

**PHARMACY COMPOUNDING OF BIOIDENTICAL HORMONE
REPLACEMENT THERAPY (BHRT): A PROPOSED NEW APPROACH
TO JUSTIFY FDA REGULATION OF THESE PRESCRIPTION DRUGS**

Bruce Patsner, M.D., J.D.
Research Professor
Health Law & Policy Institute
University of Houston Law Center
Houston, Texas 77204-6060
bpatsner@central.uh.edu
713-743-2105

Table of Contents

- I Introduction
- II FDA's History re: Pharmacy Compounding of Prescription Drugs
 - a. Past to Present
 - b. Some Problems with FDA's Current Approach to Compounding: FDA claims jurisdiction over compounding, but no one else is buying it
- III The American Pharmacy Association (APhA) On "What is Compounding?"
- IV The Rise of the Bio-identical Hormone Replacement Therapy (BHRT) Industry
 - a. Linguistic considerations: "bioidentical" and "natural"
 - b. Compounding practice has changed because of WHI and the Internet
 - c. Not all compounding pharmacies are equal.
- V The Wyeth Citizen Petition
 - a. Background and Actions Demanded
 - b. Wyeth's Arguments
 - c. A Better Argument Not Made re: Compounding versus Manufacturing
- VI FDA's Enforcement Actions Against the 7 Compounders – Why?
 - a. The Efficacy and Safety Claims made for BHRT
 - b. The Use of Unapproved Estriol
- VII Defending FDA's Actions: A New Basis for New Arguments That Some BHRT Compounding Activity is Not Compounding
 - a. The "pseudo-individualization" of dosing and "Junk Medicine"
 - b. Advertising and Promotion Practices by Select Internet-Based Compounding Pharmacies: The Solicited Wholesale Replacement of An Entire Class of Safe and Effectives Commercially Manufactured Prescription Drug Products" with Compounded Drugs and the Direct to Consumer Advertising Negate the Triad
- VIII A New Paradigm for FDA Regulation of Pharmacy Compounding of BHRT: It Isn't Compounding Anymore
- IX Conclusion: Where The Controversy Will Likely Go

I Introduction

On January 9, 2008 FDA announced that it was undertaking enforcement actions against seven pharmacies involved in the business of producing and promoting prescription drug products collectively referred to as “bioidentical” hormone replacement therapies (“BHRT”)¹ through a process known as compounding. Millions of women in the United States take these pharmacy-made prescription drugs, none of which have ever undergone the formal clinical trials all commercially manufactured prescription drugs must do to prove that they are either safe or actually do what they claim to be doing. Even the United States Senate has figured out that a potential public health disaster may be under way.²

Use of these pharmacy custom-made or “compounded” drug products, comprised of a mixture of hormones, surged following the publication in 2002 of the NIH-sponsored Women’s Health Initiative studies on the efficacy and safety of some commercially manufactured prescription drugs commonly used to treat menopausal women.³ BHRT compounded drugs have been on FDA’s radar screen since Wyeth Pharmaceuticals filed a Citizens Petition with FDA in October 2005 demanding that FDA undertake enforcement actions against several primarily Internet-based compounding pharmacies.⁴ Wyeth alleged that these compounding pharmacies were essentially manufacturing new

¹ FDA Webview, statement on Compounding, *available at* <http://www.fda.gov/oc/ohrt/> (last accessed January 10, 2008).

² The Endocrine Society, *Senate Investigates Bioidentical Hormones. The Endocrine Society As Expert Witness*, Endocrine News, June 2007. U.S. Senate Special Committee on Aging, April 19, 2007.

³ Tara Parker-Pope, *Popular Menopause Hormones Made From Plants Come Under Scrutiny*, WALL STREET JOURNAL, October 25, 2001, at D1.

⁴ Wyeth, Citizen Petition to FDA < Docket 2005-0411, 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. Submitted October 5, 2005, *available at* <http://www.fda.gov/ohrms/dockets/dockets/05p0411/05p-0411-cp00001-01-vol1.pdf> (last accessed September 19, 2006).

drugs under the guise of compounding.⁵ FDA's current "crack down" on Internet sales of "custom mixed" hormone therapies for menopausal women received extensive media coverage.⁶

FDA received almost 70,000 comments on Wyeth's Citizen Petition, and its current attempt to regulate some part of the well-funded and well-organized pharmacy compounding industry marks the latest salvo in the already heavily litigated battle over compounding of prescription drugs.⁷ FDA's January 2008 enforcement actions involved the issuing of warning letters to the offending compounding pharmacies. There is always the potential for more severe enforcement actions such as seizures of drugs or injunctions against production.⁸

On the one hand, all of FDA's enforcement actions, current and contemplated, are completely justified and long overdue. As will be shown, the fact is that some of the claims being advertised and promoted for BHRT products are either grossly misleading or simply false, pharmacy BHRT drugs undergo no testing for safety and efficacy as commercially manufactured prescription hormone therapy drugs do, the "science" behind the hormone blends in these prescription drugs is suspect, Internet promotion of BHRT to a national media audience as a potential wholesale replacement of safe and effective commercial prescription drugs is not traditional compounding in any meaningful sense,

⁵ *Id.*

⁶ Associated Press, *FDA cracks down on "bio-identical" hormones*, available at <http://www.msnbc.com/id/22575578> (last accessed January 10, 2008).

⁷ Bio-Identical Hormones: Sound Science or Bad Medicine, Hearing Before the Senate Special Committee on Aging 110th Congress (2007) (prepared statement of Steven K. Galson, M.D., Director of the Center for Drug Evaluation and Research at FDA), available at <http://www.fda.gov/ola/2007/hormone041907.html> (last accessed December 6, 2007). During this presentation Dr. Galson reiterated FDA's view that compounded drugs are "new drugs" within the meaning of the Federal Food, Drug and Cosmetic (FD&C) Act despite recent judicial rulings directly negating this precise contention. (Hereinafter abbreviated as Galson).

⁸ Food and Drug Law textbook 3rd edition

and the widespread use of unproven prescription medications falsely believed to yield health benefits is a looming potential public health disaster of major proportions.⁹

On the other hand, how is FDA going to defend its actions in the context of repetitive judicial determinations against FDA on its claimed jurisdiction over that compounded drugs, particularly its argument that they are “new drugs”?¹⁰ The Pharmacy industry will simply claim that regardless of the absolute veracity of safety and efficacy claims for prescription BHRT, FDA cannot intervene because the activity is compounding and thus subject to regulation only by individual state boards of pharmacy.¹¹

The present article suggests a different regulatory and litigation strategy for FDA when the inevitable legal challenges to its recent enforcement actions toward select compounding pharmacies occur. The thesis of this paper is FDA can best defend its enforcement actions against these compounding pharmacies by demonstrating that what pharmacists are doing is not compounding. Current regulatory approaches based on the contention that compounded drugs are “new drugs” as defined by the 1938 federal Food, Drug, and Cosmetic Act (hereinafter abbreviated as FDCA or the Act) or on attempts to label the compounding pharmacies as “manufacturers” based on crossing an indeterminate threshold volume of sales should be abandoned, at least as far as the issue of FDA regulation of pharmacy compounded BHRT is concerned.¹²

⁹ Each of these tenets will be discussed in separate sections.

¹⁰ *Medical Center Pharmacy v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex 2006).

¹¹ The issue of whether FDA has any jurisdiction over compounding at all, outside of a very narrowly defined area such as prescription drugs for which pharmacy compounding poses a unique set of technical problems, is the meta-issue behind the current dispute over pharmacy compounding of bioidentical hormone therapy prescription drugs. FDA continues to claims potential jurisdiction over all of pharmacy compounding, choosing only to exercise occasional enforcement discretion. The Pharmacy profession maintains that regulation of compounding belongs to the states. This non-meeting of the ways is evident in reading Dr. Galson’s comments to the Senate Committee, see ref. 5, *supra*.

¹² Galson, *supra* note 7.

The linguistic and scientific confusion surrounding the label “bio-identical”, a term which has been used to buttress this newer non-traditional pharmacy compounding industry will be discussed and three new concepts introduced: (1) “non-traditional” pharmacy compounding, better referred to as “not-compounding”; (2) “pseudo-individualization” of pharmacy-compounded prescription drug therapy; and (3) “junk medicine.” These terms are necessary additions to the food and drug law vocabulary on pharmacy compounding so that FDA and the courts may fully engage the new changes in the business model of compounding pharmacy practice which distinguish some Internet-based compounding pharmacies from those more traditional compounding pharmacies which FDA has no interest in regulating.

Prescription drug practice may now be viewed as a line with traditional pharmacy compounding on one end and commercial drug manufacturing on the other. Between these two must be added an Internet-focused type of pharmacy practice compounding BHRT using “junk” medicine as a sham to meet the “individualization” requirement at the core of the triad relationship underlying traditional pharmacy compounding. These pharmacies may use worthless laboratory testing of salivary hormone levels as a ruse to “individualize” the therapy. These compounded prescription drug products are promoted to an anonymous media audience as wholesale replacements for commercial prescription drug products which are known to be safe and effective for select medical conditions of menopause. Neither this manner of pharmacy practice, nor the misleading or false global promotion which accompanies it, should qualify this type of pharmacy practice as compounding. And, if the prescription drug practice is not compounding, it may be regulated by FDA regardless of what it is called.

Unlike previous FDA attempts to regulate compounding pharmacies which failed when challenged under the *Central Hudson* test for regulation of commercial speech,¹³ the proposed new attempt to reign in the advertising and promotional claims by these Internet compounding pharmacies should succeed. Some compounding pharmacies are making safety and efficacy claims, particularly superiority claims, which are so misleading or false that they should no longer be protected by the First Amendment.

There are eight parts following the Introduction. Part II briefly reviews the FDA's history with respect to attempts to regulate pharmacy compounding and highlights some current problems with FDA's current jurisdictional claim of selective enforcement. Part III reviews the American Pharmacy Association's (APhA) position statements and operational definitions of both "compounding" and "manufacturing" Part IV discusses the rise of the bioidentical hormone replacement therapy (BHRT) pharmacy prescription drug industry, the use of marketing terms as meaningless medical terms, and the changes in pharmacy compounding as a result of the convergence of the Internet and the results of the Women's Health Initiative studies on commercial hormone therapy prescription drugs. Part V discusses the substance of Wyeth's October 2005 Citizen Petition to FDA. Part VI discusses FDA's January 2008 enforcement actions against select compounding pharmacies and reviews the Agency's contentions first regarding false advertising and promotion and second regarding the drug estriol. Part VII presents a new regulatory argument to buttress FDA's new attempts to regulate pharmacy compounding of BHRT, and introduces the concepts of "non-traditional" pharmacy compounding, "pseudo-individualization" of prescription drug therapy, and "junk medicine." Part VIII summarizes the author's arguments justifying FDA's current attempt at regulation of

¹³ *Western States Medical Center v. Shalala*, 238 F. 3d 1090 (9th Circuit 2001).

select compounding pharmacies producing and promoting BHRT. Part IX concludes by examining some implications of both the author's arguments and the recent enforcement actions which FDA has already taken.

II FDA's Evolving Position on Pharmacy Compounding of Prescription Drugs

a. Past to Present

Pharmacy compounding is the preparation of an "individualized" prescription drug product by a pharmacy in response to or in anticipation of receipt of a valid medical prescription for a particular patient.¹⁴ Pharmacy compounding is recognized as an integral part of the routine practice of pharmacy.¹⁵ As a rule, FDA does not directly regulate the practice of pharmacy any more than it directly regulates the practice of medicine, which is to say not at all.¹⁶ The oversight of both of these professions is the purview of the individual states, and their respective individual state boards of medicine and/or pharmacy.¹⁷

Despite an apparent syllogism (compounding is the practice of pharmacy, FDA does not regulate the practice of pharmacy, ergo FDA does not regulate compounding of prescription drugs by pharmacies), the reality is that FDA's relationship to prescription drug pharmacy compounding is considerably more complicated and has undergone considerable change over the past fifty years.¹⁸ Much of the controversy has centered

¹⁴ *Thompson v. Western States Med. Ctr. et al.*, 535 U.S. 357, 360-61 (2002). "Drug compounding is a process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to the needs of an individual patient."

¹⁵ *Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right to Mix to Protect Patients: Hearing on Oversight Before the Senate Committee on Health, Education, Labor, & Pensions*, 108th Congress (2003) (statement of Daniel A. Herbert, RPh, President Elect, American Pharmaceutical Association) [hereinafter Herbert testimony].

¹⁶ *Id.*

¹⁷ *Id.*

¹⁸ RICHARD ABOOD, *PHARMACY PRACTICE AND THE LAW* 112- 122 (4th ed. 2005)

around two issues: (1) whether certain pharmacy activities are compounding (also referred to as “traditional compounding”, a term of usage not precisely defined) as opposed to manufacturing;¹⁹ and (2) whether pharmacy compounded prescription drugs are “new drugs” as the term is defined in the FDCA.

The 1938 Federal Food Drug and Cosmetic Act²⁰ was passed at a time when the majority of patients’ prescriptions for drugs were in fact compounded by pharmacists.²¹ It is only with the development of the present-day pharmaceutical industry following World War II that the percentage of prescription drugs compounded by pharmacies fell to less than that of commercially manufactured drug products.²² For the past decade the percent of prescription drugs compounded by pharmacies has been in the range 6% or less.²³ For sub-areas of pharmacy compounding such as compounding of bioidentical hormone replacement therapy drug products, the percentage of prescriptions may be considerably higher.²⁴

There is little in the legislative history of the Act²⁵ to suggest that Congress had specifically contemplated pharmacy compounding when the new drug approval (“NDA”) requirements of the Act were formulated.²⁶ Similarly, the 1964 Kefauver-

¹⁹ *Id.*

²⁰ Federal Food, Drug and Cosmetic Act, 21 U.S.C. (1938) [hereafter referred to as “the Act”].

