Legislation enacted in 2013 provides for increased government oversight of sterile prescription compounding facilities in order to improve the quality and safety of these medications. It also gives providers the ability to quickly and easily identify which facilities are maintaining Current Good Manufacturing Practices (cGMPs). Given that ophthalmology practices rely heavily on compounded therapies for the prevention and treatment of many different eye conditions, it is essential that physicians and staff members understand these issues. This guide provides an overview of these legislative changes and examines their potential impact on ophthalmology practices and patients.

“Compounded medications from a registered Outsourcing Facility provide greater assurance of quality than purchasing from an unregistered pharmacy, because outsourcing facilities are subject to cGMP requirements and increased federal oversight.”

– Food and Drug Administration

A Timeline of Legislative Oversight

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1820</td>
<td>Congress passes the original Federal Food and Medications Act that prohibited exaggerated claims for elixirs and other potions that claimed to cure any ailment. Not only were they not effective, many contained toxic ingredients.</td>
</tr>
<tr>
<td>1906</td>
<td>The Federal Food, Drug, and Cosmetic Act (FD&amp;C Act) was passed by Congress in 1938 in response to 107 patient deaths from a poisonous elixir.</td>
</tr>
<tr>
<td>1938</td>
<td>U.S. Pharmacopeia (USP) establishes the first compendium of standard medications for the United States.</td>
</tr>
<tr>
<td>1941</td>
<td>Nearly 300 deaths from sedative-contaminated insulin prompts the FDA to test and certify its purity and potency. The FDA revises manufacturing and quality controls drastically, the beginning of what would later be called Good Manufacturing Practices.</td>
</tr>
<tr>
<td>1952</td>
<td>Adverse side effects from an antibiotic cause 108 deaths. The FDA implements a voluntary drug reaction reporting.</td>
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The History of Legislative Oversight in the Compounding Industry

Legislation related to prescription medications has historically been enacted in response to serious issues and adverse events including patient deaths, birth defects, and the marketing of ineffective medications.\(^1\) As a result of issues like these, the U.S. Food and Drug Administration (FDA) requires that all new medications go through a lengthy approval process and be subjected to stringent manufacturing control.

Compounded medications, however, have historically been exempt from these requirements due to Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act). This exemption recognized that the rules for mass-produced medications could not be practically applied to compounded medications, which are typically “manufactured” on demand. In addition, oversight of compounding pharmacies was predominantly done by state licensing boards.

Infections Linked to Compounded Medications Drives Greater Oversight

However, a serious outbreak of life-threatening infections was tied to compounded medications in 2012 and led to new government action. In the fall of that year, contaminated syringes of compounded steroids infected an estimated 751 patients in 23 states, killing 64 people. The patients suffered from meningitis, spinal infections, and strokes after undergoing routine procedures to alleviate back and leg pain. New England Compounding Center (NECC), an unaccredited compounding pharmacy, had distributed three lots of the contaminated syringes to be used primarily for outpatient epidural injections, a relatively common but high-risk procedure.\(^2\)

After an investigation into the NECC deaths, the U.S. Senate Health, Education, Labor, and Pensions (HELP) Committee published its findings in May 2013. The report stated that prior to 2012, site inspections by the Massachusetts State Board of Pharmacy and the FDA discovered unacceptable and dangerous conditions at the facility and contaminated medications.\(^3\) Although the Board issued a Warning Letter and the FDA issued a Consent Decree, NECC continued operations. As a result, Congress developed new legislation to clarify oversight responsibility and provide for enhanced manufacturing processes.

A Timeline of Legislative Oversight (continued)

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1962</td>
<td>Thousands of babies are born with birth defects, a result of an anti-nausea pill taken by their mothers during pregnancy. The FDA requires drug manufacturers to prove their products safety and their effectiveness.</td>
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<tr>
<td>1970</td>
<td>Seven patients die from ingesting Tylenol tainted with cyanide. The FDA requires tamper-resistant packaging.</td>
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<tr>
<td>1996</td>
<td>The Food and Drug Administration Modernization Act reauthorizes the Prescription Drug User Fee Act of 1992 and mandates the most wide-ranging reforms in agency practices since 1938.</td>
</tr>
<tr>
<td>1997</td>
<td>Thousands of women suffer life-threatening side effects from birth control pills. The FDA mandates that manufacturers include Patient Package Inserts with every prescription.</td>
</tr>
</tbody>
</table>
Introduction of the Drug Quality and Security Act

The Drug Quality and Security Act (DQSA) became law on November 27, 2013. The 80-page Act has direct consequences for compounding pharmacies and providers that use their services.²

The DQSA updated the Section 503A exemption. This exemption now applies only to small compounding pharmacies that produce medications in limited quantities, allowing them to continue their operations without using the most advanced quality and manufacturing techniques. State boards will continue to provide primary oversight of these pharmacies, and each pharmacy will only be allowed to have a small percentage of their medications shipped out-of-state, assuming valid licenses in those states. In addition, the prescriptions will need to be patient-specific for each compound.

