

Pharmacy Compounding: Report on Quality Assurance Initiatives in the State of Missouri and Issues Impacting Consumer Protection

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I. Background

The practice of compounding pharmaceuticals by licensed pharmacies has provided for many avenues of debate over the past decade. The art and science of compounding has been a traditional part of the practice of pharmacy for centuries. In fact, until after World War II, when drug manufacturing became more prominent, compounding was one of the principal practices used to provide needed drugs to patients. While the need for compounding of products has changed since then, the importance of compounding certain products by prescription is still a very important and necessary part of the practice of pharmacy. Many physicians and patients across the United States depend on pharmacists to compound products that they need. This need may stem from different factors such as allergies to a commercial product, availability of the needed drug delivery system or the lack of the availability of the drug commercially¹. In any case, present day compounding has taken on a larger role through the use of new technologies and in many cases can be successful in meeting the special healthcare needs of patients.

Most of these avenues are still open for discussion and analysis as the profession and the rest of the health care community struggle with issues involving the competency of pharmacists that compound products, the need for some of the products being compounded, fair reimbursement, quality and effectiveness of products, marketing and

¹ Kinkade, Kevin R.Ph.; Written Testimony Before the Health, Education, Labor & Pensions Committee, U.S. Senate; Hearing on Federal and State Role in Pharmacy Compounding and Reconstitution, Exploring the right Mix to Protect Patients; October 23, 2003

effective regulatory oversight. Compounding has increased significantly; both in the number of pharmacies offering such services and the types of products that are being compounded. As the number of types of products compounded increases, so does the question as to whether pharmacists are prepared adequately to provide some products without additional training or whether some products that are compounded can be done so in a safe and effective manner. Literature in pharmacy is replete with incidents where consumers have been harmed or large scale compounding practices made the dispensing of sub-standard products of major significance.

Examples of bad outcomes for compounding include fungal meningitis traced to compounded methylprednisolone, meningitis traced to contaminated betamethasone compound,² inhalation compounds contaminated with bacteria and contaminated cardioplegic solutions causing patient deaths. In addition, Missouri was faced with the criminal conduct of Robert Courtney and the intentional dilution of multiple compounds to multiple patients causing complications and death of patients. These examples and more have garnered national media attention, the attention of many state boards of pharmacy and Congress as to whether pharmacy compounding of drugs is a safe and effective way to provide medications for use by consumers.

A survey of some compounded products was conducted by the FDA in 2001. Samples were collected from pharmacies that marketed their products on the internet. Out of 29 samples collected, 10 or 34% failed to meet standardized quality tests. This sampling, although small, was the first indication that quality could be a more prevalent

² Ukens, Carol, Compounding Under Siege. *Drug Topics* 2003;1:44; Vecchione, Tony, Coping with Compounding. *Drug Topics* Mar, 22, 2004; 148: HSC 1.

problem than first thought.³ State Boards of Pharmacy began to look at their regulations governing compounding. The result of this review process was the enactment of stricter regulations governing compounding by a number of states.

A senate hearing was held in Washington D.C. in October of 2003 to examine issues of safety as well as common practices within the industry. Testimony was received from the Food and Drug Administration (FDA), pharmacist practitioners, a state Board of Pharmacy and a national association representing pharmacists. While the hearings have not generated any change in federal laws to this point, the age old question of what, if any, the role is of federal agencies concerning the oversight of compounding in state licensed pharmacy operations still exists.

Presently, stakeholders such as consumer groups, medical associations, pharmacy associations and government officials are still reviewing a number of issues. These issues include: 1) the high volume of compounded dosages that some pharmacies are providing on an interstate basis; 2) the quality of certain products that may require extensive or complex manipulations; 3) the similarity of some compounded products to those that are available as FDA approved drugs from manufacturers; 4) the competency of some pharmacists that enter into compounding due to a lack of additional training or proper equipment to compound pharmaceutical agents; 5) the practice of selective enforcement by federal agencies and the lack of definition between what is considered compounding vs. manufacturing; and 6) whether states are providing adequate oversight of pharmacies involved in the compounding of drugs.