²¹ James A. Sundberg, *Extemporaneous Compounding in the Hospital Pharmacy*, 1 INTERNATIONAL JOURNAL OF PHARMACEUTICAL COMPOUNDING 314 (1997).

²² David W. Newton, *Compounding Paradox: Taught Less and Practiced More*, 7 INTERNATIONAL JOURNAL OF PHARMACEUTICAL COMPOUNDING 399 (2003).

²³ *Id.*

²⁴ BRUCE PATSNER, MD, JD, REGULATORY ISSUES OF COMPOUNDING DRUGS, PROCEEDINGS FROM THE POSTGRADUATE COURSE PRESENTED PRIOR TO THE 17TH ANNUAL MEETING OF THE NORTH AMERICAN MENOPAUSE SOCIETY (October 11, 2006)[Hereinafter Patsner].

²⁵ Peter Barton Hutt, *Drug Regulation in the United States*, 2 INT’L J. OF TECH. ASSESSMENT IN HEALTH Care 619 (1986).

²⁶ The exact reason for this is not known. It may have been because the pharmaceutical industry was undergoing a more rapid expansion than the pharmacy industry, or because the pharmacy industry was just beginning to experience some economies of scale. Alternatively, the motivation may have been the belief

Harris Amendments to the Act which expanded NDA requirements to include efficacy as well as safety, were primarily directed at commercial drug manufacturers rather than the local corner pharmacy which made compounded prescription drugs.²⁷ Literally for decades, FDA played a minor role and had a demonstrably minor interest in pharmacy compounding of prescription drugs.

Despite this clear precedent, in the early 1990's FDA changed its position on pharmacy compounding of prescription drugs largely in response to a marked increase in the volume of pharmacy compounding activity.²⁸ The new regulatory approach now held that the NDA requirements of the Act now applied to all compounded prescription drugs and that FDA had jurisdiction over the marketing and promotion of all such drugs.²⁹

This new position immediately created some problems. On the one hand, FDA tacitly acknowledged this would effectively eliminate compounding of prescription drugs since no single pharmacy (or even chain of pharmacies) had the capability to conduct the randomized, controlled clinical trials to demonstrate safety and efficacy of the drugs which the NDA requirements of the Act mandated.³⁰ All compounded drugs would thus be illegal because they failed to meet new drug safety and efficacy requirements.

On the other hand, FDA was also forced to acknowledge that pharmacy compounding of prescription drugs filled an essential niche for some patients who for whatever reason could not have their medical needs met by a prescription drug manufactured by a commercial pharmaceutical company,³¹ the most obvious example

that this policy would improve public health and be beneficial to the public. Or, Congress' intent may have truly been to not focus on pharmacy compounding at all.

²⁷ Kefauver-Harris amendment

²⁸ Galson, *supra*, note 7 at 3.

²⁹ *Id.*

³⁰ *Id.*

being the need for a liquid preparation of a prescription drug for a child incapable of swallowing pills when no commercial drug company manufactured a liquid formulation of the drug. To preserve this compounding option for some patients, FDA would have to selectively decide when to exercise its claimed global jurisdiction over a compounded prescription drug or class of drugs.³² FDA realized that any pharmacy could, given either a sufficient volume of prescriptions or appropriate motivation, essentially duplicate and sell already available commercially manufactured prescription drug products without meeting safety and efficacy requirements of the Act, in effect making an “end-run” around the Act.³³ The suspicion that this was in fact happening, that certain size compounding pharmacies were acting like drug manufacturers,³⁴ was likely the impetus behind FDA’s decision to change its position on pharmacy compounding. Ironically, the proposed change in FDA’s role in regulating compounding pharmacies came at a time when the business model for compounding pharmacies had not taken on the trajectory some current pharmacies have because the Internet was not widely used in the public domain for marketing purposes.

The result of this tension between the proposed extension of FDA’s authority and the reality of the necessity of compounded drugs for some patients was FDA’s 1992 Compliance Policy Guide on Compounding.³⁵ This document described FDA’s real

³¹ *Pharmacy Compounding: Customizing Prescription Drugs*, FDA Consumer Magazine, July-August 2000, available at http://www.fda.gov/fdac/features/2000/400_compound.html (last accessed June 15, 2005).

³² This would come back to haunt FDA in *Western States Med. Ctr. v. Thompson* 535 U.S. 357, 369 (2002) (“[T]he Government acknowledges that requiring FDA approval of all drug products compounded by pharmacies would, as a practical matter, eliminate the practice of compounding.”).

³³ Galson, *supra* note 7.

³⁴ *Id.*

³⁵ Food and Drug Administration Compliance Policy Guide 7132.16, Subject: Manufacture, distribution and promotion of adulterated, misbranded, or unapproved new drugs for human use by state-licensed pharmacies. FDA Office of Enforcement, Division of Compliance Policy, March 16, 1992, available at http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460-200.html [hereinafter “1992 Compliance Policy Guide”].

world regulatory approach as one of selective “enforcement discretion”, rather than legal exemption from the Act, as the means of intervening in the practice of pharmacy compounding of prescription drugs. This selective approach was espoused at the same time that FDA was still continuing to assert regulatory control over all of pharmacy compounding of prescription drugs based on its argument that compounded prescription drugs were new drugs and could be regulated as such.

The pharmacy profession immediately rejected this 1992 contention that FDA had any jurisdiction over pharmacy compounding of prescription drugs.³⁶ The pharmacy profession maintained the position that it is up to the Medical/Pharmacy Boards of the individual states to regulate this practice, with potentially fifty different regulatory schema over the marketing and promotion of prescription drugs affecting millions of people and exemption of compounding pharmacies from the new drug approval, adulteration, and misbranding requirements of the Act. The next half-decade witnessed a significant amount of disagreement, and threats of litigation, between FDA and compounding pharmacy professionals. A significant step towards resolution of these issues would come in 1997.

The 1997 Food and Drug Administration Modernization Act (“FDAMA”)³⁷ attempted to clarify the issue of FDA regulation of compounding under federal law. FDAMA directly reversed FDA’s strongly-held position on direct jurisdiction over pharmacy drug compounding by adding Section 503(A) to the 1938 Food, Drug and Cosmetic Act.³⁸ This amendment to the Act formally acknowledged that pharmacy

³⁶ *Federal and State Role in Pharmacy Compounding and Reconstitution: Re: October 23, 2003 Hearing Exploring the Right to Mix to Protect Patients* (statement of John A. Gans, PharmD, Executive Vice President, American Pharmaceutical Association).

³⁷ FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT OF 1997, 21 U.S.C. 301 (1997 (hereinafter abbreviated as FDAMA)).

compounded prescription drugs were not “new drugs,” as defined by the Act,³⁹ and exempted compounded drugs which satisfied certain requirements from having to satisfy three key provisions of the Act: (1) the adulteration provision of section 501(a)(2); (2) the misbranding provision of 501(f)(1), and the new drug approval provisions of section 505.⁴⁰

Unfortunately, FDAMA also include a follow-on section which attempted to regulate the advertising and promotion of the very same compounded prescription drug products that FDA had formally abdicated jurisdiction over earlier in the same section.⁴¹ This subsection of 503A included prohibitions against both the solicitation of prescriptions for pharmacy compounded drugs from physicians by the compounding pharmacies as well as direct to consumer advertising of specific compounded drugs.⁴² Advertising for providing the general service of pharmacy compounding per se was permitted.⁴³ This restriction on advertising and promotion of particular compounded prescription drugs resulted in a lawsuit against FDA by a group of pharmacies who claimed that the advertising and promotion restrictions of 503(A) were an unconstitutional restriction of commercial speech under the First Amendment.⁴⁴ Suit against FDA was brought in Federal District Court in Nevada less than a month after FDAMA became law.⁴⁵

The District Court ruled against FDA,⁴⁶ holding that the advertising and

³⁸ FEDERAL FOOD, DRUG AND COSMETIC ACT, 21 U.S.C. § 301, et. seq. (2004) [hereinafter FDCA or the Act]

³⁹ FDAMA, *supra* note 37.

⁴⁰ *Id.*

⁴¹ *Id.*

⁴² *Id.*

⁴³ *Id.*

⁴⁴ *Western States Medical Center v. Shalala*, 69 F. Supp.2d 1288 (D.Nev. 1999).

⁴⁵ *Id.*

⁴⁶ *Id.*

promotion restriction of 503(A) were an unconstitutional restriction of First Amendment commercial speech rights under the *Central Hudson* test.⁴⁷ FDA appealed the ruling to the 9th Circuit Court of Appeals⁴⁸ which both upheld the lower court ruling and further held that the advertising and promotion provisions of section 503(A) could not be “split off” from the rest of section 503(A),⁴⁹ thus the entirety of the section was invalid on First Amendment grounds. In *Thompson v. Western States Medical Center*, the Supreme Court⁵⁰ affirmed the 9th Circuit’s decision that the advertising and soliciting restrictions were unconstitutional, and elected not to comment on the severability issue, effectively letting the 9th Circuit’s determination of this statutory interpretation issue stand.

At present, FDA agrees with the 9th Circuit’s determination that the entirety of section 503A is now void.⁵¹ The net effect of this decision by the Court and by FDA has been to eliminate the entire portion of the amended Food, Drug, and Cosmetic Act which dealt with pharmacy compounding.

b. Problems with FDA’s Current Claim of Jurisdiction over Compounding

FDA’s attitude had already changed from that of benign neglect to one of asserting complete jurisdiction with “enforcement discretion” to finally relinquishing jurisdiction by the time the United States Supreme Court upheld the 9th Circuit’s decision in *Western States*. Since there was no longer any statutory basis formally dealing with compounding in the Act, did this mean that FDA had no jurisdiction over compounding, or that its level of jurisdiction was back to the pre-*Western States* situation of claiming complete jurisdiction while exercising enforcement discretion, or something in between?

⁴⁷ *Central Hudson Gas & Elec. Corp. v. Public Service Commission*, 447 U.S. 557 (1980).

⁴⁸ *Western States Medical Center v. Shalala*, 238 F.3rd 1090 (9th Circuit 2001).

⁴⁹ *Id.*

⁵⁰ *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002).

⁵¹ Galson, *supra* note 7 at 3.

In 2002 FDA again formally changed direction, choosing an “in-between” approach⁵² and again turning to the Guidance Document route to notify the pharmacy compounding community of the level of regulatory control it “had.”

FDA started de novo to impose structure on how it would approach continued concerns and controversies arising in the area of pharmacy prescription drug compounding. A Pharmacy Compounding Team⁵³ was established within the Office of Compliance of the Center for Drug Evaluation and Research (CDER) at FDA. This office subsequently re-issued a Guidance Document⁵⁴ on June 7, 2002, noting the facts of the *Western States* decisions, claiming at least some (though not complete as in 1992) continued jurisdiction over pharmacy compounding of prescription drugs,⁵⁵ and again promulgating a policy of “selective enforcement discretion.” Such enforcement discretion was characterized as a brief and non-inclusive itemization of circumstances under which FDA might take action against a compounding pharmacy, and stated that issues concerning pharmacy compounding of prescription drugs would be handled on a case by case basis.⁵⁶ This Compliance Policy Guide (CPG) contains a list of the factors FDA considers in deciding whether to exercise its enforcement discretion.⁵⁷ Among those factors are whether a compounded product may have a potential adverse effect on the public health, whether a firm is compounding finished drugs from bulk active ingredients that are not components of FDA-approved drugs, or whether a firm is compounding drugs that are “versions” of drugs that were withdrawn or removed from the market for

⁵² Galson, *supra*, note 7 at 3.

⁵³ Compliance Team

⁵⁴ FDA Compliance Policy Guide § 460.200, at Policy 1, *available at* http://www.fda.gov/ora/compliance_ref/cpg/cpgdrg/cpg460-200.html (hereinafter FDA 2002 Compliance Guide).

⁵⁵ *Id.*

⁵⁶ *Id.*

⁵⁷ *Id.*

safety reasons.⁵⁸ The CPG also notes that “FDA recognizes that pharmacists have traditionally extemporaneously compounded and manipulated reasonable quantities of human drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. This traditional activity is not the subject of this guidance.”⁵⁹ What constitutes a “reasonable” quantity of compounding is never defined. This mode of FDA action, or relative inaction, has been the case through 2008.

In retrospect, the decision to include the advertising and promotion sections in 503(A) of FDAMA was a grave tactical blunder. Had the advertising provisions relating to compounding not been included in FDAMA, the regulation of pharmacy compounding would have clearly reverted exclusively to the states and the current controversy over FDA regulation of BHRT would have never happened. Because the elimination of all of §503A by *Western States* left nothing in the Act which specifically dealt with pharmacy compounding, FDA was again faced with the “choice” of how to regulate.

FDA is still concerned about the volume of certain compounding pharmacy practices and the apparent similarity of some of their products to commercially available drug products. The core concepts at the heart of FDA’s current 2008 policy of selective enforcement oscillate between the occasional contention that compounded drugs are new drugs⁶⁰ or the related allegation that some compounders are in fact really manufacturers⁶¹ because of the volume of compounding they were engaged in. The manufacturing label places these compounding pharmacies on equal footing with commercial drug

⁵⁸ *Id.*

⁵⁹ *Id.*

⁶⁰ Galson, *supra* note 7 at 3.

⁶¹ FDA 2002 Compliance Guide, *supra* note 50.

companies: both make “new drugs”, as understood by the Act, and thus are subject to FDA jurisdiction.⁶²

This either-or approach creates statutory, practical, and operational difficulties for FDA. A more nuanced approach is needed to deal with the changes in the way certain pharmacies compounding, particularly those making “bioidentical” hormone replacement therapy products (hereinafter BHRT). There are several reasons for this.

