Assuring the safety and efficacy of pharmaceuticals is important to any managed care organization. Compounding in the pharmacy needs scrutiny.

The Quandary of Compounding for MCOs: Administrative Costs, Risks, and Waste

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ABSTRACT

Purpose: Pharmacy compounding of prescription therapies that do not have Food and Drug Administration (FDA) approval increases administrative costs to managed care organizations and may also place members at risk for poor outcomes. This paper provides health care administrators with information and tools that can be used to manage risk-encouraged practices from pharmacy compounders, and suggests methods for evaluating the medical appropriateness and benefit of such compounds.

Study design: Experiential findings.

Results: Methods indicate an effective way to manage this emerging pharmacy practice based on safety, risk avoidance, and outcomes.

Conclusion: Focused management efforts can reduce the burden of reimbursement for compounding practices that are likely to present a greater risk of medical errors than commercially prepared medications. The use of existing terms in plan contracts, such as "experimental treatments or medications," "medical necessity," or "non-FDA approved agents," can enable an editing process that provides for appropriate benefit enforcement and control.

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INTRODUCTION

Are compounded medications that are prepared in local pharmacies consistent with the goals and measures used in managed care settings? Do health care executives recognize devices or therapies that have not shown efficacy or that have no relevant clinical outcomes or evidence to support therapeutic claims?

Few, if any, managed care plans offer benefit payments for herbal remedies; most review experimental therapies and unproven medical procedures with preauthorization processes. Compounded prescriptions lack evidence of a desired therapeutic effect and pose significant opportunities for errors in the manufacturing process. The aspect of culpability will not go unnoticed by the legal profession, which is likely to seek damages from those who allow a guided choice. Recent events include the sealed settlement for Lilly and Bristol-Myers Squibb related to allegations that both pharmaceutical companies were aware of drug-use discrepancies in regards to the Robert Courtney case in Kansas City.[1] The Happle vs. Wal-Mart case that addresses a known drug allergy is under appeals. This suggests that expanded culpability is developing. There is a growing challenge to the learned intermediary statutes that have protected pharmacists from malpractice.[2]

This paper focuses on retail pharmacy compounded medications that are administered via oral, topical, and injectable routes. The author is not referring to sterile compounded prescriptions for injectable administration in a hospital setting or to radiological solutions prepared from appropriate infusion mixtures for use in inpatient settings.

Retail pharmacists have practiced prescription compounding for a long time. In managed care, this practice is expanding, and it is driven by financial incentives, growth from advertising, and the growing wellness movement in this country. Historically, pharmacists have compounded prescriptions to meet the need for medications not provided by commercial manufacturers, and for altering flavors or dose forms to make the medicine more palatable. Federal food and drug regulations (Section 503A) permit pharmacists to prepare small quantities of unapproved drugs only if the bulk drug is a component of an approved drug as listed in the United States Pharmacopoeia or the National Formulary monograph, or if it is named by the Food and Drug Administration (FDA) on a separate list.

Nevertheless, the ingredients must

follow federal FDA guidelines for appropriate use. Procedures and processes that are known to provide for stability and efficacy and that show evidence of therapeutic outcomes, as provided for commercially manufactured products, are lacking are in compounding practice. MCOs today face issues related to compounds that duplicate commercially available medications with only slight modifications.

Plans must evaluate compounded medications that are prepared in local pharmacies and determine whether the compounded drug is consistent with the goals and measures used in managed care settings for quality assurance and to maximize efficacy and safety.

Clandestine pharmacy compounds do not pass through the procedural rigors that occur with commercially prepared medications.[3] The preparation practices for compounds may have a higher likelihood of mixing errors in the filling of the prescriptions due to the pharmacist's inexperience with the compounding process.

As compounds do not have National Drug Codes (NDCs), electronic claims submissions by retail pharmacists for online payment must be done in one of three ways: If the compound is prepared from an existing prescription medication that has an NDC code, the higher cost ingredient code is generally submitted. If claims processors can assign dummy NDCs that are recognized by their systems, these may also be used, or the member must pay the pharmacist and submit a paper claim.