³ FDA Center for Drug Evaluation and Research, Report: Limited FDA Survey of Compounded Drug Products. Fda.gov; Jan. 28th, 2003.

II. Missouri Board of Pharmacy

The Missouri Board of Pharmacy is comprised of seven members. Five members are full time practicing pharmacists from various practice settings within the state. One member, by law, must be a full time pharmacist employed in an institutional setting such as a hospital or long term care facility. One member is a consumer with no ties to the pharmaceutical industry. The board licenses and regulates pharmacists, pharmacies, drug distributors (wholesalers, manufacturers) and registers pharmacy technicians. The field staff consists of seven inspectors who are all licensed pharmacists. The executive director is responsible for the operation of the board office which includes the execution and management of all policy decisions made by the Board. The practice act for pharmacy in Missouri is Chapter 338 RSMo.⁴

III. Response by Missouri

The state of Missouri has made a number of changes in order to address many of the concerns noted. Legislation was passed that provides immunity to individuals who assist the Board within investigations and also provides specific immunity to practitioners who provide prescriptions to Board personnel for the purpose of undercover buys via the internet or within pharmacies. While these changes in the law would benefit the Board within future compliance work, the biggest change came in the area of increases in the Board's budget. An overall increase of thirty-five percent was added to the budget after the Courtney case was discovered. New funding for outside contract legal counsel in order to expedite the processing of pending discipline cases, funding for two additional

⁴ Kinkade, Kevin R.Ph.; Written Testimony Before the Health, Education, Labor & Pensions Committee, U.S. Senate; Hearing on Federal and State Role in Pharmacy Compounding and Reconstitution, Exploring the right Mix to Protect Patients; October 23, 2003

inspectors and funds to begin the random testing of compounded products provided by pharmacies were added. Funds for use within the random testing program were appropriated for two purposes. To pay for the analysis done by an accredited laboratory for potency and, when indicated, sterility and pyrogenicity as well as, to reimburse for any samples of product taken so that no loss of revenue would be sustained by pharmacies due to the new testing program. While these changes were being pursued, the Board began work on changes that were needed in the regulations governing compounding of drugs by pharmacies within the state. Regulations for compounding were contained in two rules. 4CSR 220-2.400 Compounding Standards promulgated in April of 1996 covered minimum requirements to be met by all pharmacies in any compounding process. 4CSR 220-2.200 Sterile Product Compounding promulgated in February of 1993 pertained to those operations involved in providing sterile compounded products to patients. Upon review of these regulations, it was determined that enhancements to both were in order. The regulation on compounding standards was amended to address issues that include:

- Stricter definitions to better differentiate between the practice of compounding vs. manufacturing by pharmacies;
- Providing specific definitions for batch compounding and beyond use dates;
- Requirement of a separate log to record information of each product compounded. The log must include a description of methods used to compound the product; component lot numbers as well as lot numbers assigned to the compound; and the beyond use date assigned along with other identifying information;

- Outlining effective quality assurance measures that include the use of drug components that meet compendial standards or maintain a certificate of analysis; pharmacy personnel have and maintain the appropriate knowledge and expertise; and the pharmacy maintains a drug monitoring system that includes the ability to evaluate quality assurance procedures. Drug monitoring includes statistics on infection rates, adverse drug reactions, recalls and patient complaints;
- Maintaining an effective recall system that requires the prescriber be notified of any potential problems concerning a product and, if the prescriber directs, or the product defect has the potential to harm the patient, then a recall of actual product at the patient level is required. Any recall initiated by a pharmacy must be reported to the Board of Pharmacy within three business days;
- No compounding of commercially available products. Exceptions to this restriction include temporary time periods where the commercial product is unavailable or if the commercial product contains an offending agent to a patient that can be removed through the provision of a compounded product; and
- Restrictions on compounded products to where they can only be provided through the receipt of a prescription for a specific patient(s). The practice of providing compounded drugs for floor stock by physicians or other institutions is prohibited.

