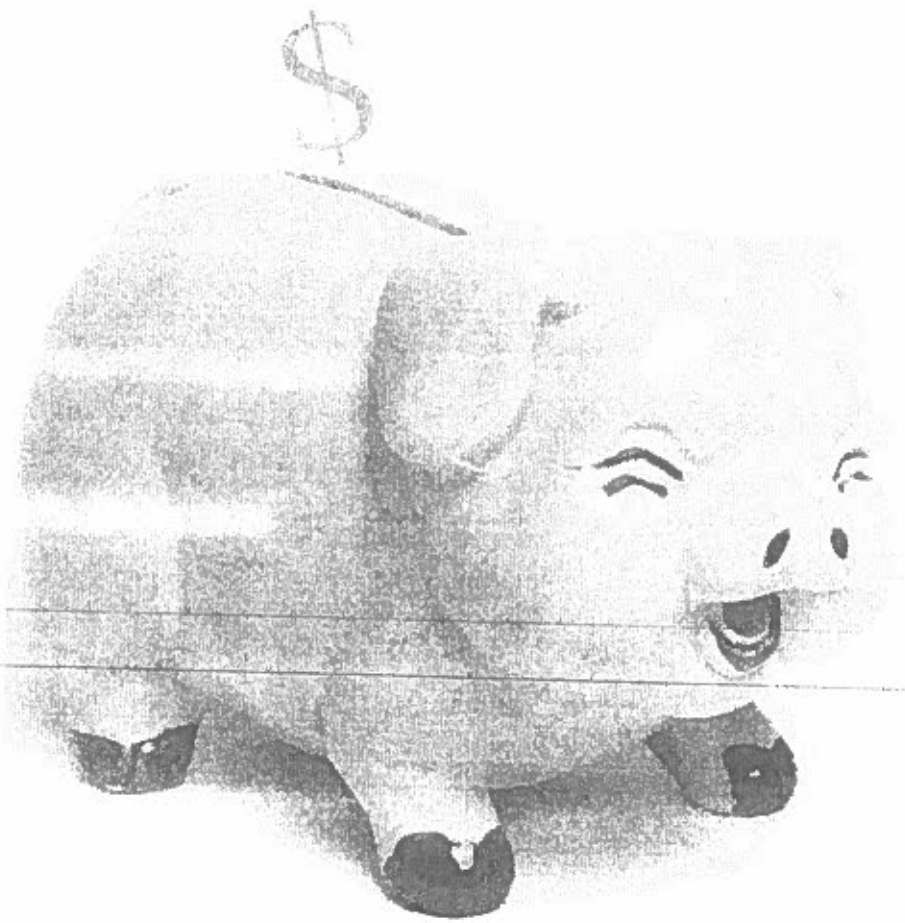
E$TRIOL:

Women's Choice vs. A Manufacturer's Greed

Jennifer Goodrum
International Academy of Compounding Pharmacists
Missouri City, Texas



ABSTRACT

The U.S. Food and Drug Administration recently took action to "halt" the compounding of hormone preparations that contain estriol, an action requested in a citizen petition filed by Wyeth Pharmaceuticals. If the Food and Drug Administration, with the support of Wyeth, is successful in its efforts, women throughout the U.S. who rely on compounded hormones containing estriol will have to discontinue their prescribed treatment. The International Academy of Compounding Pharmacists is engaged in ongoing outreach to ensure that members of Congress recognize the importance of protecting pharmacy compounding for the health and well-being of their constituents. Significant progress has been made with the recent introduction of a congressional resolution in support of estriol.

Estriol—one of three estrogens produced by the female human body—has been prescribed by healthcare providers and compounded by pharmacists for decades. Its use is accepted by all 50 state boards of pharmacy, the United States Pharmacopeial Convention, Inc. (USP), and the Pharmacy Compounding Accreditation Board (PCAB).[1] It is estimated that as many as 80%, if not more, of all compounded hormone preparations contain estriol.

In January 2008, the U.S. Food and Drug Administration (FDA) announced that it would "halt" the compounding of hormones that contain estriol. This announcement was made in the form of a press conference and a series of warning letters sent from the FDA to seven compounding pharmacies. The enforcement actions against estriol were requested in a citizen petition filed in 2005 by Wyeth Pharmaceuticals, maker of manufactured hormone products.

