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April 4, 2006

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VIA 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: Supplemental Filing to Citizen Petition, Docket Number 2005P-0411

Dear Sir or Madam:

Pursuant to 21 C.F.R. § 10.30(g), the undersigned, on behalf of Wyeth, submit this Supplement to Wyeth's above referenced petition (hereinafter "Petition") requesting the Commissioner of Food and Drugs to take certain actions to address public health and other concerns resulting from the growing, unlawful manufacture and marketing of so-called "bio-identical hormone replacement therapies" ("BHRT"). Wyeth is filing this Supplement to address some of the more serious misunderstandings and misstatements contained in comments filed in the petition docket by the International Academy of Compounding Pharmacists ("IACP")¹ and the National Community Pharmacists Association ("NCPA").²

¹ FDA Docket No. 2005P-0411/C9 (Dec. 15, 2005) (the "IACP Comments"); FDA Docket No. 2005P-0411/C3088 (Mar. 6, 2006) (the "IACP Supp. Comments").

² FDA Docket No. 2005P-0411/C515 (Jan. 30, 2006) (the "NCPA Comments"). Wyeth's Supplement focuses on the most egregious inaccuracies in the IACP and NCPA Comments. The fact that Wyeth does not respond to certain arguments contained in the IACP and NCPA filings does not mean that Wyeth agrees with those arguments.

2005P-0411

SUP 1

April 4, 2006

Page 2

A. Responses to Comments

1. Wyeth's Petition Does Not Request FDA to Interfere with Legitimate Compounding

At the outset, IACP's and NCPA's accusations that Wyeth's petition constitutes a "wholesale attack on pharmacy compounding" are false. IACP Comments at 7; *see also* NCPA Comments at 1 (claiming the relief sought by Wyeth's petition "would endanger all patients' access to pharmacist-compounded medications"). Wyeth is not attacking the traditional pharmacy practice of compounding. Rather, Wyeth is addressing a very specific set of pharmacies that are unlawfully manufacturing, selling and promoting unapproved new drugs under the guise of "compounding," thereby posing a substantial risk to women's health and safety.

Wyeth supports strongly women's access to appropriately and lawfully compounded medications, including medications containing FDA-approved hormone ingredients, in medically necessary situations.³ However, Wyeth strongly urges FDA to initiate action against and warn the public about pharmacies that

³ Wyeth does not request that FDA "prohibit pharmacists from compounding customized prescriptions upon receipt of a physician's prescription or order for bio-identical hormone replacement therapies" (NCPA Comments at 1) as long as the pharmacists have not advertised or labeled their products misleadingly, provide full risk information with their products, and do not compound medications using unapproved active drug ingredients. Instead, Wyeth's petition addresses the growing number of BHRT-specializing pharmacies who are marketing their

April 4, 2006

Page 3

- expose patients to drugs containing untested and unapproved hormone ingredients;
- mislead consumers with wholly unproven safety and efficacy claims, and
- jeopardize patients' health and safety by failing to provide risk information, including warnings that are expressly required by FDA regulations.

These pharmacies' practices deviate from traditional compounding and violate IACP's own Code of Ethics and advertising guidelines. *See* Petition at 28-30; Petition Exs. M and N. IACP has stated that it "takes no position with regard to any advertising or promotional materials disseminated by its individual members" and that "[e]ach pharmacist, in his or her own professional judgment ... decides what to say in advertising or promotional materials" (IACP Comments at 10), but it is indisputable that the pharmacies' promotional materials are inconsistent with IACP's advertising guidelines and ethical standards.

Wyeth agrees that legitimate compounding can play a valuable role in ensuring treatment options are available to individuals whose particular conditions or characteristics prevent them from successfully utilizing FDA-approved drug therapies. *See id.* at 2; NCPA Comments at 2. The pharmacies addressed by Wyeth's petition, however, market their drug products as wholesale substitutes for FDA-approved drugs that should be used by all women, not merely those with

"compounded" products as new drugs and whose activities constitute manufacturing and therefore violate FDA's existing law and policy on compounding.

April 4, 2006

Page 4

unique needs. If this practice were allowed to continue based on the pharmacies' empty claim that they are "compounding," then any pharmacy could begin to produce and market its own prescription drugs for any conceivable medical condition so long as it used the term "compounding" to describe its operation.

