



## **MARYLAND BOARD OF PHARMACY**

# **REPORT TO THE GOVERNOR AND THE GENERAL ASSEMBLY ON CHANGES TO THE DRUG QUALITY AND SECURITY ACT, AND FEDERAL GUIDANCE PROVIDED UNDER THE ACT, AS THOSE CHANGES RELATE TO THE AUTHORITY OF A STERILE COMPOUNDING FACILITY TO PROVIDE PRESCRIPTION DRUGS TO OPHTHALMOLOGISTS FOR OFFICE USE**

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## **EXECUTIVE SUMMARY**

This report is in response to Section 2 of HB 1088, Health Occupations – Compound Drugs – Provision to Ophthalmologists for Office Use, 2014, Chapter 640. The legislation requires that the Board of Pharmacy (the “Board”) monitor any changes to the federal Drug Quality and Security Act (DQSA), federal regulations proposed or adopted under the Act, and federal guidance provided under the Act as those changes relate to the authority of a sterile compounding facility to provide prescription drugs to ophthalmologists for office use and report on or before January 1, 2015, in accordance with § 2-1246 of the State Government Article, to the Governor and the General Assembly on those changes.

As described in section 503B as created by the DQSA, an outsourcing facility compounds sterile drugs, registers as an outsourcing facility, follows all of the requirements of section 503B, compounds under the direct supervision of a pharmacist whether or not it operates as a pharmacy, and may or may not obtain prescriptions for individual patients. Qualified outsourcing facilities would be exempt from portions of the Federal Food, Drug, and Cosmetic Act (the “Act”) pertaining to new drug approval and adequate directions for use, but would still be expected to comply with current good manufacturing practice. Compounders may elect not to register as outsourcing facilities, but must still comply with section 503A of the Act which addresses pharmacy compounding and requires prescriptions for individual patients, among other things. If a compounder cannot obtain exemptions either under section 503A or 503B, they would have to comply with all the mandates of the Act as required of drug manufacturers. As of December 1, 2014 there were 57 registered outsourcing facilities nationwide and none with addresses in Maryland.

Overall the Guidances that have been released by the FDA provide information regarding current good manufacturing practices, the process for registration, an explanation of the fees required, and the process for electronic reporting. There were no Guidances that relate specifically to the authority of a sterile compounding facility to provide prescription drugs to ophthalmologists for office use. The passage of HB 1088 had no effect on compounding requirements for pharmacies providing prescription drugs to ophthalmologists office use. Any sterile compounding facility that chooses to provide prescription drugs to ophthalmologists for office use should register as a 503B Outsourcing Facility with the U.S. Food and Drug Administration (FDA) or obtain a patient specific prescription before performing sterile compounding.

## **BACKGROUND**

In September 2012, the Centers for Disease Control (CDC) and U.S. Food and Drug Administration (FDA) began investigating a national outbreak of fungal meningitis that were all linked to the New England Compounding Center in Massachusetts. Per the CDC there were 751 cases in 20 states with 64 deaths. In Maryland, there were 26 cases and 3 deaths. In response to the outbreak, on November 27, 2013, President Obama signed the Drug Quality and Security Act (DQSA). It made revisions to 503A and established 503B which was intended for oversight of outsourcing facilities that compound prescription drugs without a patient specific prescription.

In the 2013 Maryland Legislative Session, SB 986 State Board of Pharmacy – Sterile Compounding – Permits, Chapter 397, passed to further protect Maryland citizens as the DQSA was not fully implemented and might not be for a year or more as guidance and regulations are developed. The goal of HB 986 was to assure that only appropriately and aseptically prepared sterile compounded drugs are

dispensed to patients residing in Maryland. Establishing a sterile compounding permit in Maryland will allow the Board to monitor most entities that perform sterile compounding, rather than only pharmacies. The sterile compounding facility permit holder will be required to follow the Board's sterile compounding regulations, COMAR 10.34.19. HB 986 was amended to include a waiver to the Sterile Compounding Permit for drug shortages and for compounding for office use in some circumstances.

