HOUSE OF REPRESENTATIVES STAFF ANALYSIS

BILL #: PCB HQS 14-01 Sterile Compounding
SPONSOR(S): Health Quality Subcommittee
TIED BILLS: **IDEN./SIM. BILLS:**

REFERENCE	ACTION	ANALYST	STAFF DIRECTOR or BUDGET/POLICY CHIEF
Orig. Comm.: Health Quality Subcommittee		Poche	O'Callaghan

SUMMARY ANALYSIS

In general, compounding is a practice in which a licensed pharmacist, a licensed physician, or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient. Compounding has been an integral part of the practice of pharmacy in the United States since the early 20th century. Commonly compounded products include lotions, ointments, suppositories, and intravenous medications.

Sterile compounding is the preparation of a custom medication or product in a sterile environment to prevent contamination and protect patient safety. This type of compounding is categorized as low, medium, or high risk compounding, depending on the difficulty associated with the act of compounding certain ingredients and the potential for ingredients to cause harm to a patient. According to the Board of Pharmacy, there are 301 registered nonresident pharmacies engaged in sterile compounding that ship, mail, deliver, or dispense sterile compounded products into the state.

States have varying degrees of regulation of sterile compounding. Some states are more stringent than others. In 2012, the New England Compounding Center (NECC), located in Framingham, MA, made and shipped contaminated steroidal medication used for spinal and joint injections to at least 20 states. As a result of the contamination, 751 people contracted fungal meningitis and other infections; 64 individuals died. In Florida, 25 people were sickened and 7 died. Subsequent investigations revealed that NECC was engaged in sterile compounding in violation of the laws and rules of Massachusetts and that inspection of the facility was lax.

To ensure the safety and quality of sterile products compounded outside of the state and dispensed to Floridians, PCB HQS 14-01 requires any nonresident pharmacy registered with the state and any outsourcing facility, as defined in federal law, to obtain a nonresident sterile compounding permit in order to ship, mail, deliver, or dispense a compounded sterile product in this state. The PCB outlines the requirements for the application and the standards that applicants, and permittees, must meet in order to ship or otherwise introduce compounded sterile products into Florida.

The PCB also grants authority to the Department of Health and the Board of Pharmacy to enforce the laws and rules governing sterile compounding, including the authority to conduct onsite inspections of out-of-state applicants and permittees and the authority to administratively discipline applicants and permittees for failing to comply with Florida law.

The fiscal impact of the PCB on the state is indeterminate.

The PCB provides an effective date of October 1, 2014.

FULL ANALYSIS

I. SUBSTANTIVE ANALYSIS

A. EFFECT OF PROPOSED CHANGES:

Background

Pharmacy Regulation

Chapter 465, F.S., regulates the practice of pharmacy in Florida and contains the minimum requirements for safe practice.[1] The Board of Pharmacy (Board) is tasked with adopting rules to implement the provisions of the chapter and with setting standards of practice within the state.[2] In order to be a licensed pharmacist in the state, a person must meet certain educational and other requirements and pass an examination.[3] A licensed pharmacist must renew her or his license every two years by paying a fee set by statute and meeting continuing professional pharmaceutical education requirements.[4]

Any person who wants to operate a pharmacy in Florida must have a permit. The following permits are issued by the Department of Health (DOH):

- Community pharmacy- A permit is required for each location where medicinal drugs are compounded, dispensed, stored, or sold or where prescriptions are filled or dispensed on an outpatient basis.[5]
- Institutional pharmacy- A permit is required for every location in a hospital, clinic, nursing home, dispensary, sanitarium, extended care facility, or other facility where medicinal drugs are compounded, dispensed, stored, or sold.[6]
- Nuclear pharmacy- A permit is required for every location where radioactive drugs and chemicals within the classification of medicinal drugs are compounded, dispensed, stored, or sold. The term "nuclear pharmacy" does not include hospitals licensed under chapter 395 or the nuclear medicine facilities of such hospitals.[7]
- Special pharmacy- A permit is required for every location where medicinal drugs are compounded, dispensed, stored, or sold if the location does not otherwise meet an applicable pharmacy definition in s. 465.003, F.S.[8]
- Internet pharmacy- A permit is required for a location not otherwise licensed or issued a permit under this chapter, within or outside this state, which uses the Internet to communicate with or obtain information from consumers in this state to fill or refill prescriptions or to dispense, distribute, or otherwise practice pharmacy in this state.[9]