2. The Pharmacies' Use of the Unapproved Ingredient Estriol Renders their Products "Drugs" and "New Drugs" Under the FDCA

IACP's defense of the pharmacies cited in the petition is based on the assumption that they are legitimately compounding medications. In fact, however, Wyeth's petition demonstrates that the pharmacies in question act as manufacturers and illegally sell and promote unapproved drugs. IACP's position here willfully ignores the facts. NCPA simply fails to address this issue.

As demonstrated in the petition, many of the pharmacies are making and selling products containing the unapproved ingredient Estriol. Estriol is a "drug" under FDCA section 201(g) (21 U.S.C. § 321(g)) because it is listed in the official U.S. Pharmacopeia. THE UNITED STATES PHARMACOPEIA 849 (U.S. Pharmacopeial Convention, 29th Revision 2006) (Ex. A). Furthermore, Estriol is a "new drug" because it is not generally recognized by qualified experts as safe and effective for the uses for which these pharmacies have labeled their drugs. *See* 21 U.S.C. § 321(p); *United States v. Articles of Drug ... Hormonin*, 498 F. Supp. 424, 435 (D.N.J. 1980), *aff'd*, 672 F.2d 904 (3d Cir. 1981), (holding that drugs containing Estriol are "new drugs" because they are not generally recognized by

April 4, 2006

Page 5

qualified experts as safe and effective for the treatment of moderate to severe vasomotor symptoms associated with menopause, atrophic vaginitis, kraurosis vulvae, female castration or primary ovarian failure). Thus, the pharmacies' sale of products containing Estriol is illegal under FDCA section 505(a), which prohibits the sale of unapproved new drugs. 21 U.S.C. § 355(a). The pharmacies' violation of section 505(a) is not a mere technicality; they are exposing their patients to a drug whose risk profile has not been established. This presents a substantial public health concern.

Thus, even without considering whether the pharmacies in question are "compounding" or "manufacturing" under FDA's Compliance Policy Guide ("CPG"),⁴ the sale of products containing Estriol violates the FDCA and threatens women's health. FDA's CPG understandably recognizes that such illegal activity cannot constitute legitimate compounding and therefore states that FDA will consider it evidence of manufacturing. *See* CPG at 3-4. As a result, the pharmacies also fail to qualify for FDA's enforcement discretion under the CPG.

While IACP and NCPA defend the pharmacies at issue, they do not explain how the pharmacies' use of the unapproved ingredient Estriol can constitute

⁴ FDA, Compliance Policy Guides Manual, Section 460.200 Pharmacy Compounding (posted June 7, 2002), http://www.fda.gov/OHRMS/DOCKETS/98fr/02D-0242_gdl0001.pdf.

April 4, 2006

Page 6

legitimate compounding.⁵ Indeed, FDA's recent actions against pharmacies utilizing the unapproved ingredient domperidone in their purported "compounding" activities would render any such defense futile. See Citizen Petition at 18. Wyeth urges FDA to take similar steps to prevent the illegal manufacture and sale of drugs containing Estriol and to alert unwitting consumers. FDA cannot permit pharmacists to promote and sell to women drugs containing this wholly unapproved ingredient as a safe and effective medication.

3. The Pharmacies' Use of Disease Claims in their Promotional Materials Renders their Products "Drugs" and "New Drugs" Under the FDCA

Rather than arguing that the promotional materials attached as exhibits to the petition comply with IACP's Code of Ethics and advertising guidelines, IACP

⁵ IACP does, however, feature on the IACP website an editorial from the CompoundingToday.com weekly newsletter that inaccurately claims that Estriol is an ingredient of an FDA-approved drug. See Loyd V. Allen, Jr., Editorial, *Commercially Manufactured Bioidentical Hormones*, COMPOUNDINGTODAY NEWSLETTER (Int'l J. of Pharm. Compounding, Beaumont, Tex.), Nov. 4, 2005, reprinted in IACP, *Compounding Today.com Editorial on BHRT and Wyeth Petition*, at <http://www.iacprx.org/CTEditorial110405.html> (last visited Feb. 14, 2006) (Ex. B). The editorial bases its claim on the prior marketing of Hormonin -- the illegal Estriol-containing drug product whose sale FDA stopped through a seizure and forfeiture action in 1980. See *Articles of Drug ... Hormonin*, 498 F. Supp. at 427. IACP presumably omits the claim from its comments to FDA because it knows the claim is false. Notably, the editor-in-chief of the CompoundingToday.com newsletter retreated from the claim in the newsletter's very next issue, by making the astonishing assertion that compounding with unapproved ingredients is not a "big deal." See Loyd V. Allen, Jr., Editorial, *Unapproved Drugs, What's the Big Deal?*, COMPOUNDINGTODAY NEWSLETTER (Int'l J. of Pharm. Compounding, Beaumont, Tex.), Nov. 11, 2005 (Ex. C).