First, there is a statutory basis for the straightforward notion that a pharmacy engaged in the practice of compounding cannot, by definition, be a manufacturer, and not subject to the manufacturing requirements of the Act.⁶³ Second, federal judges have consistently rejected the notion that pharmacy compounded prescription drugs are “new drugs.” This notion was most recently re-asserted in an August 30, 2006 decision in United States District Court for the Western District of Texas⁶⁴ in *Medical Center Pharmacy v. Ashcroft*, No. 04-CV-130 (W.D. Tex. May 25, 2006), now known as *Medical Center Pharmacy v. Gonzales*.⁶⁵ In this bench trial a federal judge granted the plaintiffs’ motion for summary judgment against FDA and held, among other things, that lawfully compounded prescription drugs for humans fall outside the definition of “new drugs”⁶⁶ (and interestingly, in a additional decision which has potentially significant

⁶² *Id.*

⁶³ Under the specific language of 21 U.S.C. §§ 360(g)(1) and 374 (a)(2)(A), pharmacies are expressly exempt from FDA registration as manufacturers FDAMA’s original provisions essentially exempted the overwhelming majority of compounded prescription drugs from the core new drug approval requirements of the Act. The FDCA does contain exemptions to its manufacturing provisions for pharmacies. The statute exempts pharmacies from the registration and inspection requirements for manufacturers provided the pharmacies meet certain requirements, such as complying with state laws and performing compounding activities in their normal course of business, and as such protects a broad range of pharmacy compounding practices from the traditional regulatory requirements of manufacturers..

⁶⁴ *Medical Center Pharmacy v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex. 2006).

⁶⁵ *Id.*

⁶⁶ *Id.*

implications for compounding drugs for humans, also overturned FDA’s long-held position that compounding from bulk ingredients for drugs for non-food-producing animals is illegal.⁶⁷ The Court specifically rejected FDA’s efforts to claim that a pharmacy compounded drug is a “new drug”, and to assert jurisdiction over prescription drug compounding by this argument.⁶⁸ Specifically, the Court found that “extemporaneous compounding of drugs is authorized under 21 U.S.C. §353a (Section 503A of the FDCA) and such compounding is thereby exempted from the [new] drug approval process and outside the scope of the definitions of ‘new drug’ and ‘new animal drug’ under sections 201(p)(1) and (v)(1) of the FDCA (21 U.S.C. §321(p)(1) and (v)(1).”⁶⁹

Although this lower court decision is currently on appeal to the 5th Circuit Court of Appeals, and the current Chief Counsel of HHS has expressed the sentiment⁷⁰ that the 5th Circuit will restore regulatory jurisdiction over prescription drug compounding back at the FDA, there is little reason to think this will happen given FDA’s sinusoidal pattern of claimed regulatory jurisdiction over compounding, and FDA’s apparent willingness to cede the entire playing field to the states in 1997.⁷¹ At present it appears that efforts at regulatory control based on the new drug argument could be doomed to fail.⁷²

A third reason is that federal judges have rejected the “volume of business”

⁶⁷ *Id.*

⁶⁸ *Id.*

⁶⁹ Covington & Burling. Food & Drug E-Alert. “Western District of Texas Compounding Decision on Medical Center Pharmacy v. Gonzales. September 27, 2006, available at www.cov.com (last accessed December 23, 2007).

⁷⁰ Daniel Meron, *Legal Developments Relevant to FDA Authority*, 62 Food & Drug L.J. 443 (2007). “This case is now on appeal to the Fifth Circuit, and we hope that the Fifth Circuit will place the task of balancing the risks and benefits of compounding back at the FDA – where it belongs.”

⁷¹ FDAMA § 503(A).

⁷² *Medical Center Pharmacy v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex. 2006). FDA’s argument is that all pharmacy compounded prescription drugs are new drugs. This argument has been rejected by courts.

argument as a way of demonstrating that “manufacturing” instead of “compounding” is occurring.⁷³ Indeed, the court in the first *Western States* decision rejected this line of reasoning in unusually forceful terms,⁷⁴ and this approach was tacitly affirmed by all courts in the subsequent *Western States* decisions.⁷⁵ Given that compounding pharmacies may prepare compound prescription drugs in reasonable anticipation of receiving a prescription, and that some compounding pharmacies will, because of economies of scale, unavoidably be involved in the production of large numbers of similar compounded prescription drugs (particularly so for BHRT), it is an unavoidable fact of the practice of pharmacy that there will be some large volume compounding by some pharmacies. Adding to the confusion is the use of the terms “traditional compounding” and “bulk compounding” by HHS Chief Counsel without providing meaningful definitions of either term.⁷⁶

Lastly, FDA has in principle and practice accepted the pharmacy industry’s own definition of what compounding is,⁷⁷ likely because the differences between FDA’s and

⁷³ *Western States Medical Center v. Shalala*, *supra* note 48.

⁷⁴ *Id.* U.S. District Court Judge David A. Ezra unequivocally held that volume “does nothing” to distinguish manufacturing from compounding.”

⁷⁵ *Western States Medical Center v. Shalala*, *supra* note 48.

⁷⁶ Merson, *Supra*, at 51, 443. “ But when volume or other circumstances of compounding suggest that the pharmacy is actually acting like a drug manufacturer, FDA will consider enforcement actions. In short, FDA has strived to preserve the many beneficial instances of traditional compounding, while at the same time making sure that abusive practices, involving bulk compounding, remain the subject of our enforcement.” The term “bulk” is not defined, and based on Chief Counsel’s arguments seems to be somewhat interchangeable with “high volume.” Courts have rejected the use of the volume of compounding to label a pharmacy a “manufacturer” and not a “compounder..”

⁷⁷ FDA CONCEPT PAPER: DRUG PRODUCTS THAT PRESENT DEMONSTRABLE DIFFICULTIES FOR COMPOUNDING BECAUSE OF REASONS OF SAFETY OR EFFECTIVENESS, *available at* <http://www.fda.gov/cder/fdama/difconc.htm> (last accessed July 25, 2005): a “compounded drug product is a drug product made in response to, or in anticipation of, receipt of a valid prescription order or a notation on a valid prescription order from a licensed practitioner that states the compounded product is necessary for the identified patient. Compounding does not include mixing, reconstituting, or similar acts that are performed in accordance with the directions contained in approved labeling provided by the product’s manufacturer and other manufacturer directions consistent with that labeling..the drug product may only be compounded if the FDA has not identified it, by regulation, as a drug product that ‘presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.’ “(Refs. Sections 503A(b)(3) and 503A(f) of the Act.

pharmacy industry's definitions are small. Based on this definition, the actual number of prescription drugs that are compounded by any one pharmacy or pharmacies is irrelevant if legitimate compounding prescribing and production is going on. In some states there might only be a small handful of pharmacies in the entire state doing all of the prescription drug compounding for a particular class of drugs,⁷⁸ and at a higher volume than other pharmacies. By necessity these pharmacies would need to either stock basic ingredients for such drugs and/or prepare some of the compounds in anticipation of receiving a valid prescription.⁷⁹

Interestingly, although FDA's position on compounding, its claimed jurisdiction over pharmacy prescription drug compounding, and its preferred regulatory approach to compounding has vacillated over the past twenty five years, the position of the pharmacy profession itself on the issue has remained constant. The pharmacy profession's current position statements on pharmacy compounding ironically provides the appropriate starting point for a proposed new approach for FDA to regulate the BHRT pharmacy compounding industry.

III The American Pharmacists Association on Compounding

The American Pharmacists Association (APhA) was founded in 1852 as the American Pharmaceutical Association and currently is the largest national pharmacist organization in the U.S., representing more than 50,000 pharmacists and pharmaceutical scientists.⁸⁰ Daniel A. Herbert, RPh, then President-elect of the APhA, testified before Congress on compounding medications⁸¹ in 2003 and presented the "party line" of the

⁷⁸ Herbert Testimony, *supra*, note 15.

⁷⁹ *Id.*

⁸⁰ Herbert Testimony, *supra*, note 15

⁸¹ *Id.*

pharmacy profession on the essential role of pharmacy compounding of prescription drug products in the United States.⁸² Dr. Herbert's testimony before Congress on compounding provided critical information to the Senate Committee on a wide range of issues surrounding the role of pharmaceutical compounding. In particular, the APhA provided both an operational definition of what pharmacy compounding is, and described the proper role pharmacy compounded prescription drug products should play in meeting patients' medical needs.

First, the APhA embraced the National Association of Boards of Pharmacy's (NABP) definition of compounding, which states:

Compounding – The preparation, mixing, assembling, packaging, or labeling of a drug or device (i) as the result of a practitioner's Prescription Drug Order or initiative based on the pharmacist/patient/prescriber relationship in the course of professional practice or (ii) for the purpose of , as an incident to research, teaching, or chemical analysis and not for sale or dispensing. Compounding also includes the preparation of drugs and devices in anticipation of Prescription Drug Orders based on routine, regularly observed patterns.⁸³

FDA has defined what a compounded drug product is in language that also reflects the "triad" relationship between individual patient, physician, and pharmacy:

A "compounded drug product is a drug product made in response to, or in anticipation of, receipt of a valid prescription order or a notation on a valid prescription order from a licensed practitioner that states the compounded product is necessary for the identified patient. Compounding does not include mixing, reconstituting, or similar acts that are performed in accordance with the directions contained in approved labeling provided by the product's manufacturer."⁸⁴

Critical to the practice of compounding is the existence of this "triad" relationship among

⁸² *Id.*

⁸³ Good Compounding Practices Applicable to State Licensed Pharmacies, Subpart A, Park Ridge, IL: NABP, 1993.

⁸⁴ US Food and Drug Administration, Center for Drug Evaluation and Research, FDA Concept Paper: Drug Products That Present Demonstrable Difficulties for Compounding Because of Reasons of Safety or Effectiveness, *available at* <http://www.fda.gov/cder/fdama/difconc.htm> (last accessed July 25, 2005).

the patient, her physician, and the compounding pharmacist. This definition of compounding is the opposite of the “preparation of massive amounts of a drug product with the contemplation of distribution to a mass market of unknown users in unknown venues.”⁸⁵ To further emphasize the individualized relationship at the core of pharmacy compounding, the APhA further states that “Because the preparation of an extemporaneous pharmaceutical dosage form is not a trivial exercise, our position is that when an FDA-approved, commercially available product can meet a patient’s needs, it should be employed as the preferred course of action. However, when a patient’s particular situation *obviates* (emphasis added) the use of commercial products...a compounding pharmacist can be extremely valuable.”⁸⁶

In other words, when a commercially available prescription drug product can meet a patient’s medical needs, i.e. the medical condition for which the drug is being prescribed, it is then inappropriate to prescribe a pharmacy-compounded prescription drug. Depending on one’s definition of what constitutes a legitimate medical need for treatment purposes, the implications of this position statement on the proper role of compounded prescription drugs in general, are for BHRT in particular, are enormous.

The APhA endorses the definition of “manufacturing” put forth by the NABP as well:⁸⁷

Manufacturing – The production, preparation, propagation, conversion Or processing of a drug or device, either directly or indirectly, by Extraction from substances of natural origin or independently by means Of chemical or biological synthesis, and includes any packaging or Repackaging of the substance(s) or Labeling or re-labeling of its Container, and the promotion and marketing of such Drugs or Devices. Manufacturing also includes the preparation and promotion of

⁸⁵ Herbert testimony, *supra* at 15.

⁸⁶ *Id.*

⁸⁷ *Id.*

Commercially available products from bulk compound for resale by Pharmacies.⁸⁸

The pharmacy industry has been clear on the critical distinction between manufacturing and compounding for years. It is not a straight line not based on some arbitrary “volume” of business but rather depends entirely on the existence of a particular patient/physician/pharmacist triad relationship: “the triad should control the preparation of a drug product.”⁸⁹ Compounded drugs are thus “personal, and responsive to a patient’s immediate needs.”⁹⁰ Legitimate prescription drug compounding must, at its core, be legitimately medically individualized.

Of course, all medical interactions between a physician and his or her patient are “personal.” The triad relationship of traditional compounding is personal in the sense that a smaller compounding pharmacy might actually know both the physician and patient. Any larger compounding pharmacy is thus less personal, though more personal than a commercial manufacturer only because the pharmacy itself receives the prescription and because the commercial manufacturer utilizes “many personnel and large scale manufacturing equipment., without knowledge of the specific patient.”⁹¹ A large compounding pharmacy, particularly one conducting the bulk of its business via the Internet, may be receiving hundreds or thousands of prescriptions from many physicians with whom it has no personal relationship and only has knowledge of the specific patient by virtue of having received a prescription. Some of these larger, Internet-based pharmacies try to “personalize” their service by having either on-line questionnaires relating to BHRT⁹² or employing health-care providers to follow-up

⁸⁸ Good Compounding Practices Applicable to State Licensed Pharmacies, *Supra*.

⁸⁹ Herbert testimony, *supra*, at 15.

⁹⁰ *Id.*

⁹¹ *Id.*

prescriptions with phone interviews to “monitor” patients.⁹³ Given the fact that it is the physician’s job to monitor patients on prescription drugs they place them on, these services by compounding pharmacies are necessary only in the sense that they are attempts to distance themselves from the non-individualized, anonymous nature of Internet-based business. One might also argue that pharmacies which “adjust” doses of compounded prescription drugs based on lab results they themselves evaluate without the input of the physician are both crossing the line from the practice of pharmacy to the practice of medicine, and are eliminating one leg of the “triad” relationship necessary for compounding activity to be said to exist. Clearly, all pharmacies compounding BHRT are not equal, nor practicing compounding as defined in the traditional sense.