A pharmacy located outside of the state and which ships, mails, or delivers, in any manner, a dispensed medical drug into the state must be registered as a nonresident pharmacy with the Board.[10] Registration requires application to the Board and payment of an initial registration fee.[11] Renewal of the registration is required every two years with payment of a fee.[12] Further, a registered nonresident

[1] S. 465.002, F.S.
[2] SS. 465.005, F.S., 465.0155, F.S., and 465.022, F.S.
[3] S. 465.007, F.S.
[4] SS. 465.008, F.S., and 465.009, F.S.
[5] SS. 465.003(11)(a)1. and 465.018, F.S.
[6] SS. 465.003(11)(a)2. and 465.019, F.S.
[7] SS. 465.003(11)(a)3. and 465.0193, F.S.
[8] SS. 465.003(11)(a)4. and 465.0196, F.S.
[9] SS. 465.003(11)(a)5. and 465.0197, F.S.
[10] S. 465.0156, F.S.
[11] S. 465.0156(2) and (3), F.S.
[12] Id.

pharmacy is required to provide services at a high level of competence and patient protection.[13] Lastly, a nonresident pharmacy must submit to the Board the following information:

- That it maintains at all times a valid, unexpired license, permit, or registration to operate the pharmacy in compliance with the laws of the state where it is located;[14]
- The location, names, and titles of all principal corporate officers and the pharmacist who serves as the prescription department manager for dispensing medicinal drugs to residents of this state;[15]
- That it complies with all lawful directions and requests for information from the regulatory or licensing agency of all states in which it is licensed as well as with all requests for information made by the Board;[16]
- That it maintains its records of medicinal drugs dispensed to patients in this state so that the records are readily retrievable;[17] and
- That during its regular hours of operation but not less than 6 days per week, for a minimum of 40 hours per week, a toll-free telephone service is provided to facilitate communication between patients in this state and a pharmacist at the pharmacy who has access to the patient's records.[18]

The Board may deny, revoke, or suspend registration of, or fine or reprimand, a nonresident pharmacy for failure to comply with s. 465.025, F.S., regarding the substitution of drugs, or with any requirement of the section.[19] In addition, the Board may deny, revoke, or suspend registration of, or fine or reprimand, a nonresident pharmacy for conduct which causes serious bodily injury or serious psychological injury to a resident of this state.[20] The Board must refer conduct that caused an injury to the regulatory or licensing agency in the state where the pharmacy is located.[21] If the regulatory or licensing agency fails to investigate within 180 days of the referral, the Board may take appropriate action.[22]

Compounding

In general, compounding is a practice in which a licensed pharmacist, a licensed physician, or, in the case of an outsourcing facility, a person under the supervision of a licensed pharmacist, combines, mixes, or alters ingredients of a drug to create a medication tailored to the needs of an individual patient.[23] Compounding has been an integral part of the practice of pharmacy in the United States since the early 20th century.[24] Commonly compounded products include lotions, ointments, suppositories, and intravenous medications.

There are two types of compounding: sterile and non-sterile. Sterile compounding is the preparation of a custom medication or product in a sterile environment to prevent contamination and protect patient safety. Sterile compounded products are used to treat a variety of diseases and conditions and are categorized as low, medium, or high risk depending upon the preparation and administration of the product. Products intended to be injected, infused, or applied to the eye must be compounded in a

[13] S. 465.0156(1), F.S.
[14] S. 465.0156(2)(a), F.S.
[15] S. 465.0156(2)(b), F.S.
[16] S. 465.0156(2)(c), F.S.
[17] S. 465.0156(2)(d), F.S.
[18] S. 465.0156(2)(e), F.S.
[19] S. 465.0156(4), F.S.
[20] S. 465.0156(5), F.S.
[21] Id.
[22] Id.
[23] U.S. Dept. of Health and Human Services, U.S. Food and Drug Administration, Compounding and the FDA: Questions and Answers, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm (last viewed on February 9, 2014).
[24] Allen, Loyd V., The Art, Science, and Technology of Pharmaceutical Compounding, 4th Ed., Chapter 1, pages 3-4 (Washington, D.C.: American Pharmacists Association; 2012).

sterile environment to provide special safeguards to prevent injury or death to the people receiving those products.