If the FDA's action is allowed to stand, it would force hundreds of thousands of women off of medications that their healthcare providers have prescribed for them—and for no scientific or medical reason. In its press conference announcing this action, the FDA admitted that its actions were not prompted by any adverse event or health issue associated with estriol, nor was the agency even aware of any such events or issues.

While estriol is not a component of an FDA-approved drug, it shares many of the characteristics of an approved drug, as follows:

- It has a long-standing USP monograph
- It has been used successfully and without problems for decades
- Its compounding is allowed by every state board of pharmacy
- It is approved and widely available in European and other countries
- It is a component of a drug now undergoing Phase II/III clinical trials

Congress has recognized that compounded medications may contain active ingredients with a USP monograph, even if they are not components of an FDA-approved drug. In addition, state boards of pharmacy, USP standards, and guidelines for compounding accreditation through the PCAB all permit the use of estriol.

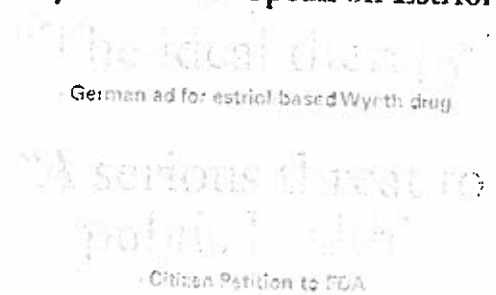
There does not appear to be a precedent for removing from the market a drug ingredient that has a USP monograph absent specific adverse events and health concerns. As such, the FDA's action appears to be directly related to Wyeth's petition to eliminate competition for its products.

WYETH PHARMACEUTICALS' INVOLVEMENT

Citizen Petition Against Compounded Hormones

Wyeth has played a significant role in this issue. On October 6, 2005, Wyeth filed a citizen petition with the FDA requesting actions that would severely restrict the availability of compounded hormone drugs, which are prescribed by licensed medical practitioners and prepared by pharmacists to meet patients' individual needs.

Wyeth Double Speak on Estriol



In its citizen petition, Wyeth stated that hormone drugs compounded with the human estrogen estriol "pose a serious threat to public health" and asked the FDA to take enforcement action against such preparations. According to the news website Pharmalot.com, however, "At the same time the petition was filed, Wyeth was selling Cyclo-Menorette, a menopausal drug, in four European countries (Estonia, Germany, Latvia, and Poland) that contained, yes, estriol." In fact, Wyeth called this product "the ideal therapy to enter into the years of change."

The FDA received a near-record 70,000 public comments in response to the petition, almost all from women and prescribers who wanted to preserve patients' access to compounded hormone therapies. Ignoring those comments, the FDA announced in January 2008 that it will restrict compounded hormones containing this one key form of estrogen. This is something Wyeth and its surrogates asked for in the petition. Unfortunately, the FDA's policy hurts women and helps Wyeth.

Groups and Experts Weighing in Against Compounded Hormones

Lack of Transparency on Their Part

Wyeth has funded a number of supposedly independent health organizations, many of which have publicly supported the company's campaign to restrict women's access to alternatives to its hormone products. Soon after Wyeth filed its citizen petition with the FDA, several organizations that purport to be independent filed public comments in support of Wyeth. In fact, though, each of these organizations has financial and other ties to Wyeth. Nearly all of the few comments filed in support of Wyeth's petition were from organizations with significant financial ties to Wyeth. Unfortunately, these organizations consistently fail to disclose their financial ties to the drug maker when voicing their support. Find out more at www.compoundingfacts.org.

Why is Wyeth Concerned about Alternatives?

The National Institutes of Health Women's Health Initiative (WHI) was cut short in 2002 after the results showed that Wyeth's synthetic hormone products increased the risk of strokes, breast cancer, heart attacks, and blood clots. According to Wyeth's annual reports, sales of Premarin-related products fell significantly, down almost 50% in 2007 from their peak in 2001. Restricting competition could help Wyeth bring its sales back to pre-WHI levels.