In the beginning of 2014, the FDA established a process for sterile compounding facilities to register as an FDA outsourcing facility if the facility chooses to compound without a patient specific prescription. Now entities that compounded for office use could register with the FDA. Since FDA outsourcing facilities are in essence distributors of prescription drug products to persons other than consumers or patients, they are required to obtain a Maryland wholesale distributor permit as well to distribute in Maryland.

At about the same time during the 2014 Maryland Legislative Session, HB 1088 Health Occupations – Compound Drugs – Provision to Ophthalmologists for Office Use, Chapter 640, passed, allowing pharmacies to compound the following items without obtaining a sterile compounding permit: (1) antibiotics for the emergency treatment of bacterial endophthalmitis and viral retinitis; and (2) antivasular endothelial growth factor agents for the emergency treatment of neovascular glaucoma, wet macular degeneration, and macular edema. The Board believed the intent of this legislation was to allow physicians to obtain sterile compounded medications from Maryland licensed pharmacies without a patient specific prescription. Under the existing law, physicians were allowed to compound these items themselves so long as they follow USP 797 guidelines and obtain, when it becomes available, a Maryland Sterile Compounding Permit. Under existing Maryland law, pharmacies may only perform sterile compounding pursuant to a patient specific prescription.

Early in 2014, with the passage of the Drug Quality and Security Act (DQSA), the FDA began accepting registration for outsourcing facilities. This registration would allow entities to compound and ship for office use without a patient specific prescription. Maryland would also require these outsourcing facilities to obtain a wholesale distributor permit. The pharmacies that compound the medications set forth in HB 1088 for office use could have simply registered with the FDA as an outsourcing facility and obtained a Maryland wholesale distributor permit using the “short form.”

In an uncodified section of HB 1088, it required the Board to monitor any changes to the DQSA, federal regulations proposed or adopted under the Act, and federal guidance provided under the Act as those changes relate to the authority of a sterile compounding facility to provide prescription drugs to ophthalmologists for office use and report on or before January 1, 2015, in accordance with § 2-1246 of the State Government Article, to the Governor and the General Assembly on those changes.

The Board has monitored the federal guidance that has been released regarding the DQSA. No further federal laws or regulations have been proposed in the past year regarding sterile compounding. Six Draft Guidances and one Request for Nominations have been released over the following months: December 2013, March 2014, July 2014, and November 2014. This report provides a summary of each. All the FDA Guidances are available on the FDA website:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm393571.htm>.

## **DRAFT GUIDANCES**

### **Guidance for Industry Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act: Draft Guidance (December 2013)**

Each facility at a separate geographical location must register separately. Facilities should send submissions via the Structured Product Labeling (SPL) format. Alternatively, an email containing the required information can be sent to [edrls@fda.hhs.gov](mailto:edrls@fda.hhs.gov), but entities are encouraged to start using the SPL format by September 30, 2014. Additionally, a waiver of the requirement for electronic submission may be attained through postal mail or the email. Information collected through submissions including product information, facility names and location, whether the facility compounds from bulk drug substances, and whether bulk substances are used for sterile or non-sterile drugs will be posted on the Internet as required by the section 503B.

### **Guidance for Industry Interim Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act: Draft Guidance (December 2013)**

Upon initial registration as an outsourcing facility, an entity must submit a report, once in June and once in December, covering all the products compounded in the previous six months. Unless granted a waiver, all reports must be submitted electronically. FDA will issue a new guidance once it is equipped to receive drug reports via the SPL format, but until then reports should be submitted as an Excel spreadsheet via an email attachment to [edrls@fda.hhs.gov](mailto:edrls@fda.hhs.gov).