Non-sterile compounding is similarly categorized depending upon the difficulty of compounding and the danger posed by the individual ingredients combined, mixed, or altered in a non-sterile environment. Simple non-sterile compounding involves mixing medications according to established formulas and creating liquid versions of drugs normally sold in tablet or capsule form. Moderate non-sterile compounding involves making preparations with harmful medications that require special handling. Complex non-sterile compounding requires advanced training and special equipment to make products such as extended-release capsules and transdermal patches.

According to the Board, there are 301 registered nonresident pharmacies engaged in sterile compounding that ship, mail, deliver, or dispense sterile compounded products into the state.[25]

Special Sterile Compounding Permit

Effective September 23, 2013, most pharmacies that engage or intend to engage in the preparation of sterile compounded products in Florida must obtain a Special Sterile Compounding Permit (SSCP).[26] Pharmacies required to obtain this permit must compound sterile products in strict compliance with standards set forth in Rule 64B16-27.797, F.A.C., which contains specific standards for compounding sterile preparations, and Rule 64B16-27.700, F.A.C., which contains standards that must be met for office use compounding.[27] The following entities are not required to obtain the SSCP:

- Stand-alone special parenteral/enteral pharmacies;
- Special parenteral/enteral extended scope pharmacies;
- Pharmacies that only perform non-sterile compounding; and
- Non-resident pharmacies.[28]

A pharmacy that is compounding sterile products under its current pharmacy permit may continue to do so, but must obtain the SSCP on or before March 21, 2014 in order to continue sterile compounding. There is no fee required for existing licensees.[29] New establishments are required to submit $255 with the application for the SSCP, in addition to the $255 fee for the primary pharmacy permit.[30]

Drug Quality and Security Act

On November 27, 2013, President Obama signed the Drug Quality and Security Act (DQSA), which contains provisions relating to the oversight of compounding. Title I of the DQSA, titled the "Compounding Quality Act," describes the conditions[31] under which certain compounded human drug products are entitled to exemptions from three sections of the Food, Drug, and Cosmetic Act (FDCA) requiring:

- Compliance with current good manufacturing practices (cGMP);[32]
- Labeling with adequate directions for use;[33] and
- Food and Drug Administration (FDA) approval prior to marketing of the drug.[34]

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[25] Florida Dept. of Health, Division of Medical Quality Assurance, Florida Board of Pharmacy Compounding Survey Report, January 23, 2013, page 15 (on file with Health Quality Subcommittee staff).
[26] Rule 64B16-28.100(8), F.A.C.
[27] Rule 64B16-28.802, F.A.C.; "Office use compounding" is the provision and administration of a compounded drug to a patient by a health care practitioner in her or his office or by the practitioner in a health care facility or treatment setting, including a hospital, ambulatory surgical center, or pharmacy.
[28] Florida Board of Pharmacy, Special Sterile Compounding Permit, available at www.floridaspharmacy.gov/latest-news/special-sterile-compounding-permit/ (last viewed on February 9, 2014).
[29] Florida Board of Pharmacy, Sterile Compounding Permit, available at www.floridaspharmacy.gov/licensing/sterile-compounding-permit/ (last viewed on February 9, 2014).
[30] Id.
[31] FDCA, s. 503(A)
[32] FDCA, s. 501(a)(2)(B)
[33] FDCA, s. 502(f)(1)

In addition, the new law permits a pharmacy or non-pharmacy engaged in compounding to voluntarily register as an "outsourcing facility."[35] An outsourcing facility will be able to qualify for exemptions from the FDA approval requirements and the requirement to label products with adequate directions for use, but not the exemption from cGMP requirements. Outsourcing facilities:

- Must comply with cGMP requirements;
- Will be inspected by FDA according to a risk-based schedule; and
- Must meet certain other conditions, such as reporting adverse events and providing FDA with certain information about the products they compound.

The FDA anticipates that state boards of pharmacy will continue their oversight and regulation of the practice of pharmacy, including traditional pharmacy compounding. The FDA has indicated its intention to continue to cooperate with state authorities to address pharmacy compounding activities that may violate the FDCA.