Wyeth's Campaign to Protect Market Share

Women's Health is Paying the Price

Wyeth Pharmaceuticals has a long history of campaigning before the FDA, as well as among media and policymakers, to restrict competition to its patented hormone products—Premarin

and Prempro—in order to protect its market share. Unfortunately, this leaves women in need of hormone treatments to alleviate the uncomfortable and distressing symptoms of menopause.

Restricting Generic Hormones

According to a 1997 report from Citizens Against Government Waste (CAGW), a Washington, DC–based think tank, Wyeth waged a political campaign to influence the FDA's decision to keep a generic version of Premarin off the market. In this campaign, Wyeth asserted that its products could not be copied by generic manufacturers. Wyeth claimed that the active ingredients in the conjugated estrogen products could not be identified adequately and, therefore, that there can be no generic copy of Premarin because the precise characteristics of the drug cannot be characterized. Wrote CAGW:

> Although the FDA and Premarin's manufacturer, Wyeth-Ayerst, would like the American public to believe that this decision was in their best interests, the reality is that it was driven by hoards of lobbyists, fraught with conflicts of interest, and characterized by questionable behind-the-scenes political maneuvering.[2]

INTERNATIONAL ACADEMY OF COMPOUNDING PHARMACISTS TAKING ACTION

Understanding the high stakes and far-reaching implications of the FDA's actions against estriol, the International Academy of Compounding Pharmacists (IACP) has committed to the fight to preserve access to this therapy. Upon the FDA's January 2008 announcement of actions against estriol, IACP immediately sprang into action, performing a detailed legal analysis of the FDA's policy, exposing Wyeth's role in influencing the FDA's change in policy to the media, and launching a massive grassroots letter-writing campaign to petition Congress and the FDA to alter this policy.

As a first step, IACP developed detailed legal arguments for why estriol is a permissible component of compounded medicines and why the FDA cannot prohibit the use of the term "bioidentical," another attack by the FDA in estriol warning letters. On February 5, 2008, IACP sent a detailed letter to FDA Commissioner Andrew C. von Eschenbach outlining these arguments and requesting a meeting to discuss the agency's new policy. IACP also provided the legal arguments as a resource to all IACP-member pharmacies that received warning letters from the FDA.

IACP worked with the American Pharmacists Association, the National Community Pharmacists Association, the National Alliance of State Pharmacy Associations, and the American College of Apothecaries to generate a joint letter to the FDA and Congress expressing the pharmacy profession's strong concerns over the FDA's decision and emphasizing the harm that this new policy would do to patients, forcing women who rely on compounded hormones to discontinue their prescribed treatments. The letter, signed by the five pharmacy organizations, was sent on February 1, 2008, to the FDA and Congress.

In mid-March, the FDA sent a notice to pharmaceutical suppliers informing them that the FDA will no longer allow them to distribute estriol to pharmacies or practitioners without an Investigational New Drug (IND) application. In response to this development, IACP organized a joint letter from the affected suppliers to the FDA registering their strong support for compounding and opposition to the agency's new restriction on estriol.

IACP also conducted meetings with staffers from key congressional offices, working with them to develop a congressional response to the FDA's actions. IACP members, constituents, and supportive members of the medical community have all met with congressional representatives to communicate the compounding community's position on the estriol issue.

IACP further organized a letter-writing campaign through the patient and prescriber advocacy organization for compounding, Patients and Professionals for Customized Care (P2C2). More than 10,000 patients, prescribers, and pharmacists have written letters to Congress and the FDA urging them to allow continued access to prescribed hormone treatments. For a comprehensive listing on everything that IACP is currently doing to help patients, providers, and pharmacists preserve access to estriol, visit www.iacprx.org/BHRResources.