The first two choices do not provide a claims processor with adequate details about the content of the compound, and may suggest that the pharmacist use an existing NDC number when the prescription is prepared from bulk drug powders. Asking a pharmacist to submit an NDC that is not used in the preparation places the pharmacist at risk for financial recoupment from audits. The paper-claim method increases administrative costs for this process. Some pharmacies refuse to adjudicate claims electronically for these reasons. Certainly, having the member pay the full price and having the member submit the claim may be a financial benefit for the compounders as well as reducing the opportunity for audit awareness of the MCO. Our claims systems provide for more than financial payment; they also provide an integral step in concurrent drug utilization evaluation (DUE) and in flagging interactions, and thus compounds fall outside a basic safety measure.

Studies in the literature address some stability issues of compounded medications being prepared from commercial tablets, capsules, or injectables.[4–6] Although stability discussed in such articles can be quoted, the fact remains that in these studies, the active ingredient has been through the quality-control process to ascertain the composition and purity of the starting materials. This is not the case for pharmacy compounding activities using bulk drug substances.

The unfortunate incident in Kansas City involving Robert Courtney, who is charged with knowingly diluting an estimated 98,000 prescriptions (possibly affecting up to 400 physicians and 4,200 patients), illustrates the worst of the worst.[7] Additionally, cases in Walnut Creek, Calif., early in 2002, involving the compounding of injectable medications, had tragic outcomes. Compounding errors led to contamination with bacteria from inadequate aseptic technique in the preparation of injectable betamethasone. The compound was used for spinal injection, resulting in three deaths and more than 30 hospital admissions.[8,9] Recently, at the request of Rep. Henry Waxman, of California, the FDA issued a letter of "cease and desist" for the compounding of nicotine lollipops. Consumer groups feared that the nicotine lollipops, which contained a chemical form of nicotine that was unregistered with the FDA, posed a health threat to children.[10] Nicotine salicylate does not meet the criteria for use in preparation of a medical product, and in this case, the lollipops are considered misbranded and illegal.

Compounding by retail pharmacists also introduces opportunities for errors related to mathematical calculations, selection of compounding chemicals, aseptic technique, or inexperience.[11,12] Moreover, as a drug's potency increases and the routes of delivery become more immediate, the likelihood of problems increases.

PAYER CONCERNS

Reimbursing claim amounts for compounded medications, as well as prescribing frequency rates, have been rising significantly for many plans in recent years. In an evaluation of claims cost experience incurred for compounds by employer groups, the range was from $10 to $71, resulting in an average of $41 per compound order. On a per-patient, per-month basis, the range was $0.11 to $0.99.[13]

Plans may decide to use appropriate existing terms that allow easy management quickly. Using existing terms of the contract can prove effective and rapid without the need for member mailings, governmental filings, and document changes that are required for new contract terms. Existing terms such as "FDA approved" or "not experimental" may be chosen by the MCO to manage compound requests.

The increased popularity of compounds is traceable to media awareness, advertising, and consumer-based marketing by compounding pharmacies. Compounding pharmacies do not practice postmarketing surveillance for adverse events or outcomes. Incidents involving medication errors add to overall patient cost, as well as morbidity and mortality. Additional concerns are ac-

knowledged when compounding pharmacists also prepare medications for veterinary care. Compounding pharmacies using the same facility, and often, the same equipment, to prepare human compounds, raise serious concerns regarding cross contamination between animal health compounds and human compounds. The Current Good Manufacturing Practice (CGMP) procedures address this risk as well as the concern for appropriate skills in the compounding process as administered by the FDA.[14]

REGULATORY JURISDICTION

The FDA has subrogated regulatory power for rule enforcement to the individual state boards of pharmacy. Each state may apply some flexibility to its own rules on compounding pharmacies, although most are similar in scope and statute. The state boards of pharmacy cooperate with the FDA regarding health risks posed by compounded products. Essentially, the FDA does not recognize the marketing and promotion of compounds as a legitimate need. Recent Supreme Court rulings nullified the 1997 FDA opinion, which promoted that advertising by compounding pharmacies was not acceptable. The appeal was upheld to allow advertising for compounding pharmacies, based on First Amendment rights.[15]

REGULATORY SUBJECTS

CGMP provides the quality systems for FDA-regulated products (foods, drugs, biologics, and devices). Such preproduction process controls are being used in automotive and most Department of Defense industries. Manufacturers now are required to incorporate a set of checks and balances in their manufacturing/design processes to assure a safe and effective finished product. Manufacturers must establish and follow quality system protocols to help ensure that their products consistently meet applicable requirements and specifications.[16]

Pharmaceutical manufacturers must also adhere to CGMP to have a new drug application (NDA) accepted for review by the FDA. CGMP requires the manufacturer to evaluate obvious variations in the development process using continuous quality improvement techniques.