The regulation on sterile product compounding was completely rescinded and replaced with new regulatory standards. Due to the costs associated with coming into compliance with the specified changes, the Board provided a grace period of one year to give pharmacies time to plan and initiate needed enhancements. The Board consulted the standards available from the United States Pharmacopeia (USP) which

were under proposed revisions at the time. The method used by USP⁵ to categorize sterile product compounding into three primary risk factors was used by the Board as the defining terminology for the regulation. The final regulation addresses areas not touched upon before that would increase requirements involving personnel education and training, facilities, equipment and end-product evaluations. The type of product produced, as well as the storage time, governs the type of quality assurance procedures (process validation and testing of product) that must be included with every batch of product produced. Those products considered to have a high risk potential in addition to process validation will need to be quarantined and tested by the pharmacy for sterility, pyrogenicity and potency. Examples of such products could include ophthalmic preparations and cardioplegic solutions. Depending on the expected shelf life of a product, pharmacies will have to arrange for an instrumental analysis of a product for a guarantee of potency.⁶

IV. Drug Testing Program

Perhaps the program that has garnered the most attention and has provided the greatest amount of information as to outcomes from compounding is the random testing program instituted by the Board. Beginning in July of 2003, the Board was able to secure an annual appropriation of approximately \$159,000 for the program. Funding is used to pay for the testing of products collected and to reimburse the pharmacies for any samples taken. Both sterile and non-sterile products are tested. Sterile products are also tested for sterility and, when appropriate, pyrogenicity. While funding levels do not permit

⁵ USP 29-NF 24: General Chapters 797 Pharmaceutical Compounding – Sterile Preparations

⁶ Kinkade, Kevin R.Ph.; Written Testimony Before the Health, Education, Labor & Pensions Committee, U.S. Senate; Hearing on Federal and State Role in Pharmacy Compounding and Reconstitution, Exploring the right Mix to Protect Patients; October 23, 2003

consistent testing of the multitude of compounded products that pharmacies offer to their patients, it can provide an important window of information as to 1) the level of competent practice patterns within a pharmacy or with a specific product class across a number of pharmacies and 2) in the remote chance that any pharmacist or pharmacy operation would contemplate a fraud on consumers, the randomization of the testing program would help dissuade such activities.⁷ Methods used to collect samples occur by one of two ways. First, when a compounded product is available from an existing inventory, the inspector will collect a sample during an inspection and arrange for payment of whatever product is taken. The second method is used when product is not available for sampling during an inspection but is found to be compounded by a pharmacy based on a review of the pharmacy's compounding records. The inspector will provide information about the product for the purpose of obtaining a prescription from a physician and arranging an undercover purchase by an investigator from the Division of Professional Registration. This method helps to ensure that the Board is receiving the same result from a compounding procedure that a consumer would receive.

All samples are sent by the person collecting the sample directly to the laboratory. Direction is provided with a form that notes whether the product is to be tested for potency, sterility and/or pyrogenicity. One laboratory, under contract with the Board, provides all services for the testing of product. A few exceptions have been made to this process when a particular product could not be tested, then the Board arranged for access to a second laboratory that was able to provide the testing of a product as required.

⁷ Kinkade, Kevin R.Ph.; Written Testimony Before the Health, Education, Labor & Pensions Committee, U.S. Senate; Hearing on Federal and State Role in Pharmacy Compounding and Reconstitution, Exploring the right Mix to Protect Patients; October 23, 2003

Laboratories involved in providing these services to the Board's random testing program must meet the following requirements:

- Maintain a current registration with the federal Food and Drug Administration (FDA);
- Maintain a current registration with the federal Drug Enforcement Administration;
- Maintain compliance with current Good Manufacturing Practices (cGMP); and
- Maintain compliance with current Good Laboratory Practices (GLP).