April 4, 2006

Page 7

instead claims that it does not expect its members to follow the organization's ethical code and advertising rules. *See* IACP Comments at 10. In truth, IACP cannot defend these materials under its rules because, inconsistent with those rules, the materials: 1) make safety and efficacy claims for the purported "compounded" medications; 2) refer to commercial products by their trade names; and 3) claim that the products advertised are safer and more effective than FDA-approved products. *See* Petition Exs. A, F, G, H, I, J, K, M, and N.

The pharmacies at issue are regularly making explicit and implicit claims that their products cure, mitigate, treat, or prevent a variety of diseases.⁶ These claims establish that the pharmacies intend consumers to purchase and use their products as treatments for the claimed indications, rendering those products drugs under the FDCA.⁷ Furthermore, these products are new drugs because they are not

⁶ *See* Petition at 33-34; Petition Exs. A, F, G, and I.

⁷ *See* 21 U.S.C. § 321(g); 21 C.F.R. § 201.128; *Whitaker v. Thompson*, 353 F.3d 947, 953 (D.C. Cir. 2004) ("claims about a product by its manufacturer and vendors, including product labeling, serve as evidence of the sellers' intent that consumers will purchase and use the product for a particular purpose -- and, therefore, as evidence whether the product is or is not a drug"); *United States v. Lane Labs-USA, Inc.*, 324 F. Supp.2d 547, 567-69 (D.N.J. 2004) (finding claims that dietary supplements are a safe and effective treatment for cancer, skin cancer, and HIV/AIDS constitute disease claims and render the products drugs under 21 U.S.C. § 321(g)); *United States v. Writers & Researchers, Inc.*, 113 F.3d 8, 11 (2d Cir. 1997) (finding a substance is a drug under 21 U.S.C. § 321(g), regardless of its classification as a homeopathic treatment, if it is promoted as a treatment or cure for cancer, AIDS, or other diseases).

April 4, 2006

Page 8

generally recognized by qualified experts as safe and effective for the uses for which these pharmacies have labeled their drugs. *See* 21 U.S.C. § 321(p). As a result, the pharmacies' sale of the BHRT drugs without prior FDA approval violates FDCA section 505. 21 U.S.C. § 355(a).

Compounding pharmacies have repeatedly argued, and the Supreme Court has recognized, that compounded medications cannot be subjected to the FDCA's new drug requirements because pharmacies are unable to establish the safety and efficacy of each drug product they customize based on the needs of an individual patient. *Thompson v. Western States Med. Ctr.*, 535 U.S. 357, 369-70 (2002).

Consistent with this view, Wyeth is not claiming that legitimately compounded medications must be proven safe and effective. But when a pharmacy affirmatively markets its untested products as safe and effective in treating disease, the products must be considered drugs, not compounded medications, and must comply with FDCA requirements.⁸ Moreover, by affirmatively promoting the therapeutic benefits of their products directly to consumers, the pharmacies at issue are

⁸ IACP is incorrect in stating that FTC is the appropriate agency to address the pharmacy marketing claims discussed in the petition. *See* IACP Comments at 10. As manufacturers and marketers of prescription drugs, these entities are regulated by FDA. 21 U.S.C. §§ 352(a), (n).

April 4, 2006

Page 9

operating outside of the traditional physician-patient-pharmacist triad and acting as manufacturers.⁹

4. *Western States Did Not Interfere With FDA's Ability to Regulate Pharmacies Whose Prescription Drug Promotional Claims Constitute Disease Claims or are False and Misleading*

IACP mistakenly asserts that, by urging FDA to take the pharmacies' promotional claims into consideration when evaluating whether they are engaged in manufacturing, Wyeth is "ignoring compounding pharmacies' First Amendment rights to engage in commercial speech." *See* IACP Comments at 6. Wyeth recognizes that pharmacies may advertise that they provide compounding services, and even that they compound BHRT products. The pharmacies cannot, however, lawfully claim that their untested and unapproved BHRT compounded medications are safe and effective, or safer or more effective than approved hormone therapy drug products. Such claims render the advertised products drugs, subject to FDCA requirements they do not meet. *See supra* at Part A.3. These wholly unsubstantiated claims are also false and misleading.