According to the FDA, there are currently 24 registered outsourcing facilities in the U.S., one of which is located in Florida.[36]

New England Compounding Center

On September 18, 2012, the Tennessee Department of Health (TDOH) was alerted by a clinician regarding a patient with culture-confirmed fungal meningitis diagnosed 46 days after an epidural steroid injection at a Tennessee ambulatory surgical center.[37] By September 27, 2012, the initial investigation, carried out by the TDOH in collaboration with the Centers for Disease Control and Prevention (CDC) and the North Carolina Department of Health and Human Services, had identified an additional eight patients with clinically diagnosed meningitis: seven in Tennessee and one in North Carolina. All nine patients had received an epidural steroid injection with preservative-free methylprednisolone acetate solution (MPA), compounded at New England Compounding Center (NECC) in Framingham, Massachusetts. Subsequent testing revealed fungal contamination of the MPA vials. After an in-depth investigation of NECC, it was determined that the MPA vials, and other products made by NECC, were compounded in violation of the laws and rules of Massachusetts governing sterile compounding. The investigation found that NECC's sterile compounding processes were not sterile and violated many provisions of the U.S. Pharmacopeia Chapter 797[38].

The infections identified as part of this investigation include fungal meningitis, spinal or paraspinal infections, and infections associated with injections in a knee, shoulder, or ankle. The majority of infections reported to the CDC were in patients with localized spinal or paraspinal infections.

The following map illustrates the number of cases of fungal meningitis and other infections in each state resulting from the contaminated MPA from NECC:[39]

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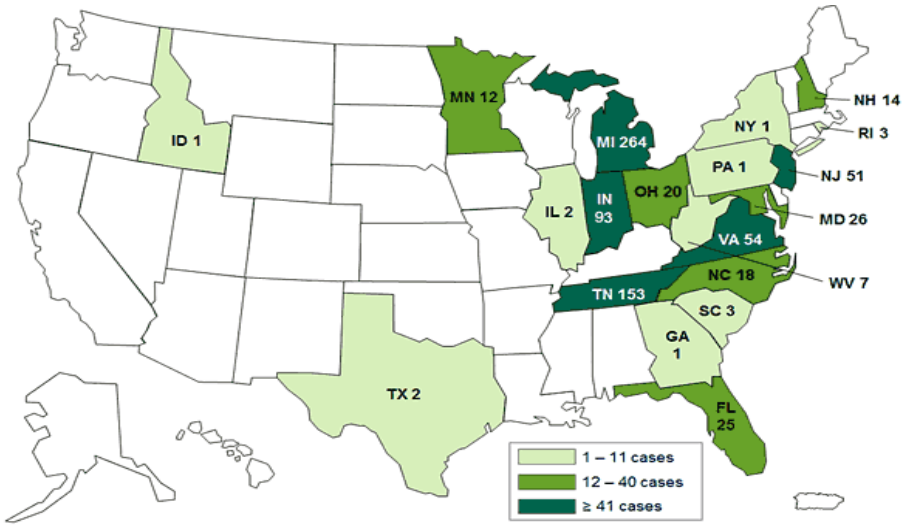
[34] FDCA, s. 505
[35] FDCA, s. 503(B)
[36] U.S. Dept. of Health and Human Services, U.S. Food and Drug Administration, Registered Outsourcing Facilities (updated as of Jan. 31, 2014), available at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm378645.htm (last viewed on February 9, 2014). The Florida-based registered outsourcing facility is KRS Global Biotechnology, Inc. in Boca Raton.
[37] Kainer, M, and Wiese, A., Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report-Multistate Outbreak of Fungal Infection Associated with Injection of Methylprednisolone Acetate Solution from a Single Compounding Pharmacy -United States, 2012, 61(41);839-842, October 19, 2012, available at www.dcd.gov/mmwr/preview/mmwrhtml/mm614a4.htm?s_cid=mm614a4_w (last viewed on February 9, 2014).
[38] See infra, *U.S. Pharmacopeia and USP 797*, page 6.
[39] Centers for Disease Control and Prevention, Multistate Outbreak of Fungal Meningitis & Other Infections-Case Count, October 23, 2013, available at www.cdc.gov/hai/outbreaks/meningitis-map-large.html (last viewed on February 9, 2014)(according to the CDC, no further case count updates were expected following the Oct. 23, 2013 update).



In total, 751 people in 20 states were sickened by the contaminated MPA injections, including 25 Floridians.[40] Of the 751 people infected, 64 people died and 7 of those deaths were in Florida.