The laboratory will complete all compendial USP testing, including microbiology.

Methodology includes High Performance Liquid Chromatograph (HPLC), gas chromatograph, ultra-violet visible spectrometer and titration assay.

The Board views the testing program as part of the inspection process unless a consumer complaint is involved. In most every case, the Board has looked to find methods on a voluntary basis that will help improve products produced by a pharmacy when such products have tested below minimum standards. Minimum standards are considered results that meet USP standards for a particular product, or in the absence of such a standard, the Board has utilized the general standard of $\pm 10\%$ (ten percent) of the desired strength or concentration. Results are shared with the pharmacy. In cases where the test result is below acceptable standards, a report is completed by the inspector providing information about the compound and the type of failure(s) observed. An area is provided on the form for a response from the pharmacist-in-charge. An explanation as to why the product may have failed the test along with any changes or corrections to improve the product, information as to whether the sampled product was dispensed to

patients and, if so, was a recall initiated are all included as part of the response. This documentation process has been very helpful, not only as a tool for information, but to also ensure that the pharmacist-in-charge is aware of the results and has given thought to improving outcomes for the compound involved. Once the documentation process is completed the Board retrieves a second sample on the same product for analysis to see if the corrective actions taken by the pharmacy have translated into improved outcomes.

V. Results

The results of the program (through the end of calendar year 2005) are a window to the state of compounding in Missouri and, due to the fact that many of the practices encountered here are promoted and utilized nationally, there is no reason why this information is not valuable to anyone interested in the quality of compounded products and the value such products bring to consumers. Results of the program include a breakdown of the type of products tested, results of tests, the number and description of product recalls, responses from pharmacists when unsatisfactory test results were observed and details of corrective actions taken by pharmacies. Table 1 shows the types of products tested. It should be noted that all products selected for testing in the program have come from various types of pharmacy operations within the retail (ambulatory) patient sector. The Board intends to expand testing into the inpatient hospital setting through an agreement with the state Department of Health which regulates hospitals in Missouri. Oral liquids which would include suspensions and capsules make up the majority of compounds tested.

Table 1.

Type and Number of Compounds Tested

Compound Type	Number Tested
Inhalation Solution	8
Suppository	19
Transdermal	17
Intravenous Solution	17
Troche	2
Tablet	5
Nasal Spray	4
Ophthalmic Solution	2
Bulk Ingredient	2
Topical Cream/Ointment	1
Injectable Solutions	18
Triturate	1
Oral Liquid	185
Parenteral Nutrition Sol.	1
Capsule	128

A total of 410 products have been tested since the inception of the program in November of 2003. Table 2 provides an overview of the compounds sampled that tested below the minimum required standards set while Table 3 shows those compounds testing above minimum standards. Potency failures ranged from a few samples that tested 0% or no product evident within the tested compound to one case where a concentration of 553% was recorded. A total of 81 compounds collected from 59 pharmacies tested outside acceptable limits, which represented an overall failure rate of 19.8%. All products that were tested for sterility or pyrogenicity passed.

A Drug Testing Quality Assurance Report form (Appendix 1) is initiated by the inspector each time a failed test result is received. The inspector completes the top half of the form with information the pharmacy will need in order to identify the problem and allow the pharmacist-in-charge to respond with any corrective actions, as well as information on any attempts to recall the product.

Results of failed tests in some cases resulted in a drug recall. Appendix 2 provides information in relation to what drugs were involved and whether the recall, which under Board of Pharmacy rules is defined to begin when the physician is notified, resulted in patient notification.

Table 2.

