Statement

of the

American Pharmacists Association

On Bioidentical Hormones: Sound Science or Bad Medicine?

Before the Special Committee on Aging United States Senate

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The American Pharmacists Association (APhA) welcomes the opportunity to present the pharmacist's perspective on pharmacy compounding and bio-identical hormones. As the medication experts on the health care team, and the front-line health professionals dedicated to partnering with patients to improve medication use, pharmacists have a unique perspective on ensuring that patients have access to safe and effective medications. APhA, founded in 1852 as the American Pharmaceutical Association, represents more than 60,000 pharmacist practitioners, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in improving medication use and advancing patient care. APhA members provide care in all practice settings, including community pharmacies, hospitals, long-term care facilities, managed care organizations, hospice settings, and the military.

APhA supports the Committee's goal that patients receive safe and effective medications. Pharmacists rely upon quality products as the first step in their work to help patients make the best use of their medications. However, when a prescriber writes a prescription for a product that is not commercially available, pharmacists use their scientific training and education to compound the medication. Compounding involves tailoring a medication to meet an individual patient's needs.

Compounding medications is an important component of pharmacy practice. Virtually all practicing pharmacists will be involved with compounding activities at some point during their career—and most practitioners engage in some element of compounding in each week of practice. Because pharmacist compounding activities are a critical component of the American health care system — allowing physicians to prescribe medication therapy to best meet the needs of their patients — APhA has a compelling interest in helping pharmacists, in collaboration with practicing physicians, compound drug formulations to meet the needs of patients.

Our comments provide a brief history of pharmacist compounding, describe the important role pharmacy compounding plays in our health care system, discuss how to distinguish between compounding and manufacturing and the current regulatory system, and describe efforts to improve the quality of the practice of compounding.

Compounding: A Traditional Component of Pharmacy Practice
Compounding is a traditional component of pharmacy practice; only the drugs, dosage forms, and equipment or techniques have changed as pharmacy practice has advanced. As noted in the *Chronicles of Pharmacy*[1], "[p]harmacy, or the art of selecting, extracting, preparing and compounding medicines from vegetable, animal, and mineral substances, is an acquirement that must have been almost as ancient as man himself on earth."

The early practice of pharmacy required the compounding of virtually all medications, because there were few, if any, commercially available products. The need for compounded products has diminished with the founding of pharmaceutical companies, although the need for this practice still exists today. Because the preparation of an extemporaneous pharmaceutical dosage form is not a trivial exercise, we believe that when an FDA-approved, commercially available product

[1] Wootton, A. C. Chronicles of pharmacy. Boston: Milford House, 1971

can meet a patient's needs, 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.

It is a fundamental responsibility of the pharmacy profession to extemporaneously compound quality prescription products for patients who have unique medication needs. Through their education and licensure, pharmacists assume an ethical obligation to the public to maximize the intended benefits of drug therapy while minimizing the unintended side effects and adverse reactions. Compounding enables pharmacists to use their unique knowledge and expertise of medication use to produce individualized, patient-specific medications that meet patient needs and improve health outcomes. Without compounding, pharmacists and physicians would be limited to a "one size fits all" strategy, which would have a direct, immediate, negative impact on the ability of health care providers to provide care to patients.

Compounding: Meeting Otherwise Unmet Health Care Needs

Compounding allows pharmacists and physicians to address the health care needs of patients who do not fall within the range of commercially available dosage strengths and formulations. Patient needs vary from extremely small doses and specific combinations of drugs, to preservative-free products, to liquid dosage forms, to delivery systems that are not commercially available. Without compounding, many patients would not have access to the correct combination of ingredients, the appropriate dose and dosage form, or the route of delivery that best meets their medical needs.

