July 31, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Docket No. FDA-2015-N-0030

Re: FDA-2015-N-0030; Comments to the Public Docket on Compounding of Human Drug Products under the Federal Food, Drug, and Cosmetic Act

Dear Sir or Madam:

Thank you for the opportunity to submit our comments on the Food and Drug Administration’s (FDA) Compounding of Human Drug Products under the Federal Food, Drug, and Cosmetic Act Public Docket. As FDA considers finalizing regulations of compounding of human drug products under sections 503A and 503B of FD&C Act, we appreciate the opportunity to share our perspectives and to work with FDA in the future on these important issues which impact prescribers, practitioners, pharmacists, and patients.

During the Pharmacy Stakeholders Listening Session held on April 30, 2015, as well as the listening session for physicians, ambulatory surgery centers, and others, FDA proposed several questions to the attendees. To provide a comprehensive set of answers, the DQSA Coalition, a group of more than 20 professional organizations representing prescribers, pharmacists, physicians, ambulatory surgery centers, and patients -- has worked diligently to provide data, examples, and responses to FDA’s questions in order to aid in the implementation of the DQSA. As a Coalition, we understand and support the need to protect public health. However, we also urge FDA to fully consider the preservation of patient access to vital compounded medications.

I. Memorandum of Understanding:

1. Define what is limited in MOU - Does taking “dispensing” out of the MOU and leaving it to “distribution” only (office-use) fix the issue?

The statutory language of 503A allows for an MOU that “addresses the issue of the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such state.” It does not require numerical or percentage limits and seeks to facilitate the investigations of complaints. This is further supported by other provisions in the DQSA that improved communications between the states and the FDA.
The statute is clear that the default 5 percent limitation only applies to compounded drugs that are distributed. In the same sentence, the statute refers to “dispensed” and “distributed” as two separate activities that are clearly differentiated. The only reasonable interpretation of this section is that distributed compounded drugs in this context apply to office use.

Taking “dispensing” out of the definition of distribution and applying the restrictions only to “distributing” (e.g., office use) may remedy the fact that the proposed MOU exceeds the authority granted by the statutory language of 503A. It would go a long way to resolving the controversy and legal uncertainty that will exist if the expanded and incorrect definition of distribution in the draft MOU is included in the final version.

2. Define limit for shipment - What is the tool for measuring how much compounded medications can be shipped over state lines? If a cap, today people have said 30% isn’t enough and one group stated 50% might work – what is the cap that works? Elaborate with comments and provide market analysis of what measurement works and why.

There is no cap or percentage limitation that is mandated by the statutory language of section 503A and the statute does not authorize any limitations over patient specific dispensing by the agency. We believe strongly that neither a percentage nor volume cap for either distribution or dispensing is necessary and appropriate and exceeds the statutory authority contained in 503A.

3. Define how a unit amount should be defined.

We have discussed this at length with pharmacists to gain some sense of how a “unit” amount should be defined. Our feeling is that as long as it’s a consistent measurement (numerator & denominator) for calculating distribution percentages provided for within the “default clause” of 503A, the percentages should be relatively similar. We feel that “Prescription or Order” would be the most representative number to use in defining a unit. Additionally many pharmacists feel that “Prescriptions or Orders per Month” would capture orders that get “refilled” every month. While any measurement is difficult because of the many variables, this may be the simplest, clearest, and consistent to use across different practice settings.

The draft MOU did not include a definition of a “unit” for the purposes of defining inordinate amounts of compounded products, despite the critical importance of that term to the calculation of inordinate amounts of compounded products. The lack of a definition of a “unit” prevents stakeholders from being able to determine the effect of this provision on patients and providers.

Based on the current proposed threshold and how it’s calculated, pharmacies that provide only compounds, and no general non-compounded prescription products, will always be at a great disadvantage when calculating what constitutes an “inordinate amount of compounded human drug products interstate”. Some DQSA organization members and pharmacies are compounding only pharmacies, and do not dispense any non-compounded prescriptions, and therefore would be at a mathematical disadvantage to their colleagues who have “hybrid” pharmacies, i.e. those that provide both traditional prescription services in addition to compounds. For example, if a compounding-only pharmacy compounds 10 medications per day and its State Board of
Pharmacy has signed the MOU as currently proposed, then this pharmacy would only be allowed to ship three compounded medications across state lines each day. In contrast, a hybrid pharmacy that dispenses 90 manufactured drug product prescriptions and 10 compounded preparations per day could, under the proposed formula, ship up to 30 compounds (or all 10 of those compounded that day) out-of-state and still be in compliance with the terms of the MOU.