Processes incorporate all aspects of finished drug storage temperature, drug stability, absorption, and particle size influence on dissolution and dispersion, with emphasis on the finished dosage forms, efficacy, and safety.

BULK DRUG SUBSTANCES

Today many chemical repackagers import potent bulk drugs from around the world for sale to compounding pharmacies. These chemicals enter the United States as imports and may or may not undergo import testing, custom declarations, or review.

The FDA works closely with the United States Customs Service to monitor goods coming into the United States but may not review chemicals that are not declared as drugs. Recent experience has shown that the United States Customs Service is understaffed and is able to check only a small number of imports. The FDA guidelines allow research quantities of drugs to be imported without consideration of trade laws and patents; these may be reviewed for adulterant components and require FDA registration, however, if found to be abusive in practice. Furthermore, the FDA offers voluntary oversight with regulations for foreign production facilities. FDA use of Drug Master Files (DMF)[17] and the requirement that pharmaceutical manufacturers adhere to CGMP with registration offer some assurance that the manufacturer is intent on complying with the rules to manufacture a consistent and pure product.

Bulk drug substances (BDSs) are components of drug products. The manufacture of BDSs should be carried out in accordance with concepts of CGMP, regardless of whether the manufacturers are required to register.[18] The manufacturer of inactive ingredients may not be required to register with the FDA, but manufacturers are not exempt from complying with CGMP concepts or exempt from inspection if the materials are used in medical products. A manufacturer of "inactive" ingredients is always subject to "for cause" inspection. Generally, however, it is reasonable to expect CGMP concepts to become applicable when a starting material enters a biological or chemical synthesis or series of processing steps, where it is known that the end product will be a BDS.

The question of when an industrial chemical becomes a BDS can be complex, and there is no satisfactory answer. Chemicals used in compounding may carry the designation "USP-NF"(United States Pharmacopoeia and National Formulary). This relates only to the process of analysis that the chemical undergoes to determine the chemical components with minimum and maximum allowable impurities. USP-NF signifies that this BDS could be used for the manufacture of pharmaceutical dosage forms. Food processors require these chemicals to use the designation of food grade/*Food Chemicals Codex*-classified materials.

The intention is to provide a standard by which the food industry is guided in manufacturing wholesome foods and added ingredients to meet Generally Recognized as Safe (GRAS) standards. The chemical industry uses other unique designations of analysis for various industrial processes needs. "Regent grade" aligns with the American Chemical Society to set allowable trace materials in chemicals used in laboratory analysis. The electronics manufacturers require ultra pure chemicals for etching chip patterns: Nano-Purity/Electronic Grade are the choice. Standards provide analytical

assurances for various industries to determine strength, concentration, dissolution properties, quality, particle sizes, and purity, identity, packaging, and labeling and storage conditions needed to provide stability for the chemical product.

SAFETY, EFFICACY, AND "DO NO HARM"

To assist the pharmacist, the FDA has published a list of medications that have been banned for human and animal use.[19] This listing is changed as needed to protect the public welfare, as well as to protect the food chain. The unknowing use of banned agents is a violation of the Compounding Pharmacy Act and carries the potential for a criminal penalty.

The following examples represent the types of compounds currently being popularized.

Hormone replacement. Hormone replacement is offered widely at compounding centers across the nation. Commonly patients believe that natural hormones are safer and better utilized by the body.[20] This leads to the belief that the existing commercially available products for hormone replacement are inferior. Compounded hormone may differ in strength from batch to batch, and compounding pharmacists use bulk hormone chemicals that have not been analyzed prior to compounding.

Outcomes are not measured scientifically using controlled studies, but they are measured only by self-testimony from the purchaser, who is generally satisfied if the hormonal symptoms decrease or change. The abatement of symptoms does not indicate appropriate outcomes or safety, but the perception is that the compound is a "wonder drug" in many cases. As estrogenic/progesteronic hormones have been implicated in thromboembolic events,[21,22] the applicability of testing the final drug concentration is of utmost importance in determining dose consistency and risk reduction from extremely potent or subpotent dosing.