## **REQUESTS FOR NOMINATIONS December 2013**

FDA is currently requesting nominations for the following:

- [Bulk Drug Substances That May Be Used to Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act Concerning Outsourcing Facilities; Request for Nominations](#)
- [Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act](#)
- [Proposed Rule: Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed From the Market for Reasons of Safety or Effectiveness](#)

Under the proposed rule, drugs on the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness would not qualify for exemptions under either section 503A or 503B. Of note for ophthalmology, there are two drugs on the list, gatifloxacin (an antibiotic) and bromfenac (a nonsteroidal anti-inflammatory drug) which have exemptions for ophthalmic solutions. In other words, ophthalmic solutions of those two drugs are still on the market.

### **Guidance for Industry Fees for Human Drug Compounding Outsourcing Facilities Under Sections 503B and 744K of the FD&C Act: Draft Guidance (March 2014)**

Beginning with the Fiscal Year 2015, outsourcing facilities registering with FDA must pay an annual establishment fee. The registration period is from October 1<sup>st</sup> to December 31<sup>st</sup> every year beginning 2014. Entities may register outside of that period, but the full fee will still apply and registration still expires at the end of the next registration period, December 31<sup>st</sup>. If a registered entity fails to pay by December 31<sup>st</sup>, on January 1<sup>st</sup> it will lose its status as an outsourcing facility and thus its sterile products would no longer be exempt under section 503B. Until fees are paid in full, that facilities' products will be considered misbranded, unapproved new drugs and thus ineligible for interstate commerce. Once registration information is submitted and approved FDA will send an invoice for payment. If the full invoiced amount is not paid within 15 calendar days of being issued, the registration will be considered withdrawn.

Establishment fee = \$15,000 x inflation adjustment factor + small business adjustment factor

The inflation adjustment factor and small business adjustment factor will be calculated and posted in the Federal Register.

Entities with gross annual sales of \$1,000,000 or less in the 12 months ending on April 1<sup>st</sup> of the of the fiscal year immediately preceding the fiscal year in which the annual fee is assessed may qualify for a small business reduction. Request for a small business reduction must be made by April 30<sup>th</sup> of the year before the fiscal year for which the reduction is being sought using Form 3908 via email or postal mail. The reduction amounts to 1/3<sup>rd</sup> of the annual establishment fee, or \$5,000 multiplied by the inflation adjustment factor. The small business adjustment factor paid by non-qualifying facilities covers the loss in fees to FDA from the small business reduction.

If re-inspections are necessary a fee of \$15,000 multiplied by the inflation adjustment factor will be assessed for each re-inspection.

No refunds will be given, but appeals will be considered such as in the case of the denial of a small business reduction.

### **Guidance for Industry Current Good Manufacturing Practice – Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act (July 2014)**

This guidance set out to describe the Current Good Manufacturing Practices (cGMP) that would be expected of outsourcing facilities. Outsourcing facilities should be designed to maintain a visibly clean environment. ISO 5 or better air quality is required in sterile production areas. Immediately adjacent to the sterile areas the air quality should be ISO 7 or ISO 8 if an isolator is used at the minimum. Layout should minimize the influx of contaminants or disruption in the unidirectional flow of HEPA filters, into critical areas. Vents should not be obstructed by large equipment. Equipment used for air quality such as HEPA filters and HVAC units should be qualified, then have follow-up testing at least twice a year. Pressure differentials, humidity, and temperature should be monitored during production through frequent checks or alarms.

Cross-Contamination should be minimized by using defined spaces and maintaining a cleaning schedule. FDA suggests that powder drugs be handled in physically distinct areas. Of note to ophthalmologic drugs, penicillin and beta-lactam products are specifically required to be in physically separated areas. Cleaning procedures should assign responsibilities which specify a schedule, methods,

equipment, and materials to be used. Sterile disinfectants, including sporicidal agents, and sterile lint-free wipes should be included in the materials.

Environmental and personnel monitoring should establish procedures for evaluating potential routes of microbial contamination via the air, surfaces, processes, operations, and personnel practices.