IACP characterizes the Supreme Court's decision in *Thompson v. Western States* as prohibiting FDA from ever regulating promotional speech by pharmacies.

⁹ Furthermore, and contrary to IACP's suggestion (*see* IACP Comments at 3-4), the FDCA does not excuse the distribution of misleading information to patients regarding prescription drugs (including legitimately compounded medications dispensed by pharmacies) simply because a learned intermediary oversees the patient's use of the drug. *See* 21 U.S.C. §§ 352(a), 353(b)(2).

April 4, 2006

Page 10

See IACP Comments at 6-7. This is a fundamental distortion. The Supreme Court's narrow holding in *Western States* was that the mere act of advertising, without more, could not render a pharmacy a "manufacturer" under the FDCA. *Thompson v. Western States Med. Ctr.*, 535 U.S. 357, 366-67 (2002). The Supreme Court did not hold that the substance of advertising claims could not be considered in determining whether a pharmacy is acting as a manufacturer under the FDCA. Thus, FDA is free to evaluate the message conveyed by particular advertising claims to determine whether (a) claims are being made that render the product a drug, or (b) claims are being made that are false and misleading.

Thus, despite IACP's arguments, *Western States* did not give pharmacies carte blanche to make whatever promotional claims they wish without risk of crossing the line into manufacturing. As Wyeth pointed out in the petition, FDA regulation of false or misleading advertising of drug products is constitutionally permissible, as is the use of advertising claims to determine intent to market a drug product. See *Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council*, 425 U.S. 748, 771 (1976); *Whitaker v. Thompson*, 353 F.3d at 953 ("the First Amendment allows 'the evidentiary use of speech to ... prove motive or intent.'") (internal citations omitted). Accordingly, these pharmacies' use of disease claims renders their products drugs under FDCA section 201(g), and their false and

April 4, 2006

Page 11

misleading safety and efficacy claims render their BHRT drug products misbranded under section 502(a). 21 U.S.C. §§ 321(g), 352(a).

5. The Supreme Court's Decision in *Gonzales* Does Not Affect FDA's Authority to Regulate Drug Manufacturing, Labeling, and Advertising

Relying on the Supreme Court's recent decision in *Gonzales v. Oregon*, 126 S. Ct. 904 (2006), IACP suggests in its supplemental comments that FDA lacks any power to regulate compounding pharmacies, even when those pharmacies are not engaged in legitimate compounding. *See* IACP Supp. Comments. In *Gonzales*, the Supreme Court invalidated an Interpretive Rule issued by the Attorney General under the Controlled Substances Act ("CSA") that would have rendered Oregon's physician-assisted suicide law ineffective by declaring the prescribing of controlled substances pursuant to the Oregon law illegitimate under the CSA. The Court concluded that the Attorney General's limited regulatory power under the CSA to combat recreational drug use did not include the power to determine legitimate medical policies and override Oregon's establishment of a policy in favor of physician-assisted suicide.

IACP argues that the *Gonzales* opinion held that federal agencies cannot selectively read statutes to impinge upon authority traditionally exercised by states and that federal regulation should always defer to states on such matters. IACP Supp. Comments at 2. However, IACP has misconstrued the scope of *Gonzales* and

April 4, 2006

Page 12

overstated its relevance here. The limited holding of *Gonzales* provides no solace to those BHRT pharmacies whose activities constitute drug manufacturing rather than legitimate compounding and who are disseminating misleading labeling and advertising.

In *Gonzales*, the Supreme Court acknowledged that determining what constitutes legitimate medical practice is an area historically regulated by doctors and the states. The Attorney General lacked both experience and expertise to make that determination. Moreover, the Attorney General did not have authority under the CSA to determine what constitutes legitimate medical practice. *Gonzales* was premised, in part, upon the Supreme Court's conclusion that "[t]he structure of the CSA ... conveys an unwillingness to cede medical judgments to an Executive official who lacks medical expertise." 126 S. Ct. at 921.