4. Define why 503A must be allowed to compound for office-use - Give examples as to office-use compounds that 503B cannot provide and that 503A must provide to physicians and practitioners.

Currently, the majority of states provide for means by which prescribers may obtain both finished manufactured drug products and compounded preparations for the administration to or treatment of patients within their practice settings. When Congress re-enacted 503A within the DQSA, numerous Statements of the Record conveyed the intent that nothing within 503A was to intrude upon existing and well-established practices. Additionally, while Congress could have explicitly prohibited the compounding of medications for office-use, it did not. Therefore, we believe that FDA guidance and regulations should reflect that practice as well as Congress’ intent by acknowledging where office-use compounding is permitted by the States.

Some examples of the medications that 503A traditional compounders currently supply for office-use in quantities that are too small or limited to justify preparation and distribution by a 503B outsourcing facility are as follows:

- Topical Phenol used by podiatrists and primary care physicians to treat in-grown toenails.
- Topical cantharidin (one strength is 52.5 mg / mL [0.7%]) used by podiatrists, primary care physicians, and dermatologists for the treatment of warts.
- Topical podophylline used by podiatrists, primary care physicians, and ob/gyns.
- Topical Diphenylcyprophenone in many strengths compounded from raw material and acetone for use by dermatologists treating alopecia areata.
- Topical Squaric acid for use by dermatologists in treating alopecia areata.
- Bleaching gels of various formulas used by dentists in teeth whitening procedures.
- Tetracaine lollipops used by dentists for non-narcotic post-op pain management after tonsillectomies.
- Glycolic acid solutions used by dermatologists in skin peel procedures.
- Trichloroacetic acid solutions used by dermatologists in skin peel procedures.
- Lidocaine, Epinephrine, and Tetracaine (LET or LAT) gel/solution and derivatives used by ERs and Primary Care Physicians as a local anesthetic used to decrease pain while suturing patients – especially pediatric patients.
- Dextrose capsules #0, 00, 000, 1, 2, 3, and 4 for use by Social Work to teach pediatric patients how to swallow capsules.
• Tamsulosin 0.2 mg capsules (open up the 0.4 mg capsules, weigh total contents then weigh in half, pack into #4 capsules) used off-label for kidney stones in pediatric patients.

• Various powder-filled capsules - many formulations out in the industry with mixtures of 3-4 ingredients that may include ciprofloxacin, amphotericin, dexamethasone, clotrimazole, and lidocaine and others for use in Sheehy-House powder insufflators for insertion into the ear to treat refractory external ear infections.

• Topical Sodium Nitrate solution used in labs for diagnosis of cystic fibrosis via sweat testing.

• Topical Pilocarpine Nitrate solution used in labs for diagnosis of cystic fibrosis via sweat testing.

• Hydroxyzine pamoate suspension for use by pediatric dentists for mild sedation

• Combination antibiotic eye drop used by ophthalmology surgery centers.

• EDTA ophthalmic eye drops for surgery

• Bevacizamab (Avastin) repack used by ophthalmology clinics for treatment of wet macular degeneration.

• Alteplase 1 mg / mL syringes when commercial vials are on backorder and shortage from manufacturers.

• Oxymetazoline Nasal Spray + Lidocaine 4% injection compounded 1:1 in an ISO 5 environment and packaged into sterile oral syringes for storage in automated dispensing cabinets for ENT to use with an automizer prior to exam in office.

• Surgical Irrigations
  o Bacitracin 50,000 units in 0.9% NaCl 3000 mL (bag).
  o Bacitracin 50,000 units in 0.9% NaCl 1000 mL (bag or bottle).
  o Bacitracin 25,000 units in 0.9% NaCl 500 mL (bottle).
  o Levofloxacin in 0.9% NaCl 500 mL (bottle).
  o Cefazolin in 0.9% NaCl 500 ml (bottle).
  o Bacitracin, Gentimicin and Cefazolin in 0.9% NaCl 500 mL or 1000 mL (bottle).

• Organ Transplant Irrigations, Soaks and Baths
  o Cardioplegia solutions (mixtures of lidocaine, electrolytes, mannitol, dextrose, etc.).
  o Epinephrine in 0.9% NaCl (bottle).
  o Phenylephrine in 0.9% NaCl (bag).