U.S. Pharmacopeia and USP 797

The U.S. Pharmacopeia (USP) is a non-profit agency that develops and publishes standards for drug substances, drug products, excipients, and dietary supplements in the U.S. Pharmacopeia–National Formulary (USP–NF). USP–NF standards play a role in the adulteration and misbranding provisions of the FDCA. USP has no role in enforcement of these or other provisions that recognize USP–NF standards, which is the responsibility of the FDA.

USP 797 refers to chapter 797, "Pharmaceutical Compounding – Sterile Preparations," in the USP-NF. It is the first set of enforceable sterile compounding standards issued by the USP. USP 797 describes the guidelines, procedures and compliance requirements for compounding sterile preparations and sets the standards that apply to all settings in which sterile preparations are compounded. Standards in USP–NF for compounded preparations may be enforced by both the states and the FDA.

The Florida Board of Pharmacy requires compliance with USP 797. At least 24 other states have practice rules which incorporate all, most, or some of the USP 797 standards.[41] Three states consider the USP 797 to be a standard of practice: Hawaii, Oklahoma, and South Carolina.[42]

Effect of Proposed Changes

To ensure the safety and quality of sterile products compounded outside of the state and dispensed to Floridians, the PCB requires any nonresident pharmacy registered with the state and any non-pharmacy outsourcing facility to obtain a nonresident sterile compounding permit in order to ship, mail, deliver, or dispense a compounded sterile product in this state. To obtain the permit, a registered nonresident pharmacy or an outsourcing facility must submit an application and fee to the DOH. The application must include the following information:

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[40] Centers for Disease Control and Prevention, Cases and Deaths with Fungal Infections Linked to Steroid Injections, available at www.cdc.gov/hai/outbreaks/meningitis-map-large.html#casecount_table (last viewed on February 9, 2014).

[41] These states are Arkansas, Colorado, Delaware, Georgia, Indiana, Iowa, Kentucky, Louisiana, Maryland, Minnesota, Missouri, Nevada, New Jersey, New Mexico, Ohio, Oregon, Rhode Island, South Dakota, Texas, Utah, Virginia, West Virginia, Wisconsin, and Wyoming. Jessen, L., Compounding: What is Manufacturing? What is Compounding?, National Association of Boards of Pharmacy 2012 Triathlon, Interactive Executive Officer Forum, PowerPoint presentation, November 13-14, 2012, slide 9 (on file with Health Quality Subcommittee staff).

[42] Id.

- Proof of registration as an outsourcing facility, if eligible pursuant to the DQSA;
- Proof of registration as a nonresident pharmacy under s. 465.0156, F.S., or, if the applicant is not a pharmacy, proof of a valid, unexpired, and unencumbered license, registration, or permit issued by the state, territory, or district where the applicant is located, which is required to compound sterile products in that jurisdiction;
- Attestation by an owner or officer and the prescription department manager or the pharmacist in charge that:
    - They have read and understand Florida law and rules governing sterile compounding;
    - Any sterile compounded product shipped or otherwise introduced into this state will meet or exceed Florida law and rules governing sterile compounding; and
    - Any sterile compounded product shipped or otherwise introduced has not been, and will not be, compounded in violation of laws and rules governing sterile compounding where the applicant is located.
- Copies of existing policies and procedures governing sterile compounding that meet certain standards; and
- A current inspection report resulting from an inspection conducted by the regulatory or licensing agency of the state, territory or district where the applicant is located.

The PCB establishes a timeframe within which an inspection report will be considered current. The inspection report must be dated no later than six months from the application for an initial permit and no later than twelve months from the application for renewal of the permit. The PCB takes into account unforeseen circumstances that prevent an applicant from submitting a current inspection report, and authorizes the Board to define what is considered unforeseen or acceptable circumstances. If an applicant claims that unforeseen or acceptable circumstances prevent it from including a current inspection report with the application, or if the applicant has never undergone an inspection by a regulatory or licensing agency, the PCB authorizes the DOH to:

- Conduct an onsite inspection of the applicant, or contract with a third party to conduct the onsite inspection;
- Accept a satisfactory inspection report, as determined by rule, from an entity approved by the Board; or
- Accept an inspection report from the FDA, conducted pursuant to the provisions of the DQSA.

A permittee may not ship or otherwise introduce a compounded sterile product into Florida that was compounded in violation of the laws and rules of the place where it is located and does not meet or exceed the standards governing sterile compounding in this state.

