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May 3, 2013

The Honorable Tom Harkin  
Chairman  
Senate Committee on Health, Education,  
Labor and Pensions  
428 Dirksen Senate Office Building  
Washington, DC 20510

The Honorable Lamar Alexander  
Ranking Member  
Senate Committee on Health, Education,  
Labor and Pensions  
835 Hart Senate Office Building  
Washington, DC 20510

Dear Chairman Harkin and Ranking Member Alexander:

On behalf of the physician and medical student members of the American Medical Association (AMA), thank you for your leadership in seeking bipartisan legislation that balances the serious safety concerns regarding certain compounding pharmacy practices with the need to ensure medically necessary treatments tailored to meet specific patient needs. In general, the AMA supports various elements of the draft legislation. Outlined below are a number of areas where we believe modifications or clarifications are needed that would strengthen the bill.

As a threshold matter, we understand that Congress and the Food and Drug Administration (FDA), along with state regulators, are confronted with difficult oversight and accountability questions as they relate to compounders, particularly those engaged in large scale, interstate compounding. We share your concern for the need to clarify appropriate federal and state roles for the oversight and regulation of compounding, especially sterile compounding of injectable drug products, in a way that will help ensure the safety of compounded drugs regardless of their production site or origin.

We agree a need exists to strengthen federal oversight of compounding activities that represent a higher degree of patient safety risk and, therefore, generally support establishing a clear distinction between regulation and oversight of compounding manufacturers (as defined) and traditional compounders that typically have been subject to state oversight. The design and implementation of effective changes must be accomplished in a manner that recognizes the widespread nature of compounding practices and the current reliance that hospitals, ambulatory care centers, and individual physician practices place on the ready availability of such products for day-to-day activities, and provision of patient care, including emergency procedures.

The AMA supports the provisions that would govern compounding manufacturers, including:

- ensure direct supervision over the operations of the compounding manufacturer by a pharmacist licensed in the state where the compounding manufacturer is located;
- FDA filings every six months that include, among other key pieces of information, a list of drugs compounded during the previous six month period;

- adverse event reporting to the FDA;
- the outlined labeling requirements; and
- registration and re-inspection fees.

An additional benefit of the registration requirement will be to establish the universe of compounding pharmacies and to better define current market segments.

### **Areas of Concern**

Deeming of Compounded Drugs as “New” Drugs. We have concerns about the impact of deeming drugs currently compounded as FDA regulated new drugs. We understand that such drugs would not be subject to all of the FDA-approved new drug requirements and others, such as those related to risk evaluation and mitigation strategies (REMS), could potentially be modified. A fuller discussion with stakeholders and the FDA would prove helpful to better understand the intended consequences and to identify any unintended and unwelcome consequences. For example, how would this status impact the framework for FDA-inspections, expiration dating and product labeling? (see below)

Definition of Compounding Manufacturer. The definition of “Compounding Manufacturer” should be based on processes and product risk. Thus, we would agree that bulk manufacturing of sterile products for introduction into interstate commerce, in the absence of a prescription order should place the facility into this category. The Committee also may wish to examine whether other factors exist (alone or in combination) that affect patient safety risk to the extent that federal oversight is advisable. These may include such elements as the product volume and/or the compounding processes used (i.e., non-sterile-to-sterile batch compounding) and (as noted in a following section) drugs that should not be compounded, due to difficulties or uncertainties in ensuring safety, effectiveness, or product integrity.

### **Definition of Traditional Compounding**

We also generally support the provisions of the draft legislation defining a **traditional compounder**. However, we request further clarification in a number of areas.

Anticipatory Demand/Office Stock. Some discretion is required to define what constitutes compounding of “limited quantities” for purposes of qualifying as a traditional compounder, but we are requesting additional clarification of congressional intent as this is subjective and could vary. It is our interpretation that the general definitions supplied permit physician practices to maintain an adequate office stock designed to address typical, as well as, urgent or emergency-based procedures.

Health System Exception. We agree that there is a need to provide an exception for compounding pharmacies **within a health system**, but clarification is required with regard to the various references to Section 506F in the draft legislation. Section 506F governs hospital repackaging of drugs in shortage. Is there any expectation that the current legislation would modify or change section 506F? If so, how? Repackaging traditional bulk oral dosage forms into unit of use doses and “repackaging” of bulk sterile product into vials or syringes intended for individual patients are different activities; the latter is defined as compounding in this legislation. It would be helpful to understand the interplay and impact of this legislation on practices within health systems. We also believe that

Congress and all impacted stakeholders should understand the scope of this exclusion—how many systems this would impact, the volume of interstate activity implicated (as state federal oversight would be ambiguous under this exclusion), and the health system checks and balances to ensure safety that should be in place. We also interpret this exclusion to apply to products that are compounded within a hospital pharmacy as opposed to products that are outsourced and obtained from an external compounding pharmacy. We would have significant concerns with the current scope of this exception if it also applies to compounded products obtained from one hospital in the health system from an outsourced compounding facility and, then shared throughout the health system including interstate transfers.