• Crash/Emergency Cart drugs/ICU/Ambulance/Helicopter/Airplane
  o Phenylephrine syringes used for Anesthesia/ER crash carts, concentrations of 50 and 100 mcg / mL that are not commercially available; there is chronic backorder and shortage from manufacturers of vials 10 mg / mL to even compound the 50 and 100 mcg / mL syringes.
- Sodium Bicarbonate used by Anesthesia/ER crash carts, a sterile drug that has been on chronic backorder and shortage from manufacturers.
- Calcium Chloride used by Anesthesia/ER crash carts/dialysis centers – chronic backorder from manufacturers.
- Calcium Gluconate used by ICUs/dialysis centers; chronic backorder from manufacturers.
- Narcotic drug syringes; fentanyl, sufentanil used for anesthesia in outpatient surgery centers and physician offices.
- Propofol repackaged into 10 and 20 mL syringes during shortages.
- Dexmedetomidine straight from diluted commercial vial or compounded with 0.9% NS and concentrated vial, then packaged in syringes.
- Heparin 500 units/mL (3 mL) compounded then packaged in syringes for dialysis.
- Heparin 2,000 units/mL (3 mL) compounded then packaged in syringes for dialysis.
- Heparin 1,000 units/mL (3 and 8 mL) packaged in syringes for dialysis.
- Lidocaine 1% buffered with NaBicarb (0.8 & 5 mL) packaged in syringes for IV starts and dialysis.
- Lidocaine with NaBicarb (0.2 mL) packaged in J-tip syringes for IV starts and shots in ER, surgery centers, inpatient and clinics.
- Morphine 1 mg/mL compounded using commercial product and 0.9% NaCl (1 mL) syringe for storage in automated dispensing cabinets, and anesthesia carts
- Hydromorphone 0.2 mg/mL for PCA (50 mL) syringe for storage in automated dispensing cabinets within health systems and long term care facilities.
- Hydromorphone 1 mg/mL for PCA (50 mL) syringe for storage in automated dispensing cabinets within health systems and long term care facilities.
- Methadone 1 mg/mL compound from commercial product and 0.9% NaCl (1 mL) syringe for storage in automated dispensing cabinets within health systems and long term care facilities.
- Morphine 2 mg/mL for PCA (25 mL) syringe prepared from commercial product and 0.9% NaCl for storage in automated dispensing cabinets within health systems and long term care facilities.
- Fentanyl 10 mcg/mL NEONATAL (1 and 10 mL) compounded from commercial product and 0.9% NaCl and packaged in bar-coded syringes for storage in automated dispensing cabinets within health systems and long term care facilities.
- Heparin 2 units/mL compounded from Heparin and 0.45% NaCl commercial products (250, 500 and 1000 mL bags) for storage in automated dispensing cabinets within health systems and long term care facilities.
- Epinephrine 0.01 mg / mL compounded from epinephrine and D5W commercial products (50 mL syringe) for storage in automated dispensing machines within health systems and long term care facilities.
- Epinephrine 0.02 mg / mL compounded from epinephrine and D5W commercial products (50 mL syringe) for storage in automated dispensing machines within health systems and long term care facilities.
- Nicardipine 0.5 mg / mL compounded from Nicardipine and D5W commercial products (50 mL syringe) for storage in automated dispensing machines within health systems and long term care facilities.
- Nicardipine 0.5 mg / mL compounded from Nicardipine and 0.9% NaCl commercial products (50 mL syringe) for storage in automated dispensing machines within health systems and long term care facilities.
- Dextrose 10% plus 14.6% NaCl or 23.4% NaCl to prepare D10 and NaCl 0.2% (250 mL) bag due to commercial product on chronic mfg b/o (prepared from commercial products).
- Dextrose 10% plus 14.6% NaCl or 23.4% NaCl plus heparin to equal 1 unit / mL to prepare D10 and NaCl 0.2% and Heparin 1 unit / mL (250 mL) bag (prepared from commercial products) may be stored in automated dispensing cabinets.
- Bupivacaine 0.25% + Epinephrine = 1:200,000 injection for use in surgery and surgery centers.
- Epinephrine 1:100,000 injection prepared from epinephrine and 0.9% NaCl commercial products for use in surgery and surgery centers.
- Epinephrine 1:400,000 injection prepared from epinephrine and 0.9% NaCl commercial products for use in surgery and surgery centers.
- Lidocaine 0.25% with Epinephrine 1:400,00 units injection prepared from commercial products in a vial for use in surgery and surgery centers.
- Lidocaine 1% with Epinephrine 1:10,000 units injection prepared from commercial products into a vial for use in surgery and surgery centers.
- Ropivacaine 0.2% with Epinephrine 1:200,000 units injection prepared from commercial products into a vial for use in surgery and surgery centers.
- Milrinone 0.2 mg / mL compounded or premix commercial product repackaged into 20 and 50 mL syringes for storage in automated dispensing cabinets.
- Pentobarbital 50 mg / mL commercial product repackaged into 1 mL syringe for cath lab and anesthesia surgery centers.
- Methadone 5 mg / 0.5 mL commercial product repackaged from large commercial vial into 0.5 mL syringes for storage in automated dispensing cabinets.
- Dopamine 1.6 and 3.2 mg / mL compounded or premix commercial product repackaged into 20 and 50 mL syringes for each for storage in automated dispensing cabinets.
Nitroglycerin 0.4 mg / mL commercial product repackaged into 20 and 50 mL syringes during commercial product manufacturing back order and shortages.