Compounding involves different activities in different pharmacy practice settings. It may mean the preparation of oral liquids, topicals, or suppositories; the conversion of one dose or dosage form into another; the preparation of specific dosage forms from bulk chemicals; the preparation of intravenous admixtures, parenteral nutrition solutions, or pediatric dosage forms from adult dosage forms; the preparation of radioactive isotopes; or the preparation of cassettes, syringes, and other devices with drugs for administration in the home setting. Examples of some of the most commonly compounded products include lotions, ointments, creams, gels, suppositories, intravenously administered fluids and medications, total parenteral nutrition products, and oral suspensions.

In addition to unique patient needs, manufacturing and market limitations may require medications to be compounded. While in many cases it may not be cost-effective for a large-scale manufacturer to tailor-make a medication, in other situations the qualities of a product prohibits its production through manufacturing. For example medications such as radioactive drugs used to diagnose or treat cancers or other diseases must be compounded because they do not have sufficient "shelf life" to withstand the commercial distribution process and therefore need to be prepared at the time of dispensing. Additionally, many manufactured "finished pharmaceutical" products are only "finished" in the sense of being ready to ship and then store in the pharmacy. These products must still be compounded, or in some cases merely reconstituted, by the pharmacist to provide a dosage form suitable for a patient's treatment.

Although compounding may be required in any pharmacy practice setting and for any type of disease, there are concentrations of compounding practice. For example, due to the nature of the care they provide, hospital pharmacies have historically had a strong compounding component to their practice. However, due to the new, more vigorous requirements for sterile compounding, some hospitals are outsourcing their sterile compounding to pharmacies in the community. Therefore, while use of sterile compounding will likely remain concentrated in hospitals, the production of such products is moving to other settings. Finally, due to the nature of the disease

and/or the patient size or age, compounding frequently occurs for patients with cancer, for pediatric care, and for hospice care.

Hospitals
Compounding in the hospital setting is a vital service that addresses the unique needs of patients requiring highly individualized medications. The primary compounding activity in hospitals is the preparation of intravenous admixtures ranging from simple fluid replacement to the delivery of complicated, individualized chemotherapy regimens. Because daily intravenous therapy is provided through compounding of medications, nearly every person who has ever been admitted to a hospital –and those who will be admitted today and likely in the future– has received a compounded medication. In fact, the immediate availability of extemporaneous compounding by a pharmacist provides the hospital physician with literally any form or strength of medication needed for a patient's specific needs.

Cancer and Pediatric Patients
Cancer patients frequently benefit from compounding pharmacists' knowledge and skills. Almost all chemotherapy involves drugs and drug combinations that are compounded, or at least reconstituted, by pharmacists. It is imperative that a patient receive the correct drug dosage based upon the patient's body size, the type of cancer, the size and type of tumor, and the clinical condition of the patient including their kidney and liver function. This can often only be accomplished by using compounded, patient-specific medication preparations.

The compounding of pediatric dosage forms has also been an area of extensive activity, because many drugs used to treat children are only available in adult dosage forms. Finding the right drug, dose and dosage form to treat sick children is a complicated task. Congress has made great strides in establishing incentives to improve the utility of manufactured products in treating children. And this year's discussions of reauthorizing the Prescription Drug User Fee Act (PDUFA) have highlighted the continued need to enhance this area of research and development. Despite these efforts, compounding is frequently the only available avenue to achieve the desired clinical outcomes for pediatric patients. Absent a pediatric formulation, commercially manufactured products for adult use must be modified and compounded for use in children. It has been estimated that more than 40% of doses given in pediatric hospitals require compounding to prepare a suitable dosage form[2]. Clearly, utilization of compounded medications is essential for the provision of medical care to hospitalized children**.**

Hospice Patients
As the Committee is aware, hospice programs provide care for patients near the end of their lives who can no longer benefit from curative treatment and generally have a life expectancy of six (6) months or less. Patients suffering from incurable cancer have very special needs. Relief of pain near the end of life is an important element of maintaining the dignity and comfort of a dying patient and their loved ones. Hospice patients often need medications to alleviate pain and to control nausea and vomiting for patients in the hospice setting. Unfortunately for many hospice patients, pain medications are often not manufactured in the required dosages. Additionally, some patients are not physically capable of swallowing the number of commercially manufactured tablets or capsules required or cannot take medications orally. If commercial products that provide the precise dose(s) required are not available, the hospice pharmacist can often remedy the situation by extemporaneously preparing an individualized product. A pharmacist can address these issues by either compounding a stronger product, by transforming tablets or

[2] Pain Palliat Care Pharmacother, 16(4): 71-78, 2002

capsules into a liquid, or by creating a preparation that can be applied topically or delivered rectally.