RECENT DEVELOPMENTS: IND APPLICATION FOR PRESCRIBING

Not long ago, the FDA adjusted its approach on estriol, clearly feeling the pressure from Congress, patients, prescribers, and the pharmacy profession. The FDA now asserts that practitioners can prescribe compounded estriol but only if they file an IND application. However, IACP has a number of serious concerns with this proposal and does not consider IND filings to be a workable solution for the following reasons:

- The IND process was designed for manufactured drugs and is incompatible with compounded medications. It is impossible for prescribers to meet the voluminous data requirements for IND submissions. Initial applications must contain, for example, a detailed investigational plan; comprehensive clinical protocols; data on drug composition, manufacturing, and controls; toxicol-

Hormone	Naturally Occuring	Bioidentical
Estriol	$C_{18}H_{24}O_3$	$C_{18}H_{24}O_3$
Estradiol	$C_{18}H_{24}O_{24}$	$C_{18}H_{24}O_{24}$
Estrone	$C_{18}H_{22}O_2$	$C_{18}H_{22}O_2$
Progesterone	$C_{21}H_{30}O_2$	$C_{21}H_{30}O_2$

U.S. Food and Drug Administration on Bioidentical Hormone:

1 The term "bioidentical" is misleading and "there is no credible science to back the claim that compounded hormones are biologically identical to the hormones produced by the body."[3]

Various professional medical societies define the term "bioidentical" as indicating that the chemical structure of a hormone drug is identical to that of the hormone produced by the human body. In the cases of estradiol, estrone, estriol, and progesterone, the term "bioidentical" accurately characterizes their chemical structure. They are all identical to those found in a woman's body.

2 **FDA Myth:** No Bioidentical hormone replacement therapy (BHRT) product has met federal standards for approval.

Since 1986, the FDA has approved at least 12 hormone replacement medications that are bioidentical and are marketed as such. Examples include Prometrium, a manufactured progesterone drug approved by the FDA in 1998 and marketed as bioidentical, and EstroGel, an estradiol product approved by the FDA in 2004, which is promoted as "an FDA-approved, bioidentical estrogen replacement therapy."

3 It is unlawful for a pharmacist to prepare bioidentical hormones containing estriol because estriol is not a part of an FDA-approved drug.

A number of drugs are commonly compounded and prescribed even if they are not components of FDA-approved drugs. This practice is long-standing, well accepted, and legal in all 50 states. The use of estriol is consistent with United States Pharmacopeia (USP) standards for pharmacy compounding in chapters <795> and <1075>, and the USP is recognized by Congress as the official standards-setting authority for all prescription medications in the U.S. The use of estriol is also consistent with the standards of the Pharmacy Compounding Accreditation Board. The FDA admitted that it has received no reports of adverse events related to the use of estriol.

4 **FDA Myth:** Compounded bioidentical hormones are unsafe because they are not FDA-approved.

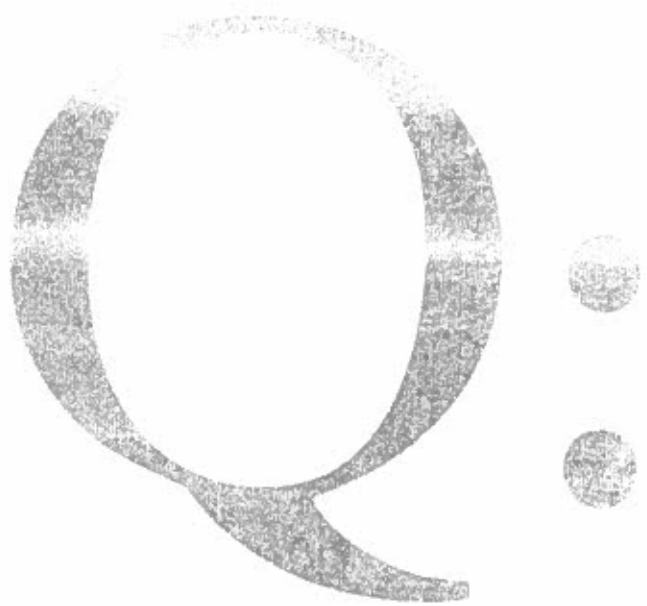
Compounded medications are regulated by state boards of pharmacy and are not subject to federal laws designed to regulate mass-produced drugs. This is because they are customized to meet the unique needs of a patient based on the specific orders of a healthcare provider. The FDA approval process is designed for mass-produced manufactured drugs; it is universally recognized that holding compounded medications to these standards would completely eliminate their availability.

5 **FDA Myth:** BHRT is unregulated.