FDA Approved Marketed Drugs. The AMA agrees that compounding pharmacies should not be permitted to make copies of a marketed approved drug, but believe explicit definitions of “copy” and “variations” are needed. We understand that the legislation provides that compounded variations are permissible if it produces a “significant difference” as determined by the prescribing practitioner. We strongly support that the determination of significant difference rests with the prescribing practitioner and urge you to clarify that the determination of significant difference should be based on an individualized, patient-centered assessment, and not imputed solely from population based studies. We also request clarification that an adequate amount of office stock could be available for emergency situations.

Drug Removed for Safety and Efficacy. The AMA understands that certain drugs that the FDA has removed from the market based on safety and efficacy concerns, should not be compounded. However, we urge Congress to clarify that this provision is not intended to prevent compounding of drugs that are on the unapproved drug list such as, certain electrolyte solutions, but do not pose apparent safety or efficacy concerns.

Prohibited Compounding Drug List. The legislation provision that would prohibit the compounding of certain drugs and biological products requires additional clarification as well. In the absence of agreed upon criteria, the authority to establish an “Interim List” is potentially problematic. We agree that, based on their nature *per se*, biological products carry a higher risk of potential problems related to stability, chemical features, etc., whenever they are manipulated. Given the wide variety of factors that may influence patient safety risk, we would urge that a science-based process involving expert input be established to address this issue.

### **Other Requirements**

Among the other requirements applicable to compounding manufacturers are those related to labeling. In addition to the technical challenges that may exist for labeling small vials or pre-filled syringes with this information, an additional concern is the evidence base which is used for establishing beyond-use dating for sterile compounded products.

### **Reference to United State Pharmacopeia Standards**

As a member organization of the United States Pharmacopeia (USP) Convention, the AMA has great respect for the standard setting activities of USP. We would note that in reference to the USP chapter on pharmacy compounding that two such general chapters exist: (797 on Sterile Compounding and

The Honorable Tom Harkin  
The Honorable Lamar Alexander  
May 3, 2013  
Page 4

795 on General Compounding). Furthermore, references exist within those chapters to other USP General Chapters.

We would also note that “new” drugs are subject to current Good Manufacturing Practices. Such practices are process-directed and based on a system of specific standard operating procedures that FDA evaluates for adherence within the manufacturer’s quality control system. While USP general chapter 797 also provides a set of standards, these comprise a broadly defined group of procedures that should be applied when compounding sterile products only in small batches. Therefore, some clarification is needed on what the framework would be for FDA-inspection of compounding manufacturers.

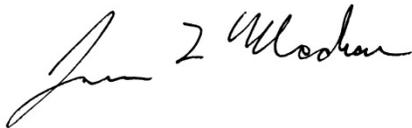
### **Relationship to Drug Shortages**

As everyone is aware, physicians and patients are grappling with persistent shortages of basic therapeutic treatments, particularly those generally in the category of sterile injectables. We believe that additional steps are needed to address these persistent ongoing shortages as these shortages may be driving the demand that supports significant output by compounding pharmacies distributing across state lines. The AMA appreciates the efforts to review this legislation to ensure that it does not inadvertently exacerbate persistent shortages.

In light of the foregoing, the most significant substantive modification that we urge you to incorporate would be to modify the provision permitting compounding of FDA-approved marketed products that the FDA has identified as being in shortage. We urge you to consider that there are recurrent regional shortages that may not be reflected on the FDA shortage list. We recommend a modification of this provision that allows state pharmacy boards to identify drugs in shortage, within their state that would permit compounding where it would otherwise be prohibited for FDA approved marketed drugs during the shortage period.

We appreciate the opportunity to address this issue of significant importance to physicians and their patients. We believe that the legislation in general, with some modifications, will enhance accountability, quality, and safety. The AMA welcomes the opportunity to engage with Congress, the FDA, and other stakeholders to address the issues raised in this letter.

Sincerely,

A handwritten signature in cursive script, appearing to read "James L. Madara".

James L. Madara, MD