- Fentanyl 50 mcg / mL injection repackaged from commercial product into 8, 24 and 50 mL syringes maybe stored in automated dispensing cabinets.

- Iopamidol (Isovue) 61% injection repackaged into 20 mL syringes during manufacturing back order and shortages.

- Botulinium Toxin solution reconstituted commercial product and packaged in syringes for office use treatment of spasticity, diagnosis of gastrointestinal disorders and which dermatologists and plastic surgeons also use.

- Ceftriaxone mixed with lidocaine to 350 mg / mL, drawn up in 1.1, 1.4 and 2.2 mL volumes in an ISO 5 environment for storage in an automated dispensing cabinet refrigerator in ERs and clinics.

It is also important to recognize that at the present time, the only compounded preparations a 503B outsourcing facility may compound and distribute using bulk ingredients are those products which appear on the FDA shortage list. Until such time as the Pharmacy Compounding Advisory Committee completes its review of bulk ingredients submitted for use by 503B outsourcing facilities, very few of these medications will be legally allowed to be compounded and distributed by them.

II. Repackaging

1. Define what is a reasonable amount. If 14 day supply is not enough, then define what is and why more is needed. Give examples of drugs.

The ability of an individual compounding to determine what amount of medicines need to be maintained on hand to fulfill prescription orders – commonly referred to as “anticipatory compounding” – based on variability in patient populations, seasonal demands, geographic variations, and other factors is needed when calculating the quantity of repackaged finished drug products. Creating an arbitrary and finite 14-day supply limit fails to take into account the inconsistencies between pharmacy practices.

It’s also important to note that because of product and manpower costs to a pharmacy, repackaging of quantities that exceed or fail to meet anticipated demand would have a negative impact on the practice’s economics. When too little is repackaged, additional workload must be incurred. When too much is repackaged, medications may need to be discarded and destroyed.

We recommend defining reasonable amount to be similar to the language used for anticipatory compounding – the quantity repackaged should be directly related to historical data of prescriptions and orders for repackaged medications received by the pharmacy.
2. Define whether to distinguish between sterile and non-sterile and timeframe for each.

Quantities permitted to be repackaged by a pharmacy should be based upon quantity demand supported by historical prescription and medical orders; that applies to both sterile and non-sterile medications.

3. Define why 503A must be allowed to repackage. – What if 503B were the only entities allowed to repackage, which raises a lot of concern as to who would provide the smaller quantities. Provide examples of drugs for office-use and repackaging that 503A traditional pharmacies must provide to fill the gap.

All pharmacies, whether they compound or not, are actively involved in the repackaging of finished manufactured drug products each and every day. That includes unit-dosing for institutional use by hospital pharmacists, long-term care pharmacists, and hospice pharmacists. That includes preparing medications for delivery to home infusion patients, and for patients in assisted living facilities. That includes a community pharmacist taking the time to fill a patient’s weekly or monthly “pill pack” to facilitate compliance and adherence. Each and every one of those examples are “repackaging” activities.

No 503B outsourcing facility is capable of that level of detailed individual patient prescription service. Therefore, repackaging of medications must continue in a manner that has always been practiced by pharmacists. To date, we have not seen any examples from the agency where the repackaging of finished manufactured drug products – especially non-sterile drugs – have compromised product safety or efficacy.

4. Define appropriate BUDs – FDA asked continuously for exact BUDs and for examples of what is needed. Explain whether FDA should distinguish between sterile and non-sterile and look to 30 day supply.

FDA’s proposed BUD guidelines for repackaging of non-sterile finished manufactured drug reads as: ”The BUD for the repackaged drug product is no longer than the expiration date on the original drug product being repackaged.” In general, we find this that reflects the standards contained within USP General Chapter <795>.

However, we must note that there are some conflicts with existing FDA guidance on unit dose packaging that most hospitals and long term care pharmacies use as a standard. The agency should take into consideration those requirements and make necessary changes to align the two guidance documents.