Equipment, containers, and closures that come in contact with the product must be evaluated for suitability for intended purpose, sterility and cleanliness at time of use. If pre-sterilized and depyrogenated single-use equipment, containers, and closures are not used, validated processes must be used for sterilization and depyrogenation. Equipment must be qualified for its purpose and routinely calibrated and maintained. Procedures for storing containers and closures must preserve sterility and reduced the risk of contamination.

Specifications should be established for components to be used in each drug product including identity and conformity. FDA proposes reducing the need for laboratory testing of incoming components. Under the proposal, a laboratory interested in providing those services would submit a Drug Master File (DMF) to FDA, once the outsourcing facility informs FDA of intent to use the laboratory, FDA would review the DMF and if there were no questions, would submit a letter to the DMF holder stating FDA has no further comments. A copy of the letter would be provided to the outsourcing facility which they could then produce when inspected.

Written procedures for production and process controls must be established and followed to ensure consistent drug products. Prior to aseptic drug processing employees must be trained on aseptic technique, cleanroom behavior, gowning, and aseptic manufacturing operations. An individual would be considered qualified in aseptic operations after at least three successful media fill simulations conducted in the same area in which production occurs.

Drug products need to be tested before release to ensure the identity and strength of active ingredients, sterility—including a limit on visible particles, and a limit on bacterial endotoxins if a non-pyrogenic claim is made. Qualified, designated members of the quality control unit are responsible for authorizing release. For batches of less than ten units, samples can be obtained from every other batch, or once at least ten units of that product has been produced. For aqueous solutions, testing for identity and strength can be performed on the bulk solution just before filling the finished drug product containers. FDA proposes that laboratory release testing does not have to be in-house if an outside laboratory follows the same procedure as for an outside laboratory testing incoming components.

Stability testing must be done to determine appropriate storage conditions and expiration dates. Three representative batches of each drug product should be tested to determine expiration date. The beyond-use date can be used as the expiration if certain criteria are met.

Packaging of sterile drugs must be appropriate to guarantee sterility and integrity of the product until it is administered to a patient. Labeling must be sufficient to prevent mix-ups.

The quality control unit has other responsibilities in addition to sampling and authorizing product release. This unit is also accountable for discrepancy and failure investigations and the development and oversight of appropriate corrective actions and preventative actions. They also evaluate complaints concerning drug products, determining the need for a full investigation, and whether a complaint



represents an adverse event that must be submitted to FDA. The quality control unit should not take on the responsibilities of other units.

**Guidance for Industry Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act (November 2014)**

This guidance provides instructions for drug reporting requirements for FDA outsourcing facilities, similar to the guidance issued in July. The FDA has modified its electronic submission system to accept electronic reports for drugs compounded by registered outsourcing facilities. When an outsourcing facility registers with the FDA it must submit a drug product report to the FDA. After initial registration the outsourcing facility is required to submit reports in June and December each year.

The report must identify all the drugs that were compounded at the outsourcing facility in the previous six months and provide the following information on each drug:

- Active ingredient and strength of active ingredient per unit;
- Source of the active ingredient;
- NDC number of the source drug or bulk active ingredient, if available;
- Dosage form and route of administration;
- Package description ;
- Number of individual units produced; and
- NDC of the final product, if assigned.

**Guidance for Industry Registration of Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act (November 2014)**

This guidance describes the process for registering as an outsourcing facility under 503B of the DQSA. It sets out who should register as an outsourcing facility. Any facility that compounds sterile drugs is required to register. The facility may, or may not be a pharmacy and it may, or may not obtain prescriptions for individual patients.