In contrast, FDA has been the expert federal agency responsible for determining what constitutes a "drug" and for regulating drug manufacturing and labeling for almost 70 years. Indeed, in the Federal Food, Drug, and Cosmetic Act ("FDCA"), Congress expressly conferred broad power on FDA to decide what products constitute "drugs" and "new drugs" requiring FDA approval prior to their manufacture and sale -- "a determination of technical and scientific questions by experts." *CIBA Corp. v. Weinberger*, 412 U.S. 640, 644 (1973).

April 4, 2006
Page 13

Thus, while in *Gonzales*, the Supreme Court rejected the Attorney General's attempt to assert power regarding matters over which he was never granted authority, the Supreme Court has long recognized that FDA "is indeed the administrative agency selected by Congress to administer the [Act]" and "FDA has power to determine whether particular drugs require an approved NDA to be sold to the public." *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 624 (1973).¹⁰ The fact that states traditionally regulate pharmacies is therefore a *non sequitur*; determining when drug manufacturing is occurring, when a drug is a "new drug," and when drug labeling or advertising is misleading are not matters traditionally regulated by the states. Rather, Congress has expressly given FDA authority to make those determinations. If pharmacies engage in such activities, FDA has statutory power to regulate them.

6. Wyeth's Petition Does Not Request Inappropriate Relief

IACP argues that FDA should reject Wyeth's petition *in toto* because it requests FDA to refer particular parties to the U.S. Attorney for enforcement actions

¹⁰ See also *Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 653 (1973) ("We think that it is implicit in the regulatory scheme ... that FDA has jurisdiction to decide with administrative finality ... the 'new drug' status of individual drugs or classes of drugs."); *CIBA Corp., supra*, 412 U.S. at 643-44 ("A decision that FDA lacks authority to determine ... the coverage of the Act it administers ... would seriously impair FDA's ability to discharge the responsibilities placed on it by Congress. ... [T]he definition of 'new drug' ... involves a determination of technical and scientific questions by experts. The agency is therefore appropriately the arm of Government to make the threshold determination of the issue of coverage.").

April 4, 2006

Page 14

in court. *See* IACP Comments at 2. This is incorrect. Wyeth's petition properly requests administrative action. *See* 21 C.F.R. §§ 10.3, 10.30. Wyeth's request for FDA enforcement action is a general one -- namely, that FDA should respond to the growing problem of illegal marketing of unapproved BHRT drugs by taking targeted action against individual violators that FDA identifies after investigation. In any event, Wyeth's primary request is for FDA to take proactive measures to prevent future violations of the law. *See* Petition at 3-6.

7. The Adequate Directions for Use Exemption Does Not Apply Where Prescription Drug Labeling Fails to Comply with FDA Regulations

IACP claims the exemption from the "adequate directions for use" requirement in FDCA section 503(b)(2) applies to the labeling distributed by the pharmacies at issue. IACP Comments at 11. The exemption is only available, however, if the prescription drug labeling satisfies the detailed conditions set forth in FDA's regulations -- a fact that IACP ignores. *See* 21 C.F.R. § 201.100.¹¹

¹¹ *See United States v. Articles of Drug*, 625 F.2d 665, 673-75 (5th Cir. 1980) (holding that the Agency's interpretation of the FDCA, that prescription drugs must always satisfy conditions for exemption established in FDA's regulations, was a reasonable implementation of a complex statutory scheme). *See also* FDA, *Guidance for Industry, "Help-Seeking" and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms*, at lines 68-71 (posted Feb. 4, 2004), <http://www.fda.gov/cder/guidance/6019dft.pdf> (explaining, "For a prescription drug or device to comply with the act's requirement of adequate directions for use (21 U.S.C. 352(f)(1)), its labeling must contain, among other information, information addressing product hazards and other risk information, as specified in FDA regulations. (21 CFR 201.100(d)(1) & (3) and 801.109(d).").