Samples Testing Below Acceptable Standards

Alprostadi/Phentolamine/Papaverine injection	1
Azathioprine oral liquid	2
Bactroban nasal spray	1
Budenoside inhalation solution	2
Clonazepam oral liquid	1
Clonidine liquid	1
Dexamethasone/Metoclopramide supp.	1
Diphenhydramine/Haloperidol/Metoclopramide Inj.	1
DMD supp.	1
Estrogens combined with other hormones (capsule)	11
Ibuprofen gel transdermal	1
Magic Mouthwash	1
Methimazole liquid	1
Metronidazole oral liquid	2
Morphine/Bupivacaine injection	1
Omeprazole oral liquid	6
Phenazopyridine oral liquid	2
Piroxicam oral liquid	2
Prevacid oral liquid	4
Prilosec oral liquid	2
Progesterone capsule	2
Progesterone tablet	1
Progesterone supp.	1
Progesterone/Melatonin/Hydroxytryptophan caps.	1
Prolox 20% gel transdermal	2
Promethazine liquid	1
Promethazine transdermal	1
T-3 (Liothyronine) capsule	1
Testosterone capsule	2
Testosterone triturate	2
Various combinations of estrogens (capsule)	8

Table 3
Samples Testing Above Acceptable Standards

Diethylstilbesterol capsule	1
Enalapril liquid	3
Haloperidol/Lorazepam/Dyphenhydramine supp.	1
Leucovorin oral liquid	1
Metronidazole oral liquid	1
Piroxicam capsule	1
Powells solution	1
T-3 (Liothyronine) capsule	1
Testosterone capsule	2
Vancomycin liquid	3

Since the inception of the random testing program, the specific corrective actions taken by pharmacies when confronted with an unsatisfactory result can be grouped into the following categories:

- Initiated a thorough review of compounding procedures and formulas – 27 responses.
- Discontinued compounding the drug product in question – 4 responses.
- Received specialized training/classes on compounding outside of the pharmacy – 3 responses.
- Purchased special compounding equipment to improve accuracy – 7 responses.
- Hired an outside laboratory for the testing of future compounded drug products – 14 responses.
- Prepared/expanded a compounding policy and procedure manual – 3 responses.
- Initiated a program requiring periodic didactic and experiential training for employees compounding drug products – 2 responses.

No disciplinary actions have been taken by the Board solely as a result of any test results since voluntary compliance measures have been deemed to have accomplished needed changes.

VI. Conclusions

As stated earlier, there are obvious and vital needs for compounded drugs that are delivered to patients for the purpose of providing appropriate care that is safe and effective. The Board does not believe that a system of testing described in this report will, by itself, guarantee that all products provided to consumers will be safe and effective. However, random testing in concert with a thorough review of pharmacy compounding operations of pharmacies through adequate inspections will improve the chances that relevant standards for compounding of drugs are in place in those pharmacies that choose to provide such products. Based on the empirical data gathered through this program and feedback provided both formally and informally by pharmacists, the Board concludes that:

- The program has made pharmacists more aware that compounding is a sub-specialty within the profession which will require specific expertise;
- The overall response from pharmacists about the program has been positive, with many being more than willing to have their products tested; and
- Improvements in product outcomes have been observed in the vast majority of products that are re-tested due to improvements in processes and quality assurance programs.

The question we are left with at this point is how the profession and the public view the present failure rate of 19.8%. While this is high and of obvious concern, factors that

determine the need for a compounded product to be used in preparing a prescription and the consequences to patient care if such products are not available are important considerations. Further study of the matter is necessary, including comparisons between pharmacies that compound a large number of prescriptions opposed to those that may only compound small quantities as to whether such practices could be a determining factor governing quality.

Indications are that most pharmacists are concerned about quality and are in favor of self-regulation to maintain public confidence in this area of practice. An interest on the national level to foster voluntary certification through private sector initiatives is another good indicator of this. Measures that afford effective and random checks of licensees compounding products for consumer use need to be the focus of state boards of pharmacy that are in the best position to initiate and maintain adequate inspections of state licensed facilities.

Inspector Sid Werges is recognized for his assistance in providing portions of the statistics used in this report.