The issue of what constitutes a legitimate medical “need” is a concept which must also be addressed. For purposes of this thesis, the legitimate patient need which a prescription drug is prescribed for is now defined as the medical condition which the drug is treating. In the case of prescription hormone drug therapy, either commercial or compounded, , the only three medical indications for which hormone therapy has been approved by FDA are treatment of vasomotor symptoms or hot flashes, treatment of vulvar-vaginal atrophy associated with the menopause, and prevention of osteoporosis.⁹⁴ An additional non-approved medical condition for which commercial HR or BHRT commonly is prescribed also includes a cluster of conditions which may be referred to

⁹² See Signature Pharmacy™, available at <http://www.signaturepharmacy.com> (last accessed February 2, 2005). “Signature pharmacy has a consultation form that you can submit over the internet. You will receive a phone call by one of our professionals to talk about the recommendations.”

⁹³ *Id.*

⁹⁴ UNITED STATES FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH (CDER), GUIDANCE FOR INDUSTRY, ESTROGEN AND ESTROGEN/PROGESTIN DRUG PRODUCTS TO TREAT VASOMOTOR SYMPTOMS AND VULVAR AND VAGINAL ATROPHY SYMPTOMS – RECOMMENDATIONS FOR CLINICAL EVALUATION, January 2003 [hereinafter FDA Estrogen Guidance Document].

collectively as either “low libido” or “hypo-active sexual desire disorders” (HSDD).⁹⁵ Even though this is not an FDA-approved indication for HRT it is the most common off-label medical condition for which these medications may be legitimately prescribed and is included in this section for completeness sake. Either way, the decision to take a prescription drug only if it is “natural” (even if the patient believes that “natural” means something other than the correct medical definition) may be a legitimate desire on the patient’s part but does not qualify as a legitimate medical need for the writing of a prescription by a physician for a bioidentical drug when the patient’s medical condition for which the drug is being prescribed can be safely and effectively treated with a commercially manufactured prescription drug product.⁹⁶

IV The Rise of Bioidentical Hormone Replacement Therapy (BHRT) Industry

a. Linguistic Considerations: “bioidentical” and “natural”

The past half-decade has witnessed an enormous increase in the number of prescriptions being written for menopausal women for treatment of menopausal conditions such as vasomotor symptoms (hot flashes), vulvar-vaginal atrophy, as well as for prevention of osteoporosis. And as previously noted, large number of prescriptions are also being written for the treatment of female sexual dysfunction (“FSD”) even though this entity has neither been defined⁹⁷ nor is currently an FDA-approved

⁹⁵ UNITED STATES FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH (CDER), GUIDANCE FOR INDUSTRY, FEMALE SEXUAL DYSFUNCTION: CLINICAL DEVELOPMENT OF DRUG PRODUCTS FOR TREATMENT, May 2000. [hereinafter FDA FSD Guidance Document].

⁹⁶ Testimony of the American Pharmacists Association before the Senate Committee on Health, Education, Labor and Pensions, “On Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients, October 23, 2003, “...our position is that when an FDA-approved, commercially available product can meet a patient’s need, it should be employed as the preferred course of action. However, when a patient’s particular situation obviates the use of commercial products, the knowledge and skills of a compounding pharmacist can be extremely valuable, even lifesaving.” The emphasis is on the words “need” and “obviates.” There are different needs, and not all of them necessarily justify use of a compounded prescription drug.

indication for hormone therapy. Precise numbers are difficult to come by, but even conservative estimates now calculate that the market for these prescription drugs is a multi-billion dollar industry and that possibly millions of women are now taking BHRT.⁹⁸

Goethe perhaps stated it best when he said “When ideas fail, words come in very handy.”⁹⁹ The term “bio-identical” is a term which has no defined meaning in any medical¹⁰⁰ or conventional dictionary.¹⁰¹ Although there is no definitive or agreed upon definition, the term bio-identical often is used in conjunction with the term “natural” (a medical term which does in fact have several defined meanings¹⁰² – “not produced or changed artificially”, or “neither artificial nor pathologic”) to describe hormone-like substances derived from plants which are then chemically altered so that they replicate the endogenous hormones (e.g. estrone, estriol, estradiol) which exist in the human body. The term bioidentical used to refer to these compounds may have no defined medical meaning, but from a marketing point of view it is a golden hook to grab potential patients. Compounding pharmacies may intentionally juxtapose defined medical terminology such as “natural,” with a term such as bioidentical¹⁰³ in order to create the impression that these prescription compounded drugs are not the industrial chemicals

⁹⁷ FDA FSD Guidance Document, *supra*, note 92.

⁹⁸ FDA has estimated that “compounding represents one percent of all the prescriptions filled each year” of the 30 billion or more written in the U.S. *Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients Hearing Before the S. Comm. On Health, Labor and Pensions*, 108th Cong. 39 (2003) (prepared statement of Steven K. Galson, M.D., Deputy Director of the Center for Drug Evaluation and Research at the FDA).

⁹⁹ Johann Wolfgang von Goethe, German dramatist, novelist, poet & scientist (1749-1832), *available at* The Quotations Page, www.quotationspage.com (last accessed January 22, 2008).

¹⁰⁰ DORLAND’S ILLUSTRATED MEDICAL DICTIONARY 1223 (30th ed. 2003).

¹⁰¹ THE NEW OXFORD AMERICAN DICTIONARY (Oxford University Press, 2001).

¹⁰² DORLAND’S ILLUSTRATED MEDICAL DICTIONARY 1223 (30th ed. 2003).

¹⁰³ Again visit Signature Pharmacy™ at www.signaturepharmacy.com for their “Natural Hormone Replacement Therapy” section of their website. Or see Natural Alternatives, Estriol USP-Bio-identical Natural Estrogen, available at http://all-new-you.com/1bioidentical_estriol.html (last accessed November 29, 2005).

which patients may erroneously think or are led to think are the only drugs formulated by large pharmaceutical companies.

Ironically, although these BHRT products are plant-derived they are not “natural” in the sense that they must be chemically altered to more closely approximate endogenous human hormones. However, as used in the advertising it would appear that anything derived from a plant is “natural.” All of this may have more to do with the fact that some patients simply do not want to take a product made by a commercial drug manufacturer than anything else. These individuals may be making assumptions that pharmacy compounded BHRT has been tested the same way as a commercial prescription hormone therapy drug is, and that it is as safe, or safer, and as effective, or more effective, as the prescription drug product they are replacing.

Even organizations such as the American College of Obstetricians and Gynecologists (ACOG), the umbrella organization of practicing obstetrician-gynecologists in the United States, have become confused by the terminology of BHRT, at least compared to the way in which the term is used by some compounding pharmacies which promote these drugs.¹⁰⁴ For example, the November 2005 Committee Opinion on “Compounded Bioidentical Hormones”¹⁰⁵ recently stated that BHRT are similar *or* identical to endogenous human Hormones,¹⁰⁶ whereas the compounding pharmacies invariably claim they are identical, not similar. Indeed, an essential part of the marketing strategy for BHRT is that they are identical to “naturally occurring” human estrogens.

¹⁰⁴ American College of Obstetricians and Gynecologists (ACOG) Committee Opinion, Committee on Gynecologic Practice, Compounded Bioidentical Hormones, No. 322, November 2005. “Bioidentical hormones are plant-derived hormones that are biochemically similar or identical to those produced by the ovary or body.” The terms “similar” and “identical” are not equivalent. “Body” may be redundant, as “ovary” is clearly part of the “body”; it would make more sense to specify the part of the body other than the ovary which is being referred to.

¹⁰⁵ *Id.*

¹⁰⁶ *Id.*

In fact, they are better than “identical”: they are “bio-identical!”

Several conclusions about BHRT must follow once attention is paid to the terminology used and how terms are defined. Once a substance, even if derived from a plant, is chemically altered to resemble something else (e.g. a human hormone) it is no longer completely “natural.” Similarly, a substance completely derived from horse urine yet not chemically altered is “natural,” and in fact is more natural than an altered plant-derived hormone. In addition, one cannot claim that a substance is “bioidentical” to a human hormone unless one actually proves that it is in fact chemically structurally identical. Medically, bioidentical can only mean identical; if the substance is only similar then the most that can be said is that it is “bio-similar”. It is essential to note that not a single BHRT compounding pharmacy advertising and promoting these products on the Internet is offering a prescription compounded BHRT drug product that has not been chemically altered in some way. Strictly speaking, none of the BHRT compounded products are wholly “natural”. But, what they all are not is commercially manufactured.

What must also be true is that an exact copy of a substance can have only the same effectiveness and side effects of the index substance. Logic dictates that a BHRT drug product by definition cannot be more efficacious, or safer, than the endogenous human hormones it claims to be duplicating. For example, if endogenous human estriol, or estradiol, or progesterone, could cause uterine cancer or breast cancer if administered to humans¹⁰⁷ then one cannot possibly truthfully claim that a BHRT estrogen,

¹⁰⁷ John J. Vogel DO, Selecting Bioidentical Hormone Therapy, in Understanding the Controversy: Hormone Testing and Bioidentical Hormones, PROCEEDINGS FROM THE POSTGRADUATE COURSE PRESENTED PRIOR TO THE 17TH ANNUAL MEETING OF THE NORTH AMERICAN MENOPAUSE SOCIETY (October 11, 2006)[“Most studies did not support a protective role for estriol, and consequently, research on estriol as a breast-safe estrogen was abandoned 20 years ago... Women who have a strong preference for use of estriol should be counseled on the entirety of the data.”

progesterone, or combination bioidentical drug product administered under the same circumstances can decrease the risk of either of these cancers. Any claim otherwise to this effect by a compounding pharmacy must be untrue.¹⁰⁸ Similarly, a lack of data on the protective effect of endogenous human estrogens against the development of certain cancers such as breast or uterus also means that such a biologically opposite, protective effect claim cannot be made for a BHRT product either. Any safety and efficacy claim for BHRT cannot circumvent these medical facts.

FDA has the discretion to define,¹⁰⁹ for its own purposes and for purposes of the pharmaceutical industry, the meaning of medical terms of usage for indications for prescription drugs. This should be particularly so where use of the terms is ubiquitous and where industry has not made a determined effort to do so. In the present case the compounding industry has taken the upper hand in marketing the terms bioidentical and natural¹¹⁰ but hasn't provided an accepted uniform medical definition of the former term. The case at hand is thus unlike FDA's earlier attempt to define the term hypoallergenic for the cosmetics industry. This effort was defeated by industry on subsequent challenge in federal court by cosmetics companies because FDA's definition was found to be arbitrary and capricious compared to the industry's existing established definition.¹¹¹ Under the *Chevron* doctrine¹¹² FDA may define the term "bioidentical", may decide that

¹⁰⁸ Again visit Signature Pharmacy™ at www.signaturepharmacy.com for their "Natural Hormone Replacement Therapy" section of their website. ["Natural hormone therapy has many potential benefits: May help protect against endometrial and breast cancers"].

¹⁰⁹ FDA defines what is "drug", a "medical device" in the Act.

¹¹⁰ There is no uniformly agreed upon definition of "bioidentical" provided by the pharmacy or pharmacy compounding industry.

¹¹¹ UNITED STATES FOOD AND DRUG ADMINISTRATION, CENTER FOR FOOD SAFETY AND APPLIED NUTRITION, OFFICE OF COSMETICS AND COLORS FACT SHEET, HYPOALLERGIC COSMETICS, available at <http://www.cfsan.fda.gov/~dms/cos-224.html> (last accessed January 22, 2008).

¹¹² *Chevron U.S.A. v. Natural Resource Defense Council, Inc.*, 467 U.S. 837 (1984).

the term “bioidentical” is either meaningless or inaccurate, and also may decide whether a particular medical condition is a legitimate medical indication for a prescription drug.¹¹³

This is not regulation of the medical profession, but a legitimate exercise of FDA’s jurisdiction over the language employed for prescription and over-the-counter drugs.

b. Compounding Practice Has Changed Because of WHI and the Internet

The explosive growth of the use of these “natural” bioidentical hormone prescription drug products is likely the result of a conflux of factors: adverse publicity resulting from medical studies published in the past half-decade which have questioned some of the health benefit claims made by commercial prescription hormone therapy drug manufacturers for their products,¹¹⁴ recent moves to increase the autonomy of patients in the medical decision-making process, adverse publicity in general against Pharma and its profits, some spill-over from the alternative/complimentary medicine movement favoring natural or plant-derived products and the American public’s on-going love affair with dietary supplements, and an unusually effective and aggressive marketing campaign, occasionally Internet-based, to promote these products to women.¹¹⁵ Of these factors, none was more devastating than the combination of the Internet and the results of the Women’s Health Initiative studies.¹¹⁶

Manufacturers of commercial prescription hormone therapy drugs have received enormous adverse publicity as a result of the findings of the Women’s Health Initiative, a large, randomized, prospective NIH-sponsored clinical trial which purported to examine

¹¹³ Galson, *supra*, note 7.

¹¹⁴ Women’s Health Initiative, *The estrogen-plus-progestin study*, available at http://www.nhlbi.nih.gov/whi/estro_pro.htm (last accessed September 18, 2006)[hereinafter WHI study].

¹¹⁵ Galson, *supra*, note 7.