BHRT
APhA's position on pharmacy compounding stands, regardless of the specific medication. In fact, APhA does not take positions on specific medications or categories of medications. That being said, the Committee is holding this hearing to address, at least in part, the issue of bio-identical hormone replacement therapy (BHRT). To provide the Committee some perspective, we asked a small group of our members to share their experience with BHRT. Every pharmacist who responded had worked with physicians to manage women's health and BHRT had provided these women relief from symptoms that either commercially available products were unable to address or that commercially products created. However, once again, APhA does not have a position on BHRT. As long as a product is compounded based upon a valid prescription from a "triad" relationship in which the patient's physician has decided that the compounded product is necessary to meet the patient's individual health care needs, and the product is not commercially available, then the compounding is appropriate. There are risks with all medication, whether manufactured or compounded. It is the responsibility of prescribers, working with patients and pharmacists, to determine whether the benefits of a medication outweigh the risks.

Compounding vs. Manufacturing
One question that continues to plague the profession and our regulators—the state boards of pharmacy—is how to distinguish between compounding and manufacturing; with one practice regulated by state boards of pharmacy and the other process, by the Food and Drug Administration (FDA).

Compounding has traditionally been characterized by the triad relationship of the physician, pharmacist and patient working together to individualize care for maximum patient benefit. Pharmacy compounding is performed in response to a prescription from a licensed prescriber, or in preparation for a reasonably anticipated prescription, based upon prior experience and expected needs of individual patients.

APhA supports the National Association of Boards of Pharmacy's[3] (NABP) definition of compounding, which states:

> "Compounding" means the preparation of components into a drug product (1) as the result of a practitioner's prescription drug order or initiative based on the practitioner/patient/pharmacist relationship in the course of professional practice, or (2) for the purpose of, or as an incident to, research, teaching, or chemical analysis and not for sale or dispensing. Compounding includes the preparation of drugs or devices in anticipation of receiving prescription drug orders based on routine, regularly observed prescribing patterns.

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. Rather, the definition supports our assertion that the purpose of pharmacist compounding is to prepare an individualized drug treatment for a patient based on an order from a licensed prescriber.

Manufacturing, on the other hand, is defined by NABP as follows:

[3] NABP's Model State Pharmacy Act and Rules (August 2006)

> "Manufacturing" means 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. Manufacturing includes the packaging or repackaging of a drug or device or the labeling or relabeling of the container of a drug or device for resale by pharmacies, practitioners, or other persons.

As clear as this difference may seem to the profession of pharmacy, it has been a difficult distinction to implement because of the complexity and range of legitimate compounding activities. In public comments, even the FDA has suggested that the difference between compounding and manufacturing is better represented by the intersection of two jagged jigsaw puzzle pieces rather than a straight line.

The fundamental difference between compounding and manufacturing, and the key element in making any such distinction, is the existence of a pharmacist/prescriber/patient "triad" relationship. This triad should control the preparation of a drug product. Furthermore, compounded drugs are not for resale, but rather, are personal and responsive to a patient's immediate needs. Conversely, drug manufacturers produce batches consisting of millions of tablets or capsules at a time for resale, while utilizing many personnel and large scale manufacturing equipment, without knowledge of the specific patient who will ultimately consume them. And finally, compounding should not occur when a commercially available product is available.

The Current Regulatory System
A strong regulatory system exists for pharmacy compounding. State Boards of Pharmacy take the lead in regulating pharmacy compounding while the Food and Drug Administration plays a role when compounding crosses the line into manufacturing.