It is also important to be aware of the hormone replacement study that was recently stopped due to higher-than-expected cancer risks for patients receiving various HRTs.[23]

Testosterone gels/ointments and progesterone. Topical hormones currently are popular in the media, with several daytime talk shows having spokespersons promoting them to reduce hot flashes, to increase libido and sexual sensation, as well as to address skin and hair texture. These hormones are mixed in various bases ranging from an ointment base to a blended hydrophilic cream base. The concern is again the variability of the dose, due to absorption differences from the vehicle chosen and the area of application.[24] The patient does not normally recognize outcomes and adverse events, and thus the concern for harm is ongoing.[25]

Hepatitis C. Another common offering is the compounding of ribavirin (Rebetron) to avoid the cost of the commercially available form when peginterferon alfa-2b (PEG-Intron) is prescribed. Patients may be offered incentives by the compounding pharmacies in the form of reduced or waived copayments or a reduced cost for the combination of two products. It is unlikely that the patient can make a truly informed decision regarding the hidden risk of subpotency or superpotency. A decision that is based on the apparent cost savings could lead to catastrophic effects for the patient if the bulk materials are not tested for potency, dissolution, and absorption. The manufacture of substitute capsules offers an unknown variable in terms of the absorption profile, dissolution rates, and the overall blood level of the drug to inhibit viral replications. Using clandestine capsules with PEG-Intron may not provide the synergistic effect that the commercial product provides in combating hepatitis C infections, and can worsen an already devastating disease.

Budesonide liquid. The compounded budesonide solution is prepared as a substitute to the commercially available form (Pulmicort Respules). Pulmicort Respules is a suspension product that offers optimized pharmacological effects when used for respiratory nebulization in treatment of airway disease. Compounding by pharmacists results in an inferior product, with poor drug delivery to the small airways of the lungs and the possibility of bacterial contamination.[26] Nebulization is affected by device, viscosity, temperature, and composition of the liquid. The commercially available suspension, however, has been formulated to provide optimized particle-size distribution to allow for drug delivery into the airway sacs.

Promethazine HCl (Phenergan) topical gel. This gel is a popular compound that seeks to control nausea through transdermal absorption. This compound is promoted to pediatricians who desire to control nausea and vomiting without the use of rectal suppositories, which are unpopular with young mothers. There is no commercial availability of a similar topical product to control nausea and vomiting except scopolamine patches used for motion sickness. Skin type, thickness, and area of application alter the absorption of topically applied medications significantly. The question remains as to how much of the drug may be absorbed.[27] The opportunity to achieve the optimal dose is rare at best, and young children's skin has a different absorption pattern than adults.

Ketoprofen gel. This gel is often prescribed to promote relief from mild exercise-induced muscle pain. The use of a topical gel containing ketoprofen and, often, other agents such as dexamethasone, provides transdermal penetration of the active drugs. The use of ketoprofen topically has not been proven more ef-

fective than the oral agent that is available in prescription and nonprescription strengths. The addition of dexamethasone or other steroid agents brings the added concern of thin skin areas developing stretch marks.

There are various formulae in the market with regional variations of steroid content and ketoprofen content, which result in wide variations in final concentrations of the active agents.[28] Contact dermatitis is mentioned in the literature as a significant side effect of topical nonsteroidal anti-inflammatory drugs.[29] Further references suggest sunlight can sensitize the patient to suffer longer-term effects.[30]

Injectable medications. Promotion of compounded injectable medications that are in a shortage status or are no longer being produced (e.g., betamethasone, testosterone enanthrate) is extremely disturbing. Compounding topical and oral-dosage forms offer higher risks than commercially prepared products, but the risks associated with compounding injectable medications are even higher.

The compounding of injectable medications underscores the importance of sterility, particle size, drug stability, and pyrogen testing, as well as the need for absolute assurance of BDS integrity. The recent tragedies that resulted in deaths and hospitalizations related to an injection compound that was contaminated with bacteria· point to this.[5] Once prepared, the injectable medications should be assayed for strength, potency, and sterility. The manufacturing of injectables necessitates both advanced methods and expensive equipment.

It is likely that compounding pharmacists who prepare injectable-dosage forms could not defend the claim of being a manufacturer, thus calling for FDA scrutiny of their operations and for compliance with CGMP.

CONCLUSION

Is the product effective in treatment? Is it safe? Does it provide the best value based on any risk that the MCO will possibly incur? Is there a basis to believe the compound medication is chemically stable? If so, for how long? Commercial pharmaceutical manufacturers offer robust and varied selections of products. The FDA has encouraged pharmaceutical manufacturers to pursue the status of "orphan drug" for small disease populations. Compounding pharmacy centers do not offer evidence-based outcomes for the products they manufacture, other than anecdotal articles and self-reported testimonials on actions or results of these medications.