¹¹⁶ David M. Herrington and Timothy D. Howard, *From Presumed Benefit to Potential Harm – Hormone Therapy and Heart Disease*, 349 N. ENGL. J. MED. 519 (2003).

the claimed cardio-protective and other benefits of Premarin® (conjugated equine estrogen) and Prempro®. (Premarin® plus progesterone) in menopausal women.¹¹⁷ The claimed health benefits for these compounds had been based on older, retrospective data with more inherent biases built into the study design. The findings of WHI were that these commercial prescription drugs surprisingly did not protect against heart disease or senile dementia,¹¹⁸ increased the risk of stroke and (at least in the case of Prempro®) increased the relative risk for breast cancer as well.¹¹⁹

The findings of the first Women’s Health Initiative studies were not presented to FDA prior to their publication in the medical literature, and FDA spent the next several years frantically working to revise all of its labels for menopausal hormone therapy products despite the fact that there were significant problems with the study design of WHI, in particular the fact that many of the women enrolled were well into menopause and that the claimed benefits of hormone therapy products may only be realized if women start on these medications when they are peri-menopausal or shortly after entering menopause.¹²⁰ Although the past several years has seen a steady stream of increasingly contentious medical literature pointing out the shortcomings of WHI, disputing its findings, and creating problems for currently existing revised labels for both commercial prescription HR products and BHRT, the adverse publicity proved an enormous boon to a compounding BHRT industry which touted the purported safety advantages of its more “natural” products than the synthetic “chemicals” women were being fed by

¹¹⁷ WHI study, *supra*, note 111.

¹¹⁸ *Id.*

¹¹⁹ Rowan T. Chlebowski, Susan L. Hendrix, Robert D. Langer et al. *The Women’s Health Initiative Randomized Trial, Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women*, 289 JAMA 3243 (2003).

¹²⁰ Hormone Therapy, *Summary of Balancing Risks and Benefits* 104(4) Supp OBSTET. GYNECOL. 128S (2004).

commercial drug manufacturers.¹²¹

As a result of WHI, there was a significant change in the patterns of hormone therapy use and prescribing patterns for commercial hormone therapy drug products.¹²² The terrible irony of WHI, however, was that many of the women who stopped taking commercial prescription hormone therapy drug products for treatment of menopausal symptoms because of relatively minor and known safety concerns ultimately ended up switching to pharmacy compounded bioidentical hormone therapy prescription drugs for which virtually nothing was known about relative safety or efficacy compared to the commercial prescription drugs already on the market.¹²³

c. Not All Compounding Pharmacies Are the Same Anymore; Some Are Doing Something Other Than Compounding

These prescriptions for BHRT drug products are filled at compounding pharmacies, some of which advertise in magazines or via the Internet. Some of these ads can be seen in in-flight magazines carried on airlines or in popular women's magazines; indeed it is often impossible to use public transportation without being confronted by advertising and promotion for these products and being bombarded by their alleged salutary effects.¹²⁴

¹²¹ See website for Profile Health, available at www.profilehealth.com/about.

¹²² Esther Hing and Kate M. Brett, *Changes in U.S. Prescribing Patterns of Menopausal Hormone Therapy, 2001-2003*, 108 OBSTET. GYNECOL. 33 (2006).

¹²³ MSNBC, 'Bioidentical' female hormone use questioned. No evidence they are safer than synthetic versions, medical group says, *available at* <http://www.msnbc.com/id/9874568> (last accessed October 31, 2005). Also see Susan Ince, *Are "Natural" Hormones Safer?* MORE, November 2005, at 187; ACOG TODAY, Clinical Issues, November-December 2005: Michele G. Curtis, MD, past vice chair of the Committee on Gynecologic Practice, "One of our concerns is quality control – there has been little clinical testing on most compounded products to determine whether they're safe or effective."

¹²³ Lila E. Nachtigall MD, Bioidentical versus Nonbioidentical Hormones, PROCEEDINGS FROM THE POSTGRADUATE COURSE PRESENTED PRIOR TO THE 17TH ANNUAL MEETING OF THE NORTH AMERICAN MENOPAUSE SOCIETY (October 11, 2006)[Hereinafter Nachtigall].

¹²⁴ Perhaps the most aesthetically displeasing is the in-flight magazine featuring a picture of a muscle-bound elderly male physician with body like Arnold Schwarzenegger's and a head like Dick Cheney's. The advertisement promotes "natural" hormone therapy for men.

The financial and public success enjoyed by some compounding pharmacies which engage in large-scale compounding and aggressively promote these products to the public has been accompanied by two paradigm shifts in the manner in which these products are promoted: (1) the promotional activities in some cases clearly advocate the wholesale replacement of commercially available prescription drug products with these compounded products; and (2) many of the prescription drug efficacy and safety benefits are either highly misleading and/or false. The former is important because it takes the production of these drugs out of the realm of “compounding”; the latter is important because, should FDA intervene, it will enable the Agency to restrict advertising and promotion because the claims are clearly false and not protected as commercial speech.¹²⁵

Attempting to promote bioidentical hormone therapies as a wholesale replacement for all women instead of commercially available prescription drugs which are known to be safe and effective is, by the Pharmacy industry’s own admission, not compounding.¹²⁶ More to the point, the Senior Counsel for the pharmacies who sued FDA in Western States, and who represented the pharmacies at every level of the *Western States* litigation, has gone on record as stating that “the opposite of a compounded drug is not a

¹²⁵ DANIEL A. FARBER. *THE FIRST AMENDMENT* 158 (Foundation Press 2003). “The Central Hudson test can be broken into two parts. The threshold inquiry is whether the regulated speech is misleading or concerns an illegal activity. If so, it receives no constitutional protection. The government can regulate truthful advertising about lawful transactions, however, only if it passes a three-prong inquiry: (a) Is the governmental interest a “substantial” one? (b) Does the regulation “directly” advance the governmental interest? (c) Is the regulation tailored to the governmental interest?”

¹²⁶ Testimony of the American Pharmacists Association before the Senate Committee on Health, Education, Labor and Pensions, “On Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients, October 23, 2003, *supra*, note 93, at 7: “The profession’s definition of compounding does not encompass the preparation of massive amounts of a drug product with the contemplation of distribution to a mass market of unknown users in unknown venues.” In fact, the widescale magazine and Internet direct to consumer advertising of BHRT to consumers is exactly that, and either places the pharmacy before the patient and physician in the “triad” relationship, or for those compounding pharmacies which conduct their own lab tests, interpret the results and then “advise” the patient, effectively eliminate the physician part of the triad, regardless of the amount of lip service paid to the physician, and negate the individualization requirement.

manufactured drug; rather, it is no suitable drug at all.”¹²⁷

V Wyeth’s Citizen Petition

a. Background and Actions Demanded

The Wyeth Pharmaceutical Company submitted a Citizen Petition to FDA¹²⁸ on October 6, 2005 in response to what it viewed as improper pharmacy compounding practices in the area of hormone replacement therapy (HRT) for treatment of menopausal conditions such as vasomotor symptoms (aka “hot flashes”) and/or vulvar-vaginal atrophy associated with the menopause. These two conditions are the only two medical conditions¹²⁹ recognized by the Division of Reproductive and Urologic Drug Products (DRUDP, now known as DRUP) of the Center for Drug Evaluation and Research (CDER) of FDA for treatment by commercially manufactured prescription drug products such as Premarin® and Provera®. The latter two products are manufactured by Wyeth and despite recent adverse publicity resulting from the findings of the Women’s Health Initiative (WHI) studies of the National Institutes of Health (NIH) still remain the most commonly prescribed commercially manufactured prescription drugs approved by FDA as safe and effective for treatment of these medical conditions. Premarin® is available in a wide range of doses (0.25 to 2.5 mg) and formulations (pill, cream). Wyeth’s products are not the only commercial prescription drug products available for treatment of

¹²⁷ Howard M. Hoffman Esq, *The Critical Role and Legality of Pharmacy Compounding in the Modern Marketplace*, FDLI UPDATE, SEPTEMBER/OCTOBER 2004, at 30. One would be hard pressed to find a better example of the law of unintended consequences than this statement. If the statement is true, it must also be true that when there is a suitable drug (suitable being a medical, not a personal determination, for a prescription drug) that is commercially available then a compounded drug is inappropriate and should not be prescribed at all.

¹²⁸ Wyeth. Citizen Petition to FDA, Docket 2005-0411, 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. Submitted October 6, 2005, available at <http://www.fda.gov/ohrms/dockets/05po411/05p-0411-cp00001-01-vol1.pdf> (last accessed September 19, 2006)[hereinafter Wyeth Citizen Petition].

¹²⁹ FDA Estrogen Guidance Document, *supra*, note 91.

menopausal conditions; there are dozens of others covering a wide range of doses, formulations, compositions, routes of administration, combinations, and degrees of “naturalness” or synthesis.¹³⁰ What all of these commercial drug products have in common is that they had to be tested for safety and efficacy by FDA in order to be sold to patients in the United States.

In general, FDA recommends that all patients be treated with the lowest effective dose of these medications for the shortest amount of time necessary.¹³¹ The effectiveness in a given patient is determined solely by clinical response of symptoms to treatment.¹³² Neither the manufacturer, the FDA, nor major medical societies such as the American College of Obstetricians and Gynecologists or the Endocrine Society endorses in any way the use of either serum or salivary hormone levels to either select or monitor the use of these medications. Indeed, both societies have publicly gone on the record to indicate the worthlessness of serum or salivary levels in either dose selection or monitoring for patients with menopausal conditions treated with hormone replacement therapy (HRT).¹³³

The rapid increase in the number of prescriptions filled in compounding pharmacies for bioidentical hormones was the result of a confluence of factors, chief among them the results of the findings of the WHI. Since Wyeth’s prescription drug products Premarin® and Prempro® were the primary drugs investigated by WHI, much of the loss in revenue by commercial hormone therapy prescription drug manufacturers came at Wyeth’s expense. In this sense it should come as no surprise that the Citizen Petition was filed by Wyeth.

¹³⁰ *Id.*

¹³¹ *Id.*

¹³² *Id.*

¹³³ American College of Obstetricians and Gynecologists (ACOG) Committee Opinion, Committee on Gynecologic Practice, Compounded Bioidentical Hormones, No. 322, November 2005.

The Citizen Petition was formally submitted to FDA on Wyeth's behalf by the law firm of Wiley, Rein, and Fielding LLP on October 6, 2005 pursuant to 21 C.F.R. §§10.20. and 10.30. The Citizen's Petition was hand-delivered to Steven K. Galson, MD, Acting Director of CDER, David J. Horowitz, Director of the Office of Compliance, Jane A. Axelrad, Director of the Office of Regulatory Policy, Sheldon T. Bradshaw, Chief Counsel of FDA, Steven D. Silverman, Director, Division of New Drugs and Labeling Compliance, and Thomas W. Abrams, Director of the Division of Drug Marketing, Advertising, and Communications (DDMAC). Additional copies were also distributed to the Division of Reproductive and Urologic Drug Products (DRUDP), and a senior medical officer was assigned to review it.

Wyeth's Citizen Petition¹³⁴ demanded that FDA undertake four actions: (1) initiate enforcement actions against pharmacies compounding BHRT drugs whose facilities or practices violate the Federal Food, Drug, and Cosmetic Act (the Act); (2) commence investigations to determine whether proper inserts concerning material facts and risk information are being provided by entities dispensing or promoting BHRT drugs; (3) require pharmacies compounding BHRT drugs to make certain labeling and advertising disclosures; and (4) issue an FDA Alert or Talk Paper addressing concerns relating to compounded BHRT drugs.

The Citizen Petition was circulated within various departments of CDER, including but not limited to DRUP, the Division of Drug Marketing, Advertising and Communications (DDMAC), and the Office of Regulatory Policy (ORP). It is possible and perhaps even likely that the FDA Commissioner's Office also reviewed the Citizen

¹³⁴ Wyeth Citizen Petition, *supra*, note 125.

Petition. A formal reply was drafted by a senior medical officer in December 2005¹³⁵ and circulated to all other relevant departments within FDA. A revised reply omitting all legal analysis and focusing on the available medical data to support safety, efficacy, and marketing claims by some of the compounding pharmacies mentioned in the Citizen Petition drafted in February 2006.¹³⁶ Some of the material and analyses contained within these two responses to the Citizen Petition was used in the decision to undertake FDA's current enforcement action.

Comments on or formal responses to the Citizens Petition were sent to FDA by A variety of grass-roots consumer health organizations, citizen public interest groups,¹³⁷ the American Pharmacists Association,¹³⁸ and the International Academy of Compounding Pharmacists.¹³⁹

The large number of comments received by FDA in response to Wyeth's Citizen Petition was comparable to the response seen in the battle between FDA and the dietary supplement industry over FDA regulation of dietary supplements, a fight which FDA lost.¹⁴⁰ Although there is some overlap between compounding of BHRT and the dietary

¹³⁵ The author wrote both of these responses to the Wyeth Citizens' Petition. The first response included both medical and legal analyses. Jane Axelrad in FDA's Office of Policy insisted that the all legal analysis be omitted from the response to the Wyeth Citizen's Petition because it was not "requested" and ordered that the Medical Officer revise the document even though it was the stated position of the Office of the Commissioner that this very practice was antithetical to FDA policy. In fact, both medical and legal questions were posed to the author, who was/is an attorney trained in food and drug law in addition to being a board-certified Obstetrician-Gynecologist. Nevertheless, in the interests of moving the response to the Citizens' Petition along the second response contained only a medical or scientific analysis of BHRT, including a detailed analysis of the scientific veracity of numerous BHRT safety and efficacy claims.

¹³⁶ *Id.*

¹³⁷ Public Citizen, *Hormone Replacement Therapy Drugs Mixed by Pharmacies Are Unsafe*, Public Citizen Reveals on WorstPills.org Web Site, available at http://www.citizen.org/pressroom/print_release.cfm?ID=2550 (last accessed August 2, 2006).

¹³⁸ American Pharmacists Association, *Response to Citizen Petition Filed on Behalf of Wyeth*, Docket No. 2005P-0411, May 3, 2006.

¹³⁹ International Academy of Compounding Pharmacists (IACP), *Comments to Citizen Petition Filed on Behalf of Wyeth*, Docket No. 2005P-0411, July 11, 2006.