A registered nonresident pharmacy which is shipping or otherwise introducing a compounded sterile product into the state may continue to do so as long as the product is compounded in accordance with all laws and rules in its home state and in Florida and it obtains a permit by February 28, 2015, which is the expiration date of all pharmacy permits in Florida. However, an applicant seeking to register as a nonresident pharmacy on or after the effective date of the PCB is required to obtain a permit before it may ship, mail, deliver, or dispense a compounded sterile product into Florida.

The PCB grants the Board authority to administratively discipline a nonresident sterile compounding permittee for failing to comply with the requirements of s. 465.0158, F.S., violating statutes that outline acts and omissions which are grounds for discipline, and violating the provisions of s. 465.0156, F.S.

The PCB gives the Board the authority to administratively discipline a registered nonresident pharmacy for failing to comply with s. 465.017, F.S., which allows the Board to inspect a nonresident pharmacy to ensure compliance with applicable laws and rules, or failing to comply with s. 465.0158, F.S. In addition, the PCB subjects a registered nonresident pharmacy to the health care fraud provisions and penalties in s. 456.0635, F.S.[43]

[43] Pursuant to s. 456.0635, F.S., each board shall refuse to admit a candidate to any examination and refuse to issue a license, certificate, or registration to any applicant if the candidate or applicant or any principal, officer, agent, managing employee, or

The PCB gives the DOH the authority to inspect a nonresident pharmacy or a nonresident sterile compounding permittee to ensure compliance with applicable laws and rules. The pharmacy or permittee is required to bear all costs of such an inspection.

Lastly, the PCB adds the definitions of "compounding" and "outsourcing facility" to chapter 465, F.S.

B. SECTION DIRECTORY:

Section 1: Amends s. 465.003, F.S., relating to definitions.
Section 2: Amends s. 465.0156, F.S., relating to registration of nonresident pharmacies.
Section 3: Creates s. 465.0158, F.S., relating to nonresident sterile compounding permit.
Section 4: Amends s. 465.017, F.S., relating to authority to inspect; disposal.
Section 5: Provides an effective date of October 1, 2014.

II. FISCAL ANALYSIS & ECONOMIC IMPACT STATEMENT

A. FISCAL IMPACT ON STATE GOVERNMENT:

1. Revenues:

The DOH will collect new fees associated with applications for initial permits and biennial renewal of permits.

2. Expenditures:

The PCB gives the DOH the authority to conduct an onsite inspection of an applicant for an initial nonresident sterile compounding permit or renewal of a permit which is located outside of Florida. The DOH has estimated the cost of conducting an onsite inspection of an out-of-state applicant to range, depending on the location of the applicant in the U.S., from $1,786 to $2,371. The average cost of an inspection is estimated to be $2,100.

While the PCB requires the applicant to bear all costs associated with the inspection, the DOH, or a third party with whom the DOH has contracted to conduct applicant inspections, will be required to pay all costs prior to reimbursement.

B. FISCAL IMPACT ON LOCAL GOVERNMENTS:

1. Revenues:

None.

2. Expenditures:

None.

C. DIRECT ECONOMIC IMPACT ON PRIVATE SECTOR:

A nonresident pharmacy or outsourcing facility is required to pay all costs associated with an inspection conducted in conjunction with an application for a nonresident sterile compounding permit. Also, a nonresident pharmacy and a nonresident sterile compounding permittee are required to pay all costs associated with an inspection pursuant to s. 465.017.

The cost for registration as an outsourcing facility is $15,000, adjusted for inflation and for small businesses as detailed in the federal law.[44] The cost for registration as an outsourcing facility charged to a small business, defined as a business with gross annual sales of $1,000,000 or less, is one-third of the establishment fee. The cost of reinspection of an outsourcing facility required by the FDA is $15,000.[45]

D. FISCAL COMMENTS:

None.

III. COMMENTS

A. CONSTITUTIONAL ISSUES:

1. Applicability of Municipality/County Mandates Provision:

Not applicable. This bill does not appear to affect county or municipal governments.

2. Other:

None.

B. RULE-MAKING AUTHORITY:

The bill provides sufficient rulemaking authority to the Department of Health to implement the provisions of the act.

C. DRAFTING ISSUES OR OTHER COMMENTS:

None.

IV. AMENDMENTS/ COMMITTEE SUBSTITUTE CHANGES

[44] DQSA, Pub. L. No. 113-54, s. 744K
[45] Id.