Bioidentical hormones—like all compounded medications—are made from FDA- and USP-registered materials—the same used by pharmaceutical manufacturers—and their preparation is well regulated by state boards of pharmacy that have responsibility for overseeing all pharmacy practice in each state. Pharmacies that compound medications, including bioidentical hormones, are regulated by state pharmacy boards—similar to the relationship prescribers have with their state medical board. There also are national standards and guidelines for compounded medications. The ingredients and their suppliers are regulated at the federal level by the FDA, with additional oversight provided by the USP.

Is the U.S. Food and Drug Administration (FDA) telling only seven pharmacies to stop compounding with estriol?

It is important to realize that the FDA's new policy against estriol does not affect only pharmacies that received warning letters. Steven Silverman, assistant director with the FDA's Office of Compliance, stated: "We expect...pharmacies [receiving warning letters] and other compounding pharmacies, unless they have an investigational new drug application, to stop compounding [preparations] including estriol." The International Academy of Compounding (IACP) strongly disagrees that pharmacies should have to discontinue compounding using estriol.



Wasn't there an FDA-approved product available in the late 1970s that contained estriol?

There is a misconception that estriol was a component of a former FDA-approved drug product, Hormonin. While Hormonin was commercially available for a period of time and did contain estriol, the product never underwent the FDA approval process and provides no safe harbor. Another product that has been brought to our attention is Organon's Ovestin; however, this product does not appear to have approval in the U.S.

Is IACP supporting bad pharmacies?

IACP consistently advises its members to avoid making claims on websites and in marketing materials. IACP has marketing guidelines available to assist to this end. IACP does not support inappropriate claims; however, the FDA's warning letters go far beyond simply warning pharmacies for making inappropriate claims. The FDA states that the use of estriol in compounded medications is illegal and that the use of the term "bioidentical" is inappropriate. These actions affect all compounding pharmacies and must be vigorously fought.

ogy and pharmacology data; and reviews of published scientific literature on the study drug. This information must be updated through information amendments, safety reports, and annual reports. Prescribers do not have the time or resources to undertake such a submission. Similarly, it would not be feasible for prescribers to undertake this for every compounded drug prescribed for every patient. These are appropriate tests for manufacturers to undertake in the process of bringing a new product to market, not for a practitioner prescribing an individualized, compounded medication for a particular patient.

- There are no streamlined IND procedures that would allow prescribers to submit an IND application for a compounded medication. Any such modifications to IND procedures would be subject to notice-and-comment rulemaking, and thus could not be immediately executed. As a result, prescribers cannot now use the IND process. It could be months or years before the FDA has the right procedure in place. In the meantime, women who are being prescribed hormones with estriol today would be forced to discontinue their treatment.
- Even if the FDA created a new IND procedure for compounded drugs containing estriol, this would not guarantee that women would continue to have access to these prescribed drugs. In fact, the FDA often refuses to even consider manufacturers' IND applications.
- A new IND procedure for compounded drugs containing estriol would only serve to further overwhelm the FDA's system. If thousands of prescribers file applications and request assistance with the new process, the FDA would be prevented from dealing with other INDs. And, if approval for IND applications for estriol is automatic, as the FDA has previously indicated, what is the rationale behind creating a substantial and unnecessary administrative burden for both prescribers and FDA staff?
- The purpose of an IND is to demonstrate the safety and effectiveness of a specific dose and particular dosage form of a drug that will be marketed in that same dose and form. Under an IND, a practitioner cannot prescribe a strength different than that authorized by the IND or adjust the dosing over time to fit a patient's needs. This is entirely inconsistent with the purpose of compounding, which is to provide individual patients with a customized dose and dosage form tailored to meet their personal needs.
- INDs require well-controlled, randomized clinical studies including a placebo or control arm. This means that some enrolled patients do not receive the desired drug. Some of the patients

seeking access to estriol-containing therapy through an IND will not receive the therapy they seek. Worse, because studies are usually blinded to eliminate bias, neither the patients nor their providers will know if they are receiving estriol. Women who are prescribed hormones with estriol expect to receive the drug that was prescribed for them. Indeed, to treat the debilitating symptoms of menopause, they need those drugs. Subjects who receive an IND drug typically are monitored very closely (e.g., multiple clinic visits, blood draws). While this process protects patients taking manufactured products that are being tested for safety and efficacy, these requirements will make participation inconvenient and unpleasant for patients taking compounded medications and would cause prescribers to incur huge costs. Again, these requirements are appropriate for new/investigational products coming to market but not for compounded medications.

