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BY ELECTRONIC SUBMISSION: http://www.regulations.gov
Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

Re: Docket No. FDA-2013-D-1444: Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act. Draft Guidance.

Dear Sir or Madam,

The Pew Charitable Trusts applauds the Food and Drug Administration for the swift release of initial guidance to implement Title I of the Drug Quality and Security Act (DQSA), as well as section 503A of the Food Drug and Cosmetic Act (FDCA) which is now uniformly enforceable due to amendments made by Title I.

Herewith please find our comments on the draft guidance on pharmacy compounding under section 503A, and related enforcement issues. We would like to address five topics:

- Anticipatory and Office stock compounding
- Quality standards
- FDA / state coordination
- MOUs to address inordinate interstate shipment of compounded drugs
- Use of bulk drug substances

Anticipatory and Office stock compounding

Anticipatory compounding is the creation of a drug product prior to receipt of a prescription. Office stock compounding is the creation of a standardized drug product to be kept as stock in a doctor's office or hospital. By definition such products are not compounded pursuant to an individual patient prescription.

Although section 503A does not discuss office stock compounding explicitly, it allows compounding in advance of a prescription only in "limited quantities" in order for a compounder to receive exemptions from federal law on drug approvals, GMPs, and labeling. The term "limited quantities" has not been defined, and this lack of clarity has perpetuated confusion about what amount of anticipatory compounding is permissible. The FDA should clarify 503A by defining "limited quantities" through guidance.

FDA enforcement activities for section 503A will also directly affect the success of section 503B – which establishes a new voluntary category of FDA-regulated "outsourcing facilities". This regulatory category offers a clear legal pathway for the compounding of sterile drugs without a prescription under FDA oversight and higher quality standards. If traditional compounders are able to continue to produce office stock products indiscriminately this will discourage registration under 503B. Compounders will not see sufficient advantage in meeting the higher quality standards and submitting to other limitations, such as a list of allowable bulk drug substances for use in compounding.

Many compounders produce medicines for office use, and while some will elect to register with the FDA, others will not. When examining those that do not register, the FDA should focus its enforcement resources on compounders producing large volumes of office stock medicine, because of the greater patient exposure if a serious product contamination were to occur, and the additional risk associated with latency between product compounding and patient use. The FDA should work with states to identify these facilities, and encourage them to register with the FDA.

Quality standards

Within language related to the use of bulk drug substances in compounded products, section 503A includes an expectation of compliance with United States Pharmacopeia (USP) chapter on compounding. In your guidance, you correctly note that USP now has two chapters on compounding: chapter <795> presenting general requirements and chapter <797> which is specific to sterile compounding.

While USP standards are not appropriate to ensure the quality of large-scale compounding that is closer to drug manufacturing, they are very important as a minimum standard for traditional compounding. The FDA should work with states to ensure that USP standards are applied and that adherence is monitored.

Although not a subject of this guidance, compounding "outsourcing facilities" that register with the FDA must now meet applicable Good Manufacturing Practice (GMP) requirements. The FDA should issue guidance on which GMP standards will be prioritized for use in inspections of outsourcing facilities.

FDA/State coordination

Coordination between the FDA and state regulators on oversight of drug compounding will be critical for the enforcement of section 503A, as well as the success of section 503B

Section 503A applies to all pharmacies that compound drugs (except facilities that register with the FDA and meet 503B requirements). But FDA does not have the resources or the mandate to oversee compliance for all compounding pharmacies in the United States. State regulators and the FDA must work in collaboration to monitor for compliance and identify facilities that are not meeting 503A criteria to receive exemptions from federal requirements for drug approvals, good manufacturing practices, and labeling. This collaboration should also include identification of pharmacies whose compounding

business models are more appropriate to FDA regulation under the voluntary 503B category, and encouragement of their participation.

The FDA should also engage with states regarding section 503B. We strongly urge the FDA to begin inspections of outsourcing facilities as soon as possible and to inform states about oversight provided to outsourcing facilities in their jurisdictions. States should also be encouraged to proactively share information about identified violations of 503A as well as any actions taken against compounders. Such communication could be required under an MOU framework as discussed below.

Section 503B is clear that any product made at a facility registered under 503B must meet the requirements set by 503B. However states should continue to regulate facilities that continue to operate as traditional pharmacies, even if owned by an entity that also has 503B facilities.

MOUs to address inordinate interstate shipment of compounded drugs

Section 503A contains a specific framework for FDA/State collaboration: the law limits the amount of compounded medicine a firm can ship out of state to 5 percent of all prescriptions unless the state in question has a memorandum of understanding (MOU) in place with the FDA to address the inordinate interstate shipment of compounded drugs.

We support FDA's expressed intention in this guidance to promulgate a draft MOU to implement this provision. Looking broadly at the amount of compounded products shipped interstate is not, however, the most meaningful way to address activities that present the highest patient risk. In an earlier draft MOU the FDA set the threshold for inordinate interstate shipment of compounded drugs at 20% of all prescriptions dispensed/distributed, or for a single compounded product 5% of all prescriptions dispensed/distributed. These percentages may represent very different volume amounts depending on the size of the business in question, and further do not take into account other important differences, such as whether or not the products were compounded pursuant to patient-specific prescriptions.

We encourage the FDA to consider including alternate parameters in the MOU to address high-volume, high-risk compounding. These could include a focus on compounders that primarily produce office stock products or compound in anticipation of prescriptions at a large scale; compounders that sell to another dispensing entity rather than dispensing drugs directly to patients; and sterile versus non-sterile compounding.

If percentage thresholds are still used, they should be much lower than 20% for sterile products not produced pursuant to individual patient prescriptions, as section 503B now allows outsourcing facilities to compound sterile drugs without a prescription under FDA oversight, and contains no limitation on the volume of drugs shipped across state lines. This decreases the need for traditional compounders to ship compounded office use products interstate.

MOUs should also ensure states share information with the FDA on known and potential violations of federal statute and serious adverse events. Section 105 of the Drug Quality and Security Act (DQSA) requires FDA to establish a process for the agency and states to share information on identified

violations of 503A as well as any actions taken against compounders. This information-sharing is voluntary for states. MOUs should require states to provide this information to the FDA, and should additionally require the sharing of information on potential violations of 503A to help direct FDA oversight, as well as serious adverse events related to compounded products.

Use of bulk drug substances

Section 503A allows compounders to use bulk substances on a list set by FDA, in addition to substances that are part of an approved drug application or the subject of a USP monograph. We support FDA's statement in this draft guidance that until the Agency promulgates a final list of such drug substances, compounders should only use bulk drugs that are components of an approved drug or have a USP monograph.

We look forward to ongoing engagement with the Agency as Title I of the Drug Quality and Security Act and Section 503A of the Food Drug and Cosmetic Act are implemented.

Sincerely,

Allan Coukell
The Pew Charitable Trusts