The proposed BUD guidelines for repackaging of sterile finished manufactured drug products are not acceptable because, as outlined within the agency’s draft guidance document, they do not conform to the standards contained within USP General Chapter <797>. 
We recommend that a minimum BUD for sterile drugs be aligned with USP <797>. We note that the proposed BUDs contained within the draft ≤ 30 hours if stored at USP controlled room temperature, ≤ 9 days if stored in a refrigerator; ≤ 45 days if stored in a solid frozen state between -25°C and -10°C; are the recommended BUDs for Medium Risk Level Compounding in USP <797>. Under USP <797>, Low Risk Compounding includes "manipulations are limited to aseptically opening ampuls, penetrating disinfected stoppers on vials and transferring sterile liquids in sterile syringes to sterile administration devices, package containers of other sterile products, and containers for storage and dispensing". We believe this would be what is involved in "repackaging" a sterile product. Therefore, the BUD should reflect that and apply the USP <797> requirements for low risk: 48 hrs at room temperature; 14 days refrigerated; 45 days frozen.

Additionally, it is also important that FDA recognizes the provisions within USP <797> that enables a practitioner to establish a BUD greater than the limits specified through study, testing and support from the medical and scientific literature.

Please note: This is for the sterile repackaged finished manufactured drug products and does not include biologics which have a different BUD per the proposed guidance for those particular products.

III. Inspections

1. Define what quality standard FDA should be using during inspections. How can FDA provide better education to their inspectors and what education is needed as to the quality standard being used.

As discussed during the most recent FDA listening session, to date, the investigations of compounding pharmacies and physicians pursuant to DQSA have raised a host of concerns. Specifically, feedback from the field indicates that inspectors may not have the education necessary to perform inspections effectively. Inspectors do not adequately differentiate between 503A and 503B pharmacies. We have heard a number of reports that inspectors have entered 503A pharmacies, which are, by the FDA’s definition, not subject to cGMP requirements, but insisted on applying those requirements anyway. Occasionally this has been the result of confusion related to state office-use laws, but in other cases it seems to have resulted from a general misunderstanding of the current regulatory framework. Application of the incorrect framework results in a skewed perception of the risks associated with a particular compounding pharmacy’s practices.

A graphic representation of this appears below.
FDA inspections of 503A traditional compounders should be conducted using the individual State pharmacy or medical practice act (statues, regulations and rules) unique to the state in which the inspected entity is located. In addition, unless specifically determined to be a 503B outsourcing facility, any inspection of a 503A traditional compounding pharmacy should be conducted using the USP General Chapter <795> for non-sterile compounded preparations and USP General Chapter <797> for sterile compounded preparations.

While we recognize that FDA is still in the process of developing guidance for compounding pharmacies, we believe it is essential that FDA increases its investment in inspector education to assure understanding and consistency. When inspectors apply the wrong requirements to pharmacies, both the FDA and pharmacies miss out on an opportunity to improve processes and procedures.
For instance, 503A pharmacies do not need to comply with cGMP requirements. Whenever an inspector evaluates pharmacies using those requirements, it will result in findings that are entirely unrelated to actual pharmacy safety. Concurrently, focusing on the wrong requirements means that despite investing time and effort in complying with the inspection process, pharmacists and physicians glean no useful information for quality improvement from them. Ensuring that all inspectors have received appropriate education related to the application of 503A and 503B requirements during investigations as well as State practice acts and USP General Chapters will result in a more effective use of both agency and pharmacy resources. This approach will result in more meaningful findings and more consistent evaluation of pharmacy safety.

To facilitate more effective inspections, we strongly encourage the FDA to consider developing “compliance toolkits” for compounding pharmacists and physicians, which should include at a minimum, inspection protocols/procedures and compliance checklists. The pharmacy associations have received member feedback that during inspections, when inspectors are questioned regarding the source of a requirement, pharmacy staff are told to “look it up” or that “they should already know.” Further, with no readily available information on the actual process for responding to findings (and in at least a few instances, agency deviation from communicated timelines for the response process), pharmacies and physician offices struggle to tailor their responses to investigations. This lack of transparency may, over time, undermine pharmacy trust and confidence in the agency because it creates an unnecessarily adversarial environment. If FDA were to help develop compliance toolkits, pharmacists and physicians would have a starting point for compliance and something to refer to as questions arise during investigations. Further, providing tools to pharmacies and physician offices may make oversight and inspection seem more like a cooperative process, rather than an antagonistic one. Pharmacy and medical organizations would welcome the opportunity to collaborate with FDA on the development of effective compounding compliance tools, including the toolkits, any practitioner subject to 503A oversight by the agency.

We, the undersigned organizations, thank you for the opportunity to submit our comments and we look forward to working with the FDA in the future on these very important issues.

Sincerely,

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