State Boards of Pharmacy
Pharmacists and pharmacies are licensed by States Boards of Pharmacy. Every state has a Pharmacy Practice Act and Board of Pharmacy Regulations that are used to regulate the profession. After sections of the Food and Drug Administration Modernization Act (FDAMA) were struck down, there was a flurry of activity by State Boards of Pharmacy to further clarify what is meant by pharmacy compounding and to explore legislative and regulatory changes to more clearly articulate the boundaries of practice for pharmacists in their jurisdiction.

Food and Drug Administration
As stated above, the FDA, which primarily regulates manufacturers, also plays a role in regulating compounding. Pharmacists rely on the FDA for strong, consistent regulation of pharmaceutical manufacturing and on the FDA to assure that these processes yield a safe and effective product.

The current regulatory system reflects the strengths of each agency and ensures patient access to medications that would otherwise be unavailable.

In the Courts
In addition to the statutory authority provided in the Food and Drug Administration Modernization Act of 1997 (21 U.S.C. § 353a), strong case law exists for exempting compounded medications from the FDA new drug approval process. In *Tommy G. Thompson, Secretary of Health and Human Services, et al., Petitioners v. Western States Medical Center et al*. in 2002, the United States Supreme Court ruled that "The Government argues that eliminating the practice

of compounding drugs for individuals would be undesirable because compounding is sometimes critical to the care of patients with drug allergies, patients who cannot tolerate particular drug delivery systems, and patients requiring special drug dosages. Preserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important governmental interest, and the Government has every reason to want as many drugs as possible to be subject to that approval process. The Government also has an important interest, however, in permitting the continuation of the practice of compounding so that patients with particular needs may obtain medications suited to those needs. And it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process. Pharmacists do not make enough money from small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible, so requiring such testing would force pharmacists to stop providing compounded drugs." (122 S.Ct 1497)

More recently, federal district court Judge Robert Junell ruled in *Medical Center Pharmacy v. Gonzales* in 2006, "Public policy supports exempting compounded drugs from the new drug definitions. If compounded drugs were required to undergo the new drug approval process, the result would be that patients needing individually tailored prescriptions would not be able to receive the necessary medication due to the cost and time associated with obtaining approval. When a licensed practitioner writes a prescription for a compounded drug for a patient, the medication is normally needed soon thereafter. It is not feasible, economically or time-wise for the needed medications to be subjected to the FDA approval process. It is in the best interest of public health to recognize an exemption for compounded drugs that are created based on a prescription written for an individual patient by a licensed practitioner. […] Compounded drugs, when created for an individual patient pursuant to a prescription from a licensed practitioner, are implicitly exempt from the new drug definitions." (451 F.Supp 2d 854)

All compounding in response to a specific patient prescription remains within the realm of pharmacy practice; and because pharmacy practice is regulated by State Boards of Pharmacy, Boards are the primary enforcers of pharmacy compounding. It, through its own investigative process, a State Board of Pharmacy determines that a pharmacy is manufacturing, then it is appropriate for the FDA to get involved. The FDA's current inspection and enforcement authority over pharmacy compounding is sufficient.

Continuous Quality Improvement

As professionals, pharmacists continually strive to provide the best patient care possible, including continuous review of practices and taking steps to improve medication use and advance patient care. Pharmacy compounding conforming to the highest possible professional standards is essential to optimal patient care. Maintaining quality and advancing practice requires the profession to be vigilant, and continually improve our professional standards and regulatory efforts. Two organizations supplement the state legislative and regulatory efforts described above. The Pharmacy Compounding Accreditation Board (PCAB) and the USP are central to ensuring that patients receive safe and effective compounded products.

Pharmacy Compounding Accreditation Board

One of the more recent steps the profession has taken to advance compounding practice as part of our ongoing commitment to providing safe and effective pharmaceutical care to patients was the creation of the Pharmacy Compounding Accreditation Board (PCAB). Founding members of PCAB include the American College of Apothecaries, the American Pharmacists Association, the International Academy of Compounding Pharmacists, the National Association of Boards of Pharmacy, the National Home Infusion Association, and the United States Pharmacopeia.