¹⁴⁰ Michael Specter, *Miracle in a Bottle*. THE NEW YORKER, February 2, 2004, at 64. ("Dietary supplements are unregulated, some are unsafe – and Americans can't get enough of them").

supplement industry in that both tend to overuse the term “natural,” and there is the potential for misleading claims when marketed over the internet,¹⁴¹ there are two enormous differences between BHRT and dietary supplements: (1) compounding BHRT pharmacies are clearly making prescription drugs and making safety and efficacy drug claims; and (2) patients cannot obtain BHRT without a prescription.

b. Wyeth’s Arguments

Wyeth states its 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 FDA-approved products,”¹⁴² and makes two arguments in its request that FDA undertake enforcement action against select pharmacies compounding BHRT: (1) the pharmacies in question are engaged in manufacturing, not compounding; and (2) these compounded BHRT prescription drugs are really new drugs.¹⁴³ In effect, Wyeth’s intent mimics FDA’s stated intent of not interfering with traditional compounding activities.¹⁴⁴ Unfortunately, both of Wyeth’s arguments are the same two arguments FDA has made in the past and which have consistently been rejected by federal courts.

Wyeth provides no real mechanism to distinguish the pharmacies Wyeth takes issue with from those that it doesn’t, and there are problems with these arguments, as noted in section II of this paper. Interestingly, the manufacturing argument could be true if there were no structural differences between the prescription BHRT drugs being compounded and formulated compared to commercially available drugs, or if the activity

¹⁴¹ Charles A. Morris and Jerry Avorn, *Internet Marketing of Herbal Products*, 290 JAMA 1505 (2003).

¹⁴² Wyeth Citizen Petition, *supra*, note 125

¹⁴³ *Id.*

¹⁴⁴ Galson, *supra*, note 7.

they are engaged were not really compounding (i.e. were labeled as something other than compounding or manufacturing). Unfortunately, Wyeth does not make either of these arguments,¹⁴⁵ and the American Pharmacists Association immediately picked up on the mistake of labeling the ongoing activities “manufacturing.”¹⁴⁶ As noted earlier, whatever one would like to label this activity, it is clearly not manufacturing, at least by the definition both FDA and the APhA accept. If all compounding pharmacies for BHRT are making their products on the basis of individual prescriptions (which they are), then they are all, at least in that respect, not engaged in manufacturing. If the prescriptions are all legitimate and appropriate, no amount of volume of business will negate the fact that it is compounding, even if the number of prescriptions is enormous. Labeling the activity in question “manufacturing”, as Wyeth does in its Citizen Petition, will likely not work once courts begin to weigh in.

The argument in the Citizen Petition on labeling is predicated on the premise that prescription compounded BHRT are new drugs.¹⁴⁷ If one acknowledges that these compounded drugs are not new drugs, then the arguments cannot work. Recent court decisions that compounded prescription drugs are not new drugs strongly negates the legitimacy of Wyeth’s argument.¹⁴⁸

The Citizen Petition appears to argue the issues backwards, i.e. first makes claims regarding BHRT based on alleged status as new drug status, and then adds that they are manufacturers. Both arguments are likely to fail. In this author’s opinion a different approach is needed: one must first show that BHRT is neither compounding nor

¹⁴⁵ Wyeth Citizen Petition, *supra*, note 125.

¹⁴⁶ American Pharmacists Association, *Response to Citizen Petition Filed on Behalf of Wyeth*, Docket No. 2005P-0411, May 3, 2006, *supra*, note 135.

¹⁴⁷ Wyeth Citizen Petition, *supra*, note 125.

¹⁴⁸ *Medical Center Pharmacy v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex. 2006), *supra*, note 61.

manufacturing, and then take on the advertised safety and efficacy claims. The manufacturing v. compounding dichotomy should be abandoned in favor of a new category which better classifies the pharmacy activity going on. The contention that compounded BHRT are “new drugs” should be abandoned in favor of an approach which demonstrates that there is no legitimate medical basis for the “individualization” of these prescriptions and that the essential “triad” of compounding¹⁴⁹ does not exist.

c. A Better Argument Not Made re: Compounding versus Manufacturing

What distinguishes some compounding pharmacies from others is not how much they are making, or even so much what they are making, but how they are advertising and promoting what they are making, and how they reach the point of needing to compound. The veracity of the safety and efficacy claims is a separate issue which should be addressed once the pharmacy activity at issue is appropriately classified.

Within the context of the advertising and promoting realm, it is not the fact that the safety and efficacy claims are false or misleading per se which gives FDA its “handle” on regulating this activity even though FDA is correct in pointing out that some claims are false and misleading. Rather, it is the clearly intended wholesale replacement of effective commercial prescription drug products with pseudo-individualized products that makes the activity non-compounding, by the industry’s own standard, and which allows distinctions among compounding pharmacies to be made.¹⁵⁰

¹⁴⁹ Herbert Testimony, *supra*, note 15.

¹⁵⁰ A quick perusal of any one of dozens of compounding pharmacy internet sites for compounded BHRT reveals a demonstrable attempt to represent these products as a legitimate replacement for commercial hormone therapy drug products. The information is not designed to emphasize the need for a “custom” medication for a medical condition (e.g. vasomotor symptoms) that is not being adequately treated with a commercial product, but rather to globally characterize one set of products as less natural, less safe, less effective than another absent any proof. There is a strange blend of both classic drug claims re: disease or prevention of disease, as well as dietary supplement claims for general health benefits (e.g. looking or feeling younger).

Rather than label this activity “manufacturing,” which it is not by both the industry’s and FDA’s definitions,¹⁵¹ there must be another category other than “manufacturer” or “compounder” to describe the activity going on. This author proposes that the activity in question be defined as either “non-compounding”, not traditional compounding, or better still as “not-compounding.” Alternatively, rather than come up with a new term, FDA can simply just state that the activity is not legitimate compounding {so long as the activity in question is not referred to as “manufacturing”}. There is no rule which states that compounding activity which is defined as not compounding must be defined as manufacturing; doing so runs into all of the problems previously described. As noted, FDA has the authority to define a new medical term such as “non-compounding”, particularly if industry has been willing to accept FDA’s own definition of “compounding” as defined in the FDC&A. Once it is “not compounding”, and is a prescription drug activity, it must come under FDA’s regulatory authority.

Although Wyeth also concedes in its Citizen Petition that it is legal for both pharmacies and pharmacists who provide compounding services to advertise those services,¹⁵² Wyeth’s attempt to apply the labeling, advertising, and promotion provisions of the FD&C Act to “drugs compounded within the triad relationship” is doomed to fail because, as noted, a compounded prescription drug is not considered to be a “new drug” for purposes of the Act. Similarly, absent an effort to categorize BHRT as something other than “drugs compounded within the triad relationship”, Wyeth’s insistence in the Citizen Petition¹⁵³ that compounding pharmacies must put together a

¹⁵¹ See section III definitions of compounding and manufacturing.

¹⁵² Wyeth Citizen Petition, *supra*, note 125.

¹⁵³ *Id.*

“brief summary of safety and effectiveness” to accompany pharmacy advertisements or a package insert which contains “adequate directions for use” cannot succeed. These provisions can only apply to either new drugs or to prescription drugs made by compounding pharmacies which can be demonstrated to not satisfy the triad of compounding, and thus are not legitimate compounding. Wyeth argues the former,¹⁵⁴ and not the latter; the latter is the stronger argument since in making the claim that they are new drugs Wyeth does nothing to disprove the legitimacy of the “compounded within the triad relationship” paradigm nor escape recent judicial decisions on the “new drug” issue. It is the latter which should be contested, not whether the compounded prescription drugs are new drugs. This basis for this argument will be discussed in section VII.

VI FDA’s Enforcement Actions Against the 7 Compounding Pharmacies

a. The Safety and Efficacy Claims for BHRT: What Do the Data Show?

The definition of “bioidentical” may be elusive, but there is no shortage of health benefit and safety claims for BHRT on the Internet. Are these claims true, only partially true and thus potentially misleading (and thus possibly protected as commercial speech), or purely false? The answer is all of the above. FDA’s first reason for its reason crack down on select compounding pharmacies making and promoting BHRT is the safety and efficacy claims being made about these prescription drug products. It is the stronger of the two reasons for taking enforcement action.

The entirety of the randomized, prospective, comparative efficacy and safety data between BHRT and commercially manufactured, prescription hormone therapy drug products may be summarized by stating that there is almost none.¹⁵⁵ There is no large

¹⁵⁴ *Id.*

¹⁵⁵ Nachtigall, *supra*, note 120.

randomized, prospective clinical trial comparing BHRT with commercial hormone therapy prescription drugs demonstrating that they are equivalent, and certainly none to demonstrate the BHRT is superior either in efficacy or in its safety profile.¹⁵⁶ A recent comprehensive review of bioidentical hormone therapy¹⁵⁷ concluded that “although individualized hormone products may decrease some symptoms of menopause, it seems they have no proven advantage over conventional hormone therapies and their use is not supported by evidence regarding pharmacokinetics, safety, and efficacy.”¹⁵⁸ This should come as no surprise. Notwithstanding this paucity of comparative data however, there is enough legitimate direct scientific literature to demonstrate that many of the medical benefit and safety claims made by some Internet-based compounding pharmacies are either blatantly false or scientifically impossible.¹⁵⁹

Commercially manufactured prescription hormone therapy drugs are new drugs, and because they are federally regulated under the Act have to prove both efficacy and safety in randomized, prospective, controlled clinical trials against placebo as well as undergo testing to establish purity and potency of their formulations.¹⁶⁰ Compounded BHRT avoid all of these medical “hurdles,” and as a result the active and inactive ingredients in compounded products can and do vary widely.¹⁶¹ Most importantly, there

¹⁵⁶ Heidi D. Nelson, *Commonly Used Types of Postmenopausal Estrogen for Treatment of Hot Flashes. A Scientific Review*, 291 JAMA 1610 (2004).

¹⁵⁷ Lisa A Boothby, Paul L. Doering and Simon Kipersztok, *Bioidentical hormone therapy: a review*, 11 MENOPAUSE 356 (2004).

¹⁵⁸ *Id.*

¹⁵⁹ Nachtigall, *supra*, note 120. See also Tara Parker-Pope, *Popular Menopause Hormones Made From Plants Come Under Scrutiny*, WALL STREET JOURNAL, October 25, 2001, at D1. The comments from medical professionals whose business is to promote bioidentical hormone therapy sometimes have to read to be believed. An excellent example is this one from Steven F. Hotze, founder of the Hotze Wellness Center in Houston and owner of a compounding pharmacy that is leading the legal fight against FDA: “Nobody ever did a double-blind study to see if we need water on grass – we just know that. We know they work because our patients get well. That is a scientific experiment of one, and it works over and over again.” One could of course make the same argument for the role of manure on grass.

¹⁶⁰ *Id.*

is absolutely no evidence to suggest, or prove, that compounded BHRT are safer or more effective for treatment of menopausal conditions than conventional prescription hormone drug products.¹⁶²

Not only is there an absence of any comparative data, there is a relative paucity of non-comparative data. The studies cited in the BHRT literature are invariably small, poorly designed, and do not use clinical endpoints for measuring efficacy agreed upon by FDA and the pharmaceutical industry.¹⁶³

Based on the available legitimate, evidence-based scientific data available, Wyeth's claim that some compounding pharmacies are engaged in false and misleading advertising and promotion claims concerning safety and efficacy is correct. Several examples from the Citizens' Petition readily illustrate this point.

Signature Hormone Pharmacy (<http://www.signaturepharmacy.com>) claims multiple grossly untrue benefits for their "natural hormone replacement therapy" including protection against breast cancer and heart disease.¹⁶⁴ The statement that "ideally, there are no side effects since the hormones are given with the intention of restoring normal hormone levels"¹⁶⁵ is at minimum misleading and essentially meaningless. Ideally no drug would have adverse effects, and the intent behind administering hormones is not predictive of whether adverse events will occur. Patients

¹⁶¹ UNITED STATES FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH, REPORT: LIMITED FDA SURVEY OF COMPOUNDED DRUG PRODUCTS, JANUARY 2003, *available at* <http://www.fda.gov/cder/pharmcomp/survey.htm> (last accessed September 19, 2006). Most compounded prescription drug products do not undergo rigorous clinical testing for safety or efficacy, and there are serious concerns regarding the purity, potency, and quality of compounded drug products. From June 2001 to December 2001 FDA analyzed 29 product samples from 12 compounding pharmacies making a variety of different medications. Of the 29 tested, 10 (34%) failed one or more standard quality tests performed. Nine of the ten failing products failed assay or potency tests.

¹⁶² Nachtigall, *supra*, note 120

¹⁶³ *Id.*

¹⁶⁴ Signature Pharmacy™, *Signature Hormone Pharmacy Specializes in Women's Health*, *available at* <http://www.signaturepharmacy.com> (last accessed February 2, 2005).

¹⁶⁵ *Id.*

with normal serum estrogen and progesterone levels may develop reproductive cancers.¹⁶⁶

Village Compounding (www.villagecompounding.com) promotes one BHRT product of “Triple Estrogen” cream (Triest) which is a blend of 10% estrone, 10% estradiol and 80% estriol and points out that bioidentical hormones offer an alternative to all women who have experienced problems with or have concerns about the use of synthetic hormones.¹⁶⁷ But, “synthetic” is not defined and many consumers will either not know that most commercial prescription drug hormone therapies are not synthetic. The website article on safety claims notes that “it’s possible to use identical-to-human hormones, which don’t have any side effects or potential long-term dangers.” This statement is, on its face, completely false, as is a subsequent statement that (human) estriol is “anti-carcinogenic” (in fact, all estrogens have some potential to cause uterine cancer) and that “hormone replacement therapy using native hormone therapy has proven to have fewer side effects.” In reality, no direct clinical trials comparing bioidentical and commercial hormone therapy prescription drug have ever been conducted. In addition, the website states unequivocally that “Estriol...is anti-carcinogenic”, a statement which is medically incorrect.¹⁶⁸

Profile Health (<http://www.profilehealth.com>) is a more sophisticated, Arizona-based website which does not specify particular drugs, noting only “custom” estrogen, testosterone, and progesterone, and which lists a physician among its management

¹⁶⁶ Patsner, *supra*, note 24.