The guidance then describes the method for registration and de-registration. Both processes use the FDA's existing structure product labeling (SPL) format and electronic registration is required, except for a few rare exceptions. A facility would have to apply for a waiver if it cannot register electronically. Instructions regarding how to apply for the waiver are included in the Guidance. Outsourcing facilities must register annually between October 1st and December 31<sup>st</sup>. There are detailed instructions regarding how to use the FDA's registration system. If registering as an outsourcing facility, the facility must submit the following information:

- Name of facility;
- Place of business;
- Unique facility identifier;
- Point of contact email address and phone number;
- Indication of whether the facility intends to compound products on the FDA's drug shortage list; and

- Indication of whether the facility compounds from bulk drug substances, and if so, whether it compounds sterile or nonsterile drugs from bulk drug substances.

The guidance states that the FDA will publish on the Internet a list of the registered outsourcing facilities. Registration is not complete until the fee is received. Fees were addressed in another Guidance.

**Guidance for Industry Fees for Human Drug Compounding Outsourcing Facilities Under Sections 503B and 744K of the FD&C Act (November 2014)**

This guidance appears to be very similar to the prior fee guidance that was released in July 2014, except for a few minor technical revisions and calendar updates. No fees or timeframes have been changed.

Under the “How to Qualify for a Small Business Reduction” section, in the subsection regarding “1. Which Entities Qualify for a Small Business Reduction?” the FDA provides a definition for “Sales” that was not in the July 2014 Guidance.

*Sales* include sales of all products, whether they are compounding-related or not. Sales are not limited to sales of drugs.

In Subsection “2. Timing of Requests” the FDA clarifies that it may request additional information from applicants and will respond in a timely fashion with the intent of sending its decision within 60 days.

Under the “How and When to Pay” section, the FDA clarifies that it will review the registration information and once it determines that it is complete it will send an invoice to the applicant. In the July Guidance the FDA has expected to send invoices within 3 days of receipt of the application. Additionally, the FDA provided an actual timeframe for issuing an invoice for reinspection (14 calendar days) and a timeframe for payment of that fee (30 calendar days).

Lastly, the only other revisions were in the section regarding “Effect of Failure to Pay Fees.” The FDA added that with respect to establishment fees, if an entity does not pay the full invoiced fee within 15 calendar days after the FDA issues an invoice, the registration will be withdrawn. With respect to the reinspection fees, if an entity does not pay the full invoiced fee within 30 days, interest will be charged at a rate set by the Department of Treasury.

## CONCLUSION

The Board's mission is to protect Maryland consumers and to promote quality healthcare. Monitoring changes in the DQSA, especially in light of the impact of the New England Compounding Center fungal meningitis outbreak in Maryland, falls within that mission. Although, there are currently no registered outsourcing facilities in the State, the program is still in its infancy so that number may increase. Regardless of the number of instate facilities, FDA outsourcing facilities may ship their products to Maryland which may eventually be administered to patients within this State. Those FDA outsourcing facilities would be required to obtain a Maryland wholesale distributor permit with an abbreviated "short form." Being registered as an outsourcing facility does not mean that a company is making FDA-approved drugs and FDA recommends that practitioners use FDA-approved drugs rather than compounded drugs when possible. Additionally, simply being registered as an outsourcing facility does not mean that a company is complying with current good manufacturing practice or any of the requirements of section 503B. However, once a facility is inspected, consumers have some assurance that the facility met FDA standards at the time of inspection. FDA will inspect outsourcing facilities on a risk-based schedule, depending on the number of registrants and other considerations. FDA expects to inspect newly registered outsourcing facilities within two months of initial registration, if not previously inspected.

The Board monitored all changes to the DQSA, federal regulations proposed or adopted under the Act, and federal guidance provided under the Act. There were no changes to the DQSA and no federal regulations were proposed. There were no changes in the Guidances released that relate specifically to the authority of a sterile compounding facility to provide prescription drugs to ophthalmologists for office use. HB 1088 was in conflict with existing pharmacy laws in Maryland, as well as the DQSA, and has no effect on pharmacies providing sterile compounded medications for office use. Facilities and pharmacies providing drugs to ophthalmologists for office use should register with the FDA as an outsourcing facility and as a Maryland wholesale distributor to be compliant with federal and State law.