DQSA also introduced a 503B exemption (designating Outsourcing Facilities) for larger sterile compounding pharmacies that requires the use of advanced manufacturing standards and imposes Federal oversight.

All Outsourcing Facilities must comply with Current Good Manufacturing Practices. (cGMPs). These cGMPs are a series of strict, detailed guidelines that must be observed during the preparation of compounded medications. These principles are designed to eliminate contamination of compounded medications, deviations from protocols or incorrect ingredients as well as other safety and quality issues. Under these requirements, a sample of each medication must be tested for the sterility and integrity of ingredients. Preparing compounded medications in a sophisticated, state-of-the-art cleanroom is also mandatory to adhere to cGMPs. Amongst other requirements, registered Outsourcing Facilities must:

- Agree to maintain stringent reporting requirements
- Submit to unscheduled on-site inspections of their facilities
- Adhere to FDA regulations regarding the bulk drug substances used to compound

As a result, providers that use compounded and sterile medications can now easily identify a pharmacy partner that meets high standards around quality control and patient safety via the Outsourcing Facility designation. While medications from pharmacies that do not register as an Outsourcing Facility may be less expensive, these facilities do not provide the same quality and safety assurance.

Avella opens its national distribution facility in Phoenix, Arizona to respond to its growing patient and provider volume. The facility houses a PCAB-accredited and USP <797> clean room for compounding.

Avella’s national distribution facility earns URAC accreditation, one of healthcare’s most prestigious accreditations, with over 600 organizations and companies accredited worldwide.

Drug Quality and Security Act becomes law on November 27, 2013.

2006

The Pharmacy Compounding Accreditation Board (PCAB) is formed and Avella of Scottsdale is the first compounding pharmacy in the nation to receive accreditation.

2012

64 patients die and 687 others are critically ill from contaminated medications compounded by New England Compounding Center.

2013

Avella registers in February as an outsourcing facility with the FDA in accordance with the Drug Quality and Security Act.
Putting These Best Practices into Action: Avella Specialty Pharmacy

Avella Specialty Pharmacy is one of fewer than 50 pharmacies currently registered with the FDA as an Outsourcing Facility. To comply with federal requirements as set forth in the DQSA, Avella is currently constructing a new, separate cGMP-compliant cleanroom.

Avella's primary focus has always been on patient safety and regulatory compliance. To achieve this aim, the company has voluntarily applied for accreditation by the most respected healthcare and pharmacy entities and adheres to current gold standards for compounding. These efforts include:

- Accreditation with the Pharmacy Compounding Accreditation Board (PCAB) Accreditation. Avella was one of the first pharmacies in the nation to earn PCAB accreditation and less than 200 pharmacies in the nation share this honor. For more information visit: www.pcab.org.
- URAC Accreditation for Specialty Pharmacy. URAC is the nation's largest accrediting body for healthcare. Compliance with URAC distinguishes organizations based on their commitment to quality and accountability. For more information visit: www.urac.org.
- Avella's standard operating procedures adhere to USP <797> for the preparation, storage, and shipping of compounded medications.
- Avella's safety measures include training, testing of personnel, personnel monitoring, environmental monitoring, and verification that sterilization equipment is working properly using various methods (bubble point, biological indicators, pyrotest). Avella also has a dedicated internal Quality Assurance department, including a staff microbiologist, and utilizes outside independent testing laboratories.

The Advantages of this Designation for Ophthalmology Practices and Their Patients

As stated by the FDA, “Compounded medications from a registered Outsourcing Facility provide greater assurance of quality than purchasing from an unregistered pharmacy, because outsourcing facilities are subject to cGMP requirements and increased federal oversight.” All physicians, and ophthalmologists in particular, should be aware of this legislation since Outsourcing Facilities can offer peace of mind to both providers and patients regarding the efficacy and safety of compounding medications.

About Avella Specialty Pharmacy

Founded in 1996 as a single pharmacy in Arizona, Avella Specialty Pharmacy has been recognized for its quality compounding capabilities for nearly 20 years. In addition to its extensive compounding laboratory, Avella has strategically expanded to become one of the nation's most respected specialty pharmacies. Avella's mission is to optimize patient health through a relentless devotion to clinical excellence.

For more information about how we meet the needs of Ophthalmology practices and their patients, please contact us at marketing@avella.com.