¹⁶⁷ Village Compounding Pharmacy, *Specialty Pharmacist Makes Custom Formulas with High-Tech Equipment and Even Higher Standards*, available at <http://www.villagecompounding.com> (last accessed February 2, 2005).

¹⁶⁸ Nachtigall, *supra*, note 120. “Due to its weaker potency, estriol can never be given in doses equivalent to estradiol, but it still carries risks associated with estrogen. These include endometrial hyperplasia and stimulation of MCF breast cancer cell lines.”

personnel. This compounding pharmacy is geared to “individualizing” the blend of bioidentical hormones based on 4 salivary hormone levels the same lab collects via mail and bills separately for. A “medical professional” analyzes the test results to determine if the individual patients “needs” a natural, bioidentical hormone prescription. The turn-around time is about a week, and the website contains extensive insurance coverage information. The website also contains safety and efficacy claims which are not true, among them “unopposed estrogen patients had a 72% higher cancer of ovarian cancer;” ProfileHealth uses only FDA-approved, natural, bioidentical hormones; “adequate levels of testosterone can help prevent heart disease, stroke, and vascular disorders such as diabetic blindness”; and “taking a natural hormone supplement, to restore a hormone already present in the body to appropriate level, will cause no negative side effects.” At minimum, the statement is highly misleading since there is no significant safety data on bioidentical hormones in the medical literature at all.

One of the worst offenders is Xcel Healthcare (www.xcelhealthcare.com), “a leading provider of pharmaceutical compounding and specialty clinic services.”¹⁶⁹ The provision of natural hormone replacement is one of a panoply of services available through its website. The website contains many medically false claims for its BHRT,¹⁷⁰ among them protection against breast and prostate cancers, protection against cardiovascular disease, normalization of blood clotting, and action as a “natural antidepressant.” The medical literature cited to support the statement that “small doses of estriol [caused] remission or arrest of metastatic tumors” in 37% of postmenopausal

¹⁶⁹ Xcel, *The Technology of Compounding*, available at <http://www.xcelhealthcare.com/techcompound.htm> (last accessed April 5, 2005).

¹⁷⁰ *Id.*

women is from ancient (1978) medical literature and is both false and dangerously misleading.¹⁷¹ No evidentiary basis is provided for any of the safety claims.

The overall impression from all of these BHRT compounding pharmacy websites is a market-driven, non-evidence based effort addressed to all women to promote products with untested and false efficacy and safety claims. All either state or strongly suggest that these products could, or should, replace commercially manufactured prescription hormone therapy drugs with known safety profiles and a long track record of effective treatment for the appropriate conditions they are prescribed for.

b. The Use of Unapproved Estriol

The second reason cited by FDA for its recent crackdown on select pharmacies selling BHRT is that some compounded prescription drug mixtures contains estriol, an ingredient which FDA states it has never approved. Unlike the false promotional claims rational, which can be defended as a legitimate Agency regulation of some compounding pharmacies based on the fact that the activity these pharmacies are engaged in is not true compounding, the estriol rational for enforcement actions against compounding pharmacies is a much different argument. In this author's opinion it is unnecessary if FDA would argue that the prescription drug activities it is attempting to regulate are not really compounding. Absent that, it must be addressed.

There are problems with FDA's statements about estriol.¹⁷² First, FDA's regulation of prescription drug hormone therapy for menopause has been anything but consistent, and an argument could be made that the decision to single out estriol is arbitrary and capricious. FDA has knowingly and willingly allowed Solvay

¹⁷¹ Nachtigall, *supra*, note 120

¹⁷² Galson, *supra* note 7.

Pharmaceuticals in Marietta Georgia to market Estratest® as a prescription drug despite the fact that (1) FDA's own evaluation of the addition of testosterone to estrogen demonstrated only increased risk without any demonstrable benefit; (2) testosterone has never been proven to be safe and effective for treatment of menopausal conditions; (3) no NDA and formal approval for marketing in the United States was ever granted; and (4) there is existing appellate court legal precedent questioning FDA's baffling inability and/or unwillingness to pull Estratest® from the market despite these known regulatory shortcomings.¹⁷³ If compounded BHRT is illegal because it contains estriol, then compounded or commercial prescription HR products containing testosterone or methyl-testosterone are as well.

Second, estriol is one of the three ingredients contained in Tri-Est®, one of the most commonly used prescription BHRT drug products.¹⁷⁴ If estriol's approval status really is an issue, the logic of FDA's position must be that virtually every compounding pharmacy in the United States compounding this, not just those engaged in the questionable false and misleading internet promotional practices, must change its compounding practice. This would effectively put FDA in the position of direct regulation of many if not most traditional compounding pharmacies, something the Agency has stated¹⁷⁵ publicly that it has no interest in doing.

Third, estriol is almost certainly contained in Premarin®, the most widely used commercially manufactured prescription hormone therapy drug product (and one which

¹⁷³ A nice overview of this issue is provided by Prescription Access Litigation, Current Lawsuits, available at http://www.prescriptionaccess.org/lawsuitssettlements/current_lawsuits?id=0012.

¹⁷⁴ MARCIE K. RICHARDSON, COUNSELING PATIENTS ABOUT BIOIDENTICAL HORMONE THERAPY, PROCEEDINGS FROM THE POSTGRADUATE COURSE PRESENTED PRIOR TO THE 17TH ANNUAL MEETING OF THE NORTH AMERICAN MENOPAUSE SOCIETY (October 11, 2006)[Hereinafter Richardson].

¹⁷⁵ Galson, *supra* note 7.

is manufactured by Wyeth Pharmaceuticals, which brought the original Citizen Petition against compounding pharmacies to FDA). Premarin® is derived from pregnant mares' urine and contains dozens or more hormonally active mammalian molecules of which one, estriol, is manufactured by equine ovaries and excreted in the urine. Wyeth has resisted all attempts to fully characterize the chemical composition of Premarin®, in large part to avoid having a generic version of the drug appear on the market. Compounding pharmacies selling BHRT could easily argue that estriol has, in effect, already been approved by FDA.

Fourth, even if not approved, estriol is a well-characterized molecule which has been around for decades. As such, pharmacies could legitimately argue that estriol is no different than multiple other common medications such as Lasix or Digoxin which are mainstays of medical therapy for legitimate medical indications and which have also never undergone the rigorous safety and efficacy testing that new prescription drugs normally do. It could easily be argued that estriol is "GRAS", i.e. generally recognized as safe and effective.

Lastly, any argument based on estriol clearly muddies the waters in trying to come up with a rational basis to distinguish those pharmacies who have received warning letters from those which have not. The advertising and promotion rational for enforcement action by FDA actually does allow FDA to distinguish traditional compounders from those "non-compounders" who in fact are not, by pharmacy industry statements, compounding anymore. A rational based on using estriol in BHRT compounding mixtures does not help FDA discriminate among different compounding pharmacies as use of estriol in drug mixtures is ubiquitous.

VII Justifying FDA's Actions: A New Basis for FDA's Arguments That Some BHRT Compounding Activity is Not Compounding

FDA's announcement that it was issuing warning letters to several compounding pharmacies was accompanied by an explanation of the regulatory basis for FDA's assertion of jurisdiction over pharmacy compounding based on the premise that all compounded prescription drugs are really "new drugs" and FDA's claimed ability to exercise "enforcement discretion." Because FDA is not interested in eliminating pharmacy compounding completely it must choose to interfere only when there is something about the compounded drugs, or their pharmacies, that distinguishes it in some other way from other compounded prescription drugs or pharmacies since all compounded drugs are new drugs.

If this is true, then BHRT drugs and pharmacies must then be separated from other compounded prescription drugs or pharmacies either because of the amount of drug being produced (i.e. the compounding pharmacies are really "manufacturers"), or because their advertising and promotional claims are false and misleading. But, the terms "false and misleading" are terms which only apply to new drugs, ie to drug products FDA has clear jurisdiction over. And, as we have seen, recent federal court decisions have stated that compounded drugs are not "new drugs". What this all means is that if the 5th Circuit Court of Appeals elects not to overturn the federal district court decision in *Gonzales*¹⁷⁶ (as FDA seems to be counting on),¹⁷⁷ FDA will once again have a problem when they return to court, as they almost surely will when their recent enforcement actions are challenged. A new argument is needed

¹⁷⁶ *Medical Center Pharmacy v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex. 2006)

¹⁷⁷ Daniel Meron, *Legal Developments Relevant to FDA Authority*, 62 Food & Drug L.J. 443 (2007). "This case is now on appeal to the Fifth Circuit, and we hope that the Fifth Circuit will place the task of balancing the risks and benefits of compounding back at the FDA – where it belongs."

In this paper I argue for that different approach. The new approach is for FDA to argue that the those pharmacy BHRT compounding activities in question are not legitimate compounding. FDA may do so on two grounds. First, we will show that the global advertising and promotion of these compounds is grossly inconsistent with the entire concept of prescription drug compounding. Second, as we will now argue, FDA may act because the activities in question are not remotely consistent with the Pharmacy industry's own concept of legitimate "individualization" required for the classic triad compounding relationship. As current practiced by some pharmacies compounding BHRT, the individualization is a "sham" because the science behind the pseudo-individualization of dosing is demonstrably "junk medicine."

a. The "Pseudo-Individualization" of Dosing and "Junk Medicine"

The decision to treat a woman with menopausal conditions such as vasomotor symptoms/hot flashes or vulvar-vaginal atrophy is one made by the patient with her physician during consultation and examination arising in the course of the physician-patient relationship. The decision to treat these conditions pharmacologically is one based on physical examination and symptom information the patient provides during her history, not on any measurement of serum hormone levels.¹⁷⁸ The severity of the conditions determined by the degree of symptomatology of hot flashes or vulvar atrophy,¹⁷⁹ and the degree of severity is used to determine if pharmacotherapy is the therapy of choice. This treatment philosophy is the standard practice of medicine in the obstetrics-gynecology community,¹⁸⁰ and is contained in the FDA Guidance for Industry

¹⁷⁸ FDA Estrogen Guidance Document, *supra*, note 91.

¹⁷⁹ *Id.* The determination of menopausal status is based on measurement of serum FSH (follicle-stimulating hormone) and LH (leuteinizing hormone), not serum estrogen or progesterone levels

¹⁸⁰ *Id.*

document¹⁸¹ “Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation.” A key aspect of the recommendations is the selection of the “lowest effective dose” (aka “LED”) of a commercially available drug product for the shortest amount of time for treatment for any given patient.¹⁸² Advocating use of the LED is a cornerstone of pharmacological treatment for these conditions, in part to minimize any drug-related safety concerns based on either too high a dose or treatment for too long a period of time. The initial dose selection, and subsequent dose titration, is based on clinical response only.¹⁸³

There are no valid medical reasons to test for baseline serum estrogen, progesterone, or testosterone levels in normal menopausal or peri-menopausal women even as part of a determination as to whether a woman is menopausal.¹⁸⁴ Serum levels are neither used to start patients on prescription hormone therapy for treatment of menopause-related conditions such as vasomotor symptoms (hot flashes) or vulvar-vaginal atrophy,¹⁸⁵ nor are serum levels of these hormones used to either monitor ongoing therapy nor to adjust the doses of therapy.¹⁸⁶ The medical profession and FDA both make treatment determinations based on presence of symptoms to which lowest effective doses are titrated, and these are individualized determinations. The type of

¹⁸¹ *Id.*

¹⁸² *Id.*

¹⁸³ *Id.* See also clinical guidelines on hormone replacement therapy published by the American College of Obstetricians and Gynecologists (ACOG).

¹⁸⁴ ROBERT T. CHATTERTON, PHD, VALIDATION OF HORMONE TESTING, PROCEEDINGS FROM THE POSTGRADUATE COURSE PRESENTED PRIOR TO THE 17TH ANNUAL MEETING OF THE NORTH AMERICAN MENOPAUSE SOCIETY (October 11, 2006) (“Salivary assays used to measure estradiol and progesterone are generally not recommended for clinical use because of variable concentrations...individual cycles show substantial variability from day to day and are, therefore, of limited value.”)

¹⁸⁵ Richardson, *supra*, note 170.

¹⁸⁶ *Id.*

individualization needed to use BHRT is a worthless medical test; absent this test, there is no basis for the individualized types of preparation of BHRT and no claim of individualized therapy for these products exists. In all instances appropriate dose adjustments are based solely on the clinical response of the individual patient to the particular prescription drug hormone therapy formulation.¹⁸⁷

The use of serum hormone levels to select the dose of a pharmacological agent for treatment of menopausal conditions is, quite simply, incorrect medically, and has been scientifically shown to be worthless in individual patient management. Treatment methodologies proven to be scientifically invalid yet which are used as a foundation for clinical practice that provides no clinical benefit should be defined as “junk medicine”. FDA has the discretion¹⁸⁸ to decide if it will recognize the medical science behind “junk medicine” while at the same time not regulating the practice of medicine. FDA is not telling physicians they cannot practice medicine this way, only that they will not recognize the science as legitimate for purposes of supporting a prescription for a drug.