April 4, 2006

Page 15

Because the BHRT pharmacies' labeling typically fails to qualify for the exemption, the labeling violates the adequate directions for use requirement, and the BHRT drug products are misbranded.¹²

Moreover, those drug products containing Estriol cannot be exempt from the adequate directions for use requirement because they are new drugs within the meaning of FDCA section 201(p) (21 U.S.C. § 321(p)) and they lack approved applications filed pursuant to section 505 of the Act (21 U.S.C. § 355). 21 C.F.R. § 201.115; *see also* Warning Letter to Cape Drugs from Steven D. Silverman, FDA (July 11, 2005), http://www.fda.gov/foi/warning_letters/g5429d.htm (drugs containing the unapproved ingredient domperidone are not exempt from the requirement that their labeling bear adequate directions for use.). As a result, all products containing Estriol are misbranded under FDCA section 502(f)(1) (21 U.S.C. § 352(f)(1)). Similarly, those BHRT products that are marketed with disease claims, and are unapproved new drugs for that reason, are not exempt from the adequate directions for use requirement and are misbranded. *See, e.g.*, Warning Letter to Healthy Days, Inc. from Joseph R. Baca, FDA (Nov. 9, 2005), <http://www.cfsan.fda.gov/~acrobat/hrtltr7.pdf>.

¹² Although FDA exercises enforcement discretion with respect to the adequate directions for use requirement for those pharmacies that are engaged in legitimate compounding, any pharmacy whose activities constitute manufacturing, such as the BHRT pharmacies at issue, must satisfy FDA's conditions for exemption.

April 4, 2006

Page 16

8. The Brief Summary Requirement is Applicable to Pharmacy Advertisements that Contain Drug Efficacy Claims

IACP also argues that the BHRT pharmacies' advertisements are not subject to the brief summary requirement. *See* IACP Comments at 11. Again, IACP has assumed that the pharmacies in question are acting as legitimate compounders, rather than as manufacturers. Because Wyeth's petition demonstrates that the companies at issue are engaged in "manufacturing" under the CPG, the plain language of the FDCA requires that their advertisements provide a brief summary. *See* 21 U.S.C. § 352(n).

Furthermore, even if the pharmacies were not deemed "manufacturers" under the criteria listed in the CPG, FDA's prescription drug advertising regulation would nonetheless require them to include a brief summary of risk information in any ads in which they make efficacy claims for their prescription drug products. *See* 21 C.F.R. §§ 202.1(e)(1), (2).¹³ FDA's regulation requires that "[a]ll advertisements for any prescription drug" must present the brief summary. *Id.* at § 202.1(e)(1). Regardless of whether FDA has affirmatively applied the brief

¹³ There is no reason for FDA to exercise enforcement discretion for compounded medications with respect to the brief summary requirement in FDCA section 502(n). Neither the FDAMA provision on pharmacy compounding, FDCA section 503(b)(2), nor FDA's CPG provides an exemption to pharmacies from complying with section 502(n). *See* 21 U.S.C. § 353a; Petition at 30, n.21. Indeed, the brief summary requirement in no way interferes with pharmacies' ability to engage in legitimate compounding, so there is no public policy justification for permitting pharmacies to be exempt from the requirement.

April 4, 2006

Page 17

summary requirement to pharmacies (*see* IACP Comments at 11), the pharmacies' activities fall within the plain language of FDA's regulation. Therefore, the pharmacies must provide the brief summary when their ads include statements relating to their compounded drug products' indications.¹⁴ Moreover, because the pharmacies at issue are making numerous efficacy claims in their product ads and are omitting all discussion of risk, FDA's application of the brief summary requirement would be particularly appropriate. Indeed, it is necessary to protect the public health.

9. Significant Confusion Exists Among Consumers Regarding the Nature, Safety and Efficacy, and Regulatory Status of "Compounded" BHRT

On November 10, 2005, FDA issued sixteen warning letters to marketers of dietary supplements and hormone creams who were selling their products with unproven claims that the products were safe and could treat and prevent disease, including claims that the products were "natural" or "safer" than FDA-approved

¹⁴ Although the FDCA refers to advertisements by a drug's manufacturer, packer, or distributor (*see* 21 U.S.C. § 352(n)), FDA's regulation appropriately recognizes that, regardless of who sponsors a prescription drug advertisement, the ad must provide important risk information to consumers. At any rate, under FDA's regulations pharmacies are the "manufacturers" of their compounded medications for purposes of the brief summary requirement. *See* Petition at 31-32; 21 C.F.R. § 201.1(b).