These groups saw the value of voluntary programs to improve compounding activity. The initial work of PCAB included the development of compounding principles that must be followed by pharmacies that choose to be PCAB accredited. The PCAB principles are as follows:

- Compounding is the preparation of components into a drug product either as the result of a practitioner's prescription drug order based on a valid practitioner/patient/pharmacist relationship in the course of professional practice, or for the purpose of, or as an incident to, research, teaching, or chemical analysis that are not for sale or dispensing. Compounding is a part of the practice of pharmacy subject to regulation and oversight from the state boards of pharmacy. Compounded medication may be dispensed to prescribers for office use, where applicable state law permits. Office use does not include prescribers reselling compounded medications.

- Compounding may be conducted in anticipation of receiving prescription orders when based on routine, regularly observed prescribing patterns. Anticipatory compounding is limited to reasonable quantities, based on such patterns.

- Compounding does not include the preparation of copies of commercially available drug products. Compounded preparations that produce, for the patient, a significant difference between the compounded drug and the comparable commercially available drug product or are determined, by the prescriber, as necessary for the medical best interest of the patient are not copies of commercially available products. "Significant" differences may include, for example, the removal of a dye for a medical reason (such as an allergic reaction), changes in strength, and changes in dosage form or delivery mechanism. Price differences are not a "significant" difference to justify compounding.

- Both the prescriber (via the prescription) and the patient (via the label) should be aware that a compounded preparation is dispensed.

- The pharmacy may advertise or otherwise promote that it provides prescription drug compounding services. Such advertising should include only those claims, assertions, or inference of professional superiority in the compounding of drug products that can be independently and scientifically substantiated.

United States Pharmacopeia
In addition to the collective effort represented by PCAB, individual organizations have pursued improvements in pharmacy compounding practice. The United States Pharmaceopeia (USP), the official drug standard setting body for our country, has a long history of addressing pharmacy compounding. The USP establishes standards for compounding medications. Recently, the USP has strengthened its USP Chapter <795> Nonsterile Compounding and USP Chapter <797> Sterile Compounding standards.

Conclusion
Through compounding, pharmacists fulfill a legitimate and essential need –providing patients with medications tailored to their needs. The professional education and training of pharmacists provides the unique knowledge and skills necessary to fulfill this health care need. By working together, prescribers and pharmacists help patients access otherwise unavailable therapies such as cream for breast cancer patients' radiation burns, or anticonvulsants in a suppository form when patients' veins are not accessible for injection. Without compounding, many physicians, pharmacists and patients would lose access to valuable treatments.

APhA supports the Committee's efforts to discuss this important issue and appreciates the opportunity to share the perspective of pharmacists on this issue. While pharmacist compounding improves patients' lives every day, we must continually improve our practices to provide the best patient care. Improving our efforts to provide quality compounded products will require collaborative efforts of consumers, the profession, State Boards of Pharmacy, and the FDA. Each stakeholder has an expertise that is essential in assuring the continued availability of this practice with the quality patients deserve.

Consumers must play a role in all of these efforts, as we are pursuing this work for them. The profession must take the lead in guiding the regulatory agencies in how to draw the line between compounding and manufacturing, and in developing guidelines and voluntary accreditation or certification processes to demonstrate compliance with those guidelines. The State Boards of Pharmacy, responsible for regulating the profession, should maintain their primary regulatory role of pharmacy practice, including compounding. The FDA has a role in regulating manufacturers, as well as defining some broad guidance, such as the identification of substances that should not be used in manufacturing or compounding because the substances have been withdrawn from the market for safety and efficacy concerns.

All of these efforts require collaboration, coordination, and ongoing communication. To that end, pharmacists are ready to partner with stakeholders to develop effective strategies to improving the quality of compounding practices. Thank you for the opportunity to present the views of the nation's pharmacists. APhA looks forward to working with the Committee to ensure that patients are receiving quality compounded products.