As bad as use of serum hormone levels for selecting or monitoring of BHRT dosing might be, the use of salivary hormone levels by some pharmacies (and clinicians) is even worse. Simply put, “There is no evidence that hormonal levels in saliva are biologically meaningful.”¹⁸⁹ The junk medicine of salivary hormone levels is necessary, however, if one is going to make the claim that a compounded BHRT drug is

¹⁸⁷ FDA Estrogen Guidance Document, *supra*, note 91.

¹⁸⁸ *Chevron U.S.A. v. Natural Resource Defense Council, Inc.*, 467 U.S. 837 (1984).

¹⁸⁹ American College of Obstetricians and Gynecologists (ACOG) Committee Opinion, Committee on Gynecologic Practice, Compounded Bioidentical Hormones, No. 322, November 2005. The Committee goes on to write “The problem with salivary testing and monitoring of free hormone levels is twofold: 1) there is no biologically meaningful relationship between sex steroidal hormone concentrations and free serum hormone concentrations and 2) there is large within-patient variability in salivary hormone concentrations. Salivary hormone levels vary depending on diet, time of day of testing, the specific hormone being tested, and other variables.”

“individualized.” Absent this claim of “individualization” (which is needed to compound a defined mix of dose ranges, just like commercial prescription drug hormone therapies do), there is no real individual aspect of the therapy which is the heart of pharmaceutical compounding. If the manner in which dose “individualization” is really junk medicine, then we have “pseudo-individualization” of therapy. And, if the individualization of dosing/formulation at the core of the triad relationship is not legitimate, we do not have legitimate compounding. Discredited medical practice means pseudo-individualization of therapy, which means illegitimate compounding.

Ironically, use of the salivary levels may end up placing the patients on a dose of medication which is higher than the lowest effective dose (LED), the treatment standard for hormone therapy of menopausal conditions advocated both by FDA¹⁹⁰ and The American College of Obstetricians and Gynecologists,¹⁹¹ and may be placing patients at higher risk for drug-safety related disease. The medical conditions for which menopausal hormone therapy prescriptions are written include vasomotor symptoms (hot flashes) and vulvar-vaginal atrophy, osteoporosis, and occasionally female sexual dysfunction.¹⁹² There is ample scientific data to demonstrate that commercially available drug products provide proven therapeutic benefit for treatment of the conditions being treated across a wide range of doses and formulations for virtually all women, and an established track record on safety.¹⁹³ By the American Pharmacy Association’s own standards, the use of compounded prescription drugs is not justified when the medical condition to be treated can be just as easily treated with a commercially manufactured

¹⁹⁰ FDA Estrogen Guidance Document, *supra*, note 91.

¹⁹¹ American College of Obstetricians and Gynecologists (ACOG) Committee Opinion, Committee on Gynecologic Practice, Compounded Bioidentical Hormones, No. 322, November 2005, *supra*, note 185.

¹⁹² FDA Estrogen Guidance Document, *supra*, note 91

¹⁹³ *Id.*

prescription drug.¹⁹⁴

A patient's insisting that one receive a "bioidentical" hormone (erroneously believed to be natural even though correctly known to be plant-derived) may be a legitimate patient preference, but preference for one prescription drug product over another is not the same thing as demonstrating that a commercial prescription drug product does not work, i.e. is not safe and effective or is not commercially available in the formulation or delivery system the patient needs. The latter is the standard for prescribing a compounded product instead of a commercially available drug product according to the pharmacy industry's own guidelines. A patient preference for a medication is not the same thing as a legitimate medical indication.

An analogy may be drawn to the choice of generic versus non-generic drugs. A patient may insist that a non-generic medication is the only medication that will meet their needs either because it is what they want or because they believe (erroneously) that generics do not work as well. The patient's need is avoid a generic medication, but if the generic and the non-generic are essentially identical there is no reason not to give the generic. In this situation physicians may even write the prescription for the non-generic, insurers will likely deny the non-generic in this situation and invariably pharmacists will substitute the generic for the non-generic on their own. Why? Because there is no medical reason not to do so. The situation is no different with BHRT and commercial prescription hormone therapy drug products.

¹⁹⁴ Testimony of the American Pharmacists Association before the Senate Committee on Health, Education, Labor and Pensions, "On Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients, October 23, 2003, "...our position is that when an FDA-approved, commercially available product can meet a patient's need, it should be employed as the preferred course of action." *supra*, note 90.

FDA has the discretion to determine what constitutes a medical indication for a prescription drug without being accused of regulating the practice of medicine. FDA also has the jurisdiction to decide whether the scientific basis supporting drug prescribing practices is legitimate,¹⁹⁵ and even if it does not, FDA certainly has the jurisdiction to embrace the findings of the most prestigious medical specialty societies that the science behind select prescribing practices is worthless.¹⁹⁶ The legitimacy of prescription drugs should be based on medical practice that is evidence-based and not rejected by relevant professional societies.

The “individualization” of the dosing for BHRT is a sham for other reasons as well. First, the type of “individualization” of therapy in BHRT is not the type needed to make a compounded drug which is contemplated in the APhA’s and NABP’s definitions of compounding.¹⁹⁷ Electively replacing a commercial prescription drug felt not to be “natural” with a BHRT product is not the same thing as being required to have a drug compounded because no available formulation (e.g. a skin cream) is available for any commercial drug product. Second, commercial hormone therapy prescription drugs are not the one-size-fits-all model some compounding pharmacies have portrayed.¹⁹⁸ In fact, there is little difference between the relatively fixed array of “customized” compounding hormone mixtures and the range of doses offered by already existing commercial drug products. There is a relatively standard set of combinations of products dosing for BHRT, even ones based on worthless salivary estrogen levels, which is directly analogous to

¹⁹⁵ Chevron. *supra*, at 184.

¹⁹⁶ The Endocrine Society Position Statement on Bioidentical Hormones, October 2006, *available at* http://www.endo-society.org/publicpolicy/insider/2006/Postition_Statement_onBHArt1.cfm (last accessed January 23, 2008).

¹⁹⁷ Herbert Testimony, *supra*, note 15.

¹⁹⁸ This comment appears on multiple compounding pharmacy internet website.

those for commercial drug products. Absent a novel formulation or delivery system, there is little substantively unique or individualized about BHRT.

Those pharmacies which arrange to have medical personnel employed or contracted with or who provide laboratory services to measure worthless salivary hormone levels have essentially cut the physician out of the loop and kill the “triad.” By turning the patient relationship into a commercial, direct to consumer advertising relationship where prescription business is actively solicited and lab tests done without the initial involvement of the physician, the physician is little more than a conduit. One could also easily argue that the promotion of various ancillary services and therapies such as “symptom evaluation and corresponding dose adjustment”¹⁹⁹ by compounding pharmacies and pharmacists falls clearly under the practice of medicine. The selection of formulation and dose for a compounded drug, to be legitimately individualized under the “triad” of the compounding relationship, must derive from the interaction of patient and physician. When this relationship becomes simply patient and pharmacists, the triad, and compounding as defined, no longer exist.

The Pharmacy profession might argue that FDA simply has no jurisdiction over compounded prescription drugs, so whether the prescription is based on discounted, discredited, or “junk medicine” is irrelevant. But that cannot be the case if the essence of compounding is the generation of a prescription for a compounded drug for a legitimate medical of a patient. Not all patient needs are legitimate from a prescribing point of view. As noted this is the case for prescriptions for generic medications. And, sometimes the United States government, not the medical profession, gets to decide whether an

¹⁹⁹ Wolf Utian MD, letter to ACOG from North American Menopause Society, Gyn Practice Committee Notes, Pharmaceutical Compounding Outline, Committee on Gynecologic Practice, November 15, 2004.

indication for a drug is legitimate (medical marijuana is a perfect example).²⁰⁰

b. Advertising and Promotion Practices by Select Internet-Based Compounding Pharmacies: The Solicited Wholesale Replacement of An Entire Class of Safe and Effectives Commercially Manufactured Prescription Drug Products” with Compounded Drugs and the Direct to Consumer Advertising Negate the Triad

The national promotion and advertising of BHRT as a wholesale replacement for commercially manufactured prescription drug products known safe and effective for almost all patients takes this pharmacy practice out of the realm of compounding, according to APhA, for two reasons. First, the American Pharmacy Association’s own statements at Congressional hearings.²⁰¹ Second, some large compounding pharmacies are bypassing clinicians directly and advertising directly to consumers, who the return to their clinicians demanding prescriptions for these drugs. The determination for use of these compounds originates with the health consumer, not the physician. The relationship is really one of pharmacy→patient→doctor→pharmacy rather than patient→doctor→pharmacy, a dramatic change from the traditional situation in which a physician realizes that there is no commercially available drug product that can successfully treat the medical condition for which the drug is being prescribed. This direct to consumer advertising to create a non-medical indication or demand for BHRT negates the traditional “triad” at the core of the compounding relationship. The physician is involved only to the extent that he or she is needed to write the prescription. Compounding pharmacies might contend that the advertising is really to physicians and health providers for educational purposes to promote the availability of their products but

²⁰⁰ *Gonzales v. Raich*, 545 U.S. 1 (2005). In this case the Supreme Court held that the dispensing of new, unapproved drugs (in this case Cannabis) had to await federal approval, even when both their physicians and an individual state (in this case California) approved of its use.

²⁰¹ Herbert Testimony, *supra*, note 13.

even a cursory viewing of the websites reveals that the information is directed at consumers.

VIII A New Paradigm for FDA Regulation of BHRT: It Isn't Compounding Anymore

Based on the discussion in section V and VI, we can conclusively state that some pharmacies making BHRT are no longer compounders not because their volume of business has passed a certain tipping point that somehow makes them manufacturers of new drugs, nor because their particular compounded BHRT drugs are “new drugs,” nor because the safety and efficacy claims for some BHRT drugs are false and/or misleading, but because (1) they are advertised and promoted as replacements for safe and effective commercial hormone therapy prescription drugs which meet the patient’s medical need, i.e. safely and effectively treat the medical condition for which the drug is indicated, and (2) there is both discredited junk medical science underlying the individualization of Therapy and the role of the physician may be marginal, both of which defeat the essential ‘triad’ at the core of legitimate pharmacy compounding. As Oliver Wendell Holmes once stated: “A pseudo-science consists of nomenclature, with a self-adjusting arrangement, by which all positive evidence, or such as favors its doctrines, is admitted, and all negative evidence, or such as tells against it, is excluded. It is invariably connected with some lucrative practical application.”²⁰²

IX Conclusion: Where The Controversy Will Likely Go

FDA can, should, and must regulate the select pharmacies marketing BHRT. This new activity may not be either manufacturing or compounding, as defined, but whatever new term it is called it FDA has the statutory authority to regulate it.

²⁰² OLIVER WENDELL HOLMES, THE PROFESSOR AT THE BREAKFAST TABLE, 1839.

Admittedly, much of the BHRT compounding activity in question could not exist, at least in the magnitude in which it exists, without the cooperation of physicians, and the minimal self-regulation of physician practices by their respective professional societies and state medical boards. Exploration of this issue is beyond the scope of this paper, and beyond the regulatory power of FDA as well. These facts are simply additional reasons why FDA must take strong action.

There will likely be legal challenge to FDA's enforcement actions. The Pharmacy industry will likely argue that there is ample judicial precedent protecting pharmacy compounding from FDA encroachment and that regulation of this practice is up to the individual states. Although judicial precedent (*Gonzales, Western States*) will negate FDA's arguments that compounded drugs are either new drugs or that the volume of compounding is so great that the pharmacies are really manufacturers, no current judicial precedent will apply if the pharmacy activity in question can be shown to be something other than compounding. This paper offers an avenue for FDA to argue this very critical point.

There will likely be a grass-roots, "patient empowerment" challenge, similar to that seen with the battle over FDA's attempt to regulate dietary supplements. Will this be DSHEA all over again?²⁰³ One would hope not. Dietary supplements are over the counter and rarely harmful unless taken in extreme amounts (they may be rarely beneficial too, but that is a separate issue). With BHRT we are dealing with prescription drugs, with real drug efficacy claims and indications, and the potential for significant safety issues. This crucial difference makes all the difference. As the recent *Abigail Alliance*

²⁰³ Steven H. McNamara, *Dietary Supplement of Botanicals and Other Substances: A New Era of Regulation*, 50 FOOD AND DRUG L. J., 341 (1995).

decision²⁰⁴ demonstrated, there are limits to patient autonomy and self-determination when it comes to prescription drugs. And time to draw another line in the sand with respect to BHRT.

There will likely be a legal challenge on First Amendment grounds. So be it. Commercial speech protection is not extended to overtly false statements, and the First Amendment is no shield for lying and fraud. Many of the safety and efficacy claims for BHRT clearly have crossed this line. These compounding pharmacies are not entitled to even reach *Central Hudson* this time.

Further regulatory enforcement actions against these, and additional BHRT pharmacies, must follow based on the arguments presented here. Even if the false and misleading advertising and promotion is eliminated, pharmacies engaged in compounding now must avoid any activity which might be construed as advertising and promoting BHRT as a general replacement for commercially available prescription hormone therapy drugs, since this activity is one of the two things which makes them “non-compounders”. The pharmacy industry may attempt to redefine, or restate, what it means to engage in prescription drug pharmacy compounding, as a way of countering this.

More importantly, the ultimate issue is what will come of FDA’s warning letters. FDA has issued warning letters to marketers before as part of FDA’s hormone therapy campaign in 2005, with no result. The issue of FDA regulation of pharmacy prescription drug compounding, even only one slice of the BHRT component of all of compounding, will likely once again be headed for court, hopefully supported by the arguments presented here.

²⁰⁴ *Abigail Alliance for Better Access to Developmental Drugs and Washington Legal Foundation v. von Eschenbach*, 445 F.3d 470 (D.C. Cir. 2006).

14222w