April 4, 2006

Page 18

hormone therapies.¹⁵ FDA's action will protect women from potentially ineffective or even harmful drug products. Although the recent warning letters did not target the same practices and parties that the citizen petition addresses, the warning letters did recognize the significant public health concerns associated with untested "alternative" hormone therapies and the deceptive marketing claims under which they are currently sold.

Wyeth's petition requests, in part, that FDA take enforcement action against violative pharmacies; but more proactive and prospective administrative action will be critical to address adequately the problems created by the illegal sale and marketing of BHRT drugs. The BHRT products, unlike the supplements and creams targeted by the recent FDA action, are sold under prescription, and consumers are therefore more likely to assume that FDA has approved them as safe and effective.¹⁶ Furthermore, the pharmacies market BHRT drugs as wholesale

¹⁵ See Press Release, FDA, FDA Issues Warning Letters to Marketers of Unapproved 'Alternative Hormone Therapies' (Nov. 10, 2005), <http://www.fda.gov/bbs/topics/news/2005/NEW01260.html>.

¹⁶ Informal survey evidence indicates that patients believe FDA has determined BHRT products to be safe and effective. *Women Confused about New Trends in Hormone Therapy Treatments; National Survey Finds Menopausal Women Unaware of Potential Risks with Customized Formulations Treatments*, Business Wire, Apr. 12, 2005 (Ex. D) (In a February 2005 survey, 86% of women reported they were unaware that compounded hormone therapy drugs were not FDA approved; 75% of these respondents said that FDA approval was important to them when considering a hormone therapy treatment option).

April 4, 2006

Page 19

substitutes for approved products and as safer and more effective options. These misleading marketing practices have been so widespread that there is substantial consumer confusion regarding the characteristics of these products and their actual risks and benefits. In this context, IACP's refusal to take a position against the BHRT pharmacies' illegal promotional materials is even more problematic. Many of the individual patient comments submitted to the petition docket (ironically, in support of IACP's position) inadvertently reveal the harmful effect of the pharmacies' misleading labeling and advertising:

- Based on the pharmacies' misleading claims, one patient erroneously believes that BHRT products "are NOT drugs" and that they are "natural occurring" in women's bodies, rather than synthetic chemicals that are formulated in a laboratory. FDA Docket No. 2005P-0411/EC1 (Oct. 27, 2005). She also believes that BHRT products have no potential side effects (stating, "They are NOT dangerous") and that they appropriately "replenish" hormones that her body is no longer producing (*id.*), even though there is not adequate clinical evidence supporting the efficacy of BHRT drug products and FDA has determined that "natural" estrogen therapies should be presumed to have the same risk profile as synthetic estrogens.¹⁷

¹⁷ Contrary to IACP's claim, Wyeth did not suggest that the Women's Health Initiative ("WHI") studied compounded bioidentical hormone therapies. See IACP Comments at 8. The WHI studies used Premarin[®] and Prempro[®] to measure the potential effects of hormone therapy. In the absence of any comparable clinical evidence studying particular "bioidentical" hormone therapies, however, FDA has adopted the findings of the WHI studies for all estrogen products. See Petition at 25-26.

April 4, 2006

Page 20

- Another patient states that by taking BHRT, “I feel I am protecting myself from Cancer [sic].” FDA Docket No. 2005P-0411/EC8 (Dec. 19, 2005).
- One patient believes that compounded progesterone cream “will reverse osteopenia” and “rebuilds new bone,” in comparison with an FDA-approved treatment, which “rebuilds old bone.” FDA Docket No. 2005P-0411/EC26 (Dec. 21, 2005). These indications have not been demonstrated by reliable clinical evidence or approved by FDA.
- Yet another writes that “natural [sic] formulated hormones do not” increase the risk of cancer. FDA Docket No. 2005P-0411/C29 (Dec. 27, 2005). And another explains, “I feel that this is a natural product – no side effects that would concern me.” FDA Docket No. 2005P-0411/C38 (Dec. 20, 2005).

All of these patients need and deserve accurate information about the BHRT drugs they are taking. An FDA Talk Paper is the proper vehicle to educate the public affirmatively, and is therefore essential.

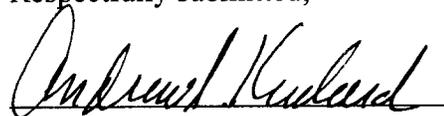
April 4, 2006

Page 21

B. 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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