filling sterile, aerosol, or gaseous drugs into dispensing containers. *See* 21 C.F.R. § 201.1(b). BHRT compounding pharmacies obviously engage in some or all of these activities. In short, BHRT pharmacies are subject to the brief summary requirement with regard to any advertisements for BHRT compounded products.²²

The brief summary regulations require all advertisements and other printed materials promoting drug products to contain a true statement of information related to side effects, contraindications, and effectiveness of the drug. Furthermore, all information relating to the safety and effectiveness of the drug must be fairly balanced with information relating to the side effects and contraindications. 21 C.F.R. § 202.1. As demonstrated directly below, many BHRT pharmacies' promotional materials do not satisfy this requirement, rendering the compounded products misbranded.

ii. The BHRT Pharmacies Have Completely Ignored the FDCA's Brief Summary Requirement

Many advertisements promoting compounded BHRT products fail to contain any information regarding the side effects and contraindications associated with the

²² As the Supreme Court noted in *Western States*, the First Amendment does not prohibit all regulation of commercial speech by FDA. 533 U.S. at 367. Rather, as the Court ruled in *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council*, "[u]ntruthful speech, commercial or otherwise, has never been protected for its own sake." 425 U.S. 748, 771 (1976). Thus, FDA regulation of false or misleading advertising of drug products, like the advertising at issue here, is permissible. *Id.*

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compounded drug products that they promote. This type of omission is a serious violation of section 502(n) that subjects users of these products to unknowing potential health risks that FDA cannot countenance. Compounded drug products advertised in this manner are misbranded and subject to seizure or injunction. *See* 21 U.S.C. §§ 352(n), 332, 334.

The following are examples of BHRT promotional materials that make explicit and implied safety and effectiveness claims, without complying with the brief summary requirement and providing a balance of side effect and contraindication information:

- PenCol Medisave Pharmacy's promotional pamphlet contains a section entitled "Benefits of BHRT," which promises "reduction or complete resolution" of side effects associated with the use of FDA-approved hormones. Ex. G. The section entitled "Bio-Identical Hormone Replacement Therapy (BHRT)" also contains safety and effectiveness claims, including "few side effects, alleviating uncomfortable symptoms, and decreasing the potential long-term risks that come along with synthetic hormone replacement." *Id.* Despite making these express safety and efficacy claims, the pamphlet contains no information on the side effects or contraindications of the advertised BRHT products.
- Silverbow Rx Compounding Pharmacy's promotional pamphlet contains effectiveness claims in the section entitled "Goals of Bio-Identical HRT." Ex. F. The pamphlet claims that the product will "alleviate the symptoms caused by the natural decrease in production of estrogens by the body [and] give the protective benefits which were originally provided by naturally occurring hormones." *Id.* Another section states "Bio-identical hormones have been shown to be clinically effective for the treatment of menopausal symptoms; for the treatment of postmenopausal problems . . . ; [and] in decreasing the risk of Alzheimer's disease and colorectal cancer." *Id.* There are other efficacy claims throughout the pamphlet. In addition, the pamphlet discusses claimed health risks posed by hormone treatments, implying that this pharmacy's compounded products do not pose similar risks and are

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therefore safer. Again, however, the patient and doctor are given no side effect or contraindication information in these advertisements.

- Rancho Park Compounding Pharmacy's promotional brochure contains a long list of risks purported to be associated with non-bio-identical hormones (*e.g.*, blood clots, gallbladder disease, endometrial and breast cancer) and a long list of benefits supposedly provided by BHRT products (*e.g.*, relieves menopausal symptoms, reduces risk of hip fractures, prevents and reverses osteoporosis) like those being compounded and promoted by this pharmacy; the brochure contains no information alerting doctor or patient to any side effects, risks, or contraindications associated with the BHRT products being advertised. Ex. I.

The failure to provide a brief summary in advertising materials is a severe violation that endangers the health and safety of women who purchase BHRT compounded products, unaware of the potential risks, contraindications and safety parameters of the products. FDA cannot allow this practice to continue.

3. Failure of BHRT Pharmacies' Manufacturing Practices to Conform to Current FDCA Requirements for Good Manufacturing Practices Would Render the Products Adulterated

Although Wyeth cannot determine the precise manner in which BHRT compounding pharmacies are producing their BHRT products, it is highly unlikely that they are in conformance with the current good manufacturing practices required by section 501(a)(2)(B) of the FDCA. 21 U.S.C. § 351(a)(2)(B).²³ Because many BHRT pharmacies are engaging in manufacturing, rather than traditional

²³ The FDCA requires that the methods used in the manufacturing, processing, packing and holding of a drug conform to "current good manufacturing practice to assure that [the] drug meets the requirements of [the Act] as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." 21 U.S.C. § 351(a)(2)(B) (emphasis added).

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compounding activities, this failure to conform to section 501(a)(2)(B) would render the products adulterated. *See* 21 U.S.C. § 351(a)(2)(B); 2002 CPG at 4.

In 2001, FDA conducted a limited survey of compounded drug products by collecting samples that could be ordered over the Internet. *See* CDER Report: Limited FDA Survey of Compounded Drug Products, at 1 (last updated Jan. 28, 2003), <http://www.fda.gov/cder/pharmcomp/survey.htm>. FDA collected 37 products made by 12 compounding pharmacies, and conducted tests on 29 of these products, which included compounded hormonal products. *Id.* Of the products tested, 34% (10 out of 29) “failed one or more standard quality tests,” and “nine out of the 10 products with failing analytical results failed . . . potency testing” as well (*i.e.*, they were subpotent). *Id.* at 3. In contrast, “[t]he analytical testing failure rate for commercially-produced drug samples has been less than 2%” since 1996, and FDA remarked that the failure rate for the compounded products tested was “higher than expected.” *Id.* at 5. While this survey was limited, FDA acknowledged that the results “provided valuable, preliminary information on the quality of selected compounded drug products currently marketed.” *Id.*

These results confirm that many compounded BHRT products would likely fail standard quality tests, and perhaps potency testing. This evidence of non-compliance with cGMPs should not be ignored, especially considering the substantial public health interests at stake and the current concerns relating to the WHI study findings which have made this patient population a target of unscrupulous businesses. FDA should take prompt action to end this serious violation of the Act.

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III. Environmental Impact

As provided in 21 C.F.R. § 25.30, the petitioners believe this petition qualifies for a categorical exclusion from the requirement to submit an environmental assessment or environmental impact statement. To the petitioners' knowledge, no extraordinary circumstances exist.

IV. Economic Impact

As provided in 21 C.F.R. § 10.30(b), the petitioners will submit economic impact information upon request of the Commissioner.

V. Certification

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,



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