The FDA lacks the authority to enforce this policy. The agency claims to derive its authority over compounded medications from the Federal Food, Drug and Cosmetic Act (FDCA). It is this authority that it needs to require practitioners to submit IND applications in order to prescribe compounded hormones containing estriol. A federal court ruled, however, that the FDCA does not subject compounded medications to FDA authority and that it is not in "the best interest of the public health" to do so.

Clearly, the IND procedure does not provide a viable means by which women can receive the estriol that their providers are currently prescribing for them.

INTO THE FUTURE: LEGAL ALTERNATIVES AND CAPITOL HILL

IACP continues to explore legal and legislative options to address the FDA's policy [illegible] due to ongoing litigation in the Midland case (*Medical Center Pharmacy, et al. v. Gonzalez*). At the heart of this case, which began in 2004 when ten pharmacies filed suit against the FDA for improperly criminalizing pharmacy compounding and preventing access to vital, legal bulk drug ingredients, lays the core issue of whether the FDA has authority to regulate compounding pharmacies. In 2006, the court ruled that compounded drugs for humans are not new, unapproved drugs and are not subject to FDA approval, and that pharmacies are exempt from FDA enforcement action. Regrettably, this decision has not brought much change in FDA's demeanor toward compounding pharmacies, as demonstrated by recent actions against estriol. The FDA continues to disregard rulings that are unfavorable to its positions against compounding. This case is currently under appeal and a decision may be issued as early as this summer. The ruling from this case will have a direct impact on the legal status of the FDA's new policy on estriol, and we are taking this into account as we assess our legal recourses.

On the legislative front, significant progress has been made in our campaign against the FDA's new policy to "ban" the compounding of compounded hormones containing estriol. In early May 2008, Representatives Mike Ross (D-Ark.) and Jo Ann Emerson (R-Mo.) introduced a Sense of the Congress resolution that raises direct concerns with the FDA's policy on estriol. The resolution, which includes original co-sponsors Tammy Baldwin (D-Wis.), Michael Burgess (R-Texas), John Carter (R-Texas), Sam Farr (D-Calif.), and Gabrielle Giffords (D-Ariz.), deems the FDA's policy "improper" and urges its reversal. The resolution also affirms that prescribers are in the best position to determine which medications are most appropriate for their patients and that the FDA should respect this important prescriber-patient relationship. Senator John Cornyn (R-Texas) and original co-sponsor Jim Bunning (R-Ky.) introduced a counterpart resolution in the Senate in early June.

This group of legislators has consistently demonstrated their support of pharmacy compounding, and this action is just the latest in a series of their efforts to protect patient access to [illegible]

DO YOUR PART!

IACP applauds those pharmacists who have already written letters to their members of Congress on this issue, but we continue to need your help. Please contact your Senators and Representative and urge them to support HCR 3[illegible] and S. Con. Res. [illegible]. The more [illegible] the louder our message becomes. We need to preserve patient's access to estriol and options in womens' health. Take action today at www.SaveMyBHRT.org

REFERENCES

1. Cyclo-Menorette German ad for estriol-based Wyeth drug; 1996.
2. CompoundingFacts.org. Setting the Record Straight. [CompoundingFacts.org Website.] Available at: www.compoundingfacts.org/info.cfm?News_ID=93. Accessed May 28, 2008.
3. Boodman SG. Hormone Group Protests Crackdown. [washingtonpost.com Website.] February 12, 2008. Available at: www.washingtonpost.com/wp-dyn/content/article/2008/02/08/AR2008020803414.html. Accessed May 28, 2008.

Address correspondence to Jennifer Goodrum, Regulatory Affairs Director, International Academy of Compounding Pharmacists, 4638 Riverstone Blvd., Missouri City, TX 77459. E-mail: jennifer@iacprx.org