In managed care, we continually strive for nonplacebo comparative drug studies with valid outcomes and numbers needed to treat. Few, if any, of the above compounds have well-documented stability studies for retention of drug potency. If the MCO does reimburse for a compounded medication, then how does the compound fit the prescription drug benefits for days' supply with regard to drug potency/stability?

Is it safe? Modern pharmacy is at the point of developing a new paradigm. The effort to change the role of the pharmacist from a dispenser of medication to one who provides consultative care is moving slowly. The significant shortage of pharmacists today, with the estimation of over four billion prescriptions being filled per year by 2004, is a staggering thought. The opportunity to provide better patient care is enhanced by the adoption of electronic methods to improve accuracy of prescriptions as well as the reduction in drug interaction errors. Huge efforts are being made to validate process flows to reduce errors; efforts also are being made to transform risk into nonrisk with applicable technology.

Employer-powered groups, such as the Leapfrog Group, or public interest groups, such as the Agency for Healthcare Research and Quality, the National Patient Safety Foundation, the Institute for Safe Medications Practices, and Medicare strive to establish quality as a primary driver for vendor choice by members.

MCOs seek quality measures essential to maintaining accreditation by the Utilization Review Accreditation Committee, the National Committee for Quality Assurance, the Joint Commission on the Accreditation of Healthcare Organizations, and other private and governmental groups. Health plans use the pharmacy and therapeutics committee process to evaluate the safety, efficacy, and value of medications for placement onto the formulary. Highly sophisticated manufacturing processes evaluated by the FDA provide the patient, prescriber, and payer with a degree of assurance that the medication and the delivery device are effective and safe.

Given all the effort that is going toward safety and quality of medications, why should MCOs and pharmacy benefit managers continue to accept requests for medications that pose a greater risk of harm?

REFERENCES

1. Margulies, D. Star wants court files to be unsealed in lawsuits against drug makers. *Kansas City Star.* Aug. 24, 2002. Available at: «www.kansascity.com/mld/kansascity/news/local/3926863.htm».
2. *Happel v. Wal-Mart*, Ill. App.3d (Second District, No. 2-99-1154, 9-29-2000).
3. Cooney P. Sterile drug products 2001 Aug 8: [presentation at FDA meeting]. Available at: «www.fda.gov/ohrms/dockets/ac/00/slides/3634s2_01_cooney/sld001.htm».
4. Johnson CE, Price J, Hession JM. Stability of norfloxacin in extemporaneously prepared oral liquid. *Am J Health Syst Pharm.* 2001;58(7): 577–579.
5. Nahata MC. Development of two stable oral suspensions for gabapentin. *Pediatr Neurol.* 1999;20(3):195–197.

6. Abdel-Raham SM, Nahata MC. Stability of terbinafine hydrochloride in an extemporaneously prepared oral suspension at 25 and 4 degrees C. *Am J Health Syst Pharm.* 1999;56(3):243–245.
7. Morris M. Bond wants federal review of Courtney case. *Kansas City Star.* April 30, 2002.
8. Zamora J. Walnut Creek druggist is suspended in meningitis deaths. *San Francisco Chronicle.* March 14, 2002.
9. Vermeij P. Extemporaneous preparation of an injection is issue of quality, not ethics [letter]. *Am J Health Syst Pharm.* 1996;53(18):2219.
10. Waxman H. Letter to Tommy Thompson, Dept. of Health and Human Services. Action to halt compounding of nicotine lollipops. Apr 3, 2002.
11. Perrin JH. Comments on drugs difficult to compound and the quality of chemicals to be used in compounding. *Drug Dev Ind Pharm.* 1999;25(4):553–557.
12. Johnson P, Jones G. Pharmacist compounding of analgesic medications: the risk of a little-known practice. *J Fla Med Assoc.* 1997;84(1):13–15.
13. Blended data from two mid-central claims processors (PBMs) — 1-year experience 2001 — 58 million pharmacy claims, based on personal request.
14. Code of Federal Regulations. Title 21, Parts 207.3(a)(4).
15. U.S. Supreme Court 2002, Thompson, Secretary of Health and Human Services, et al v. Western States Medical Center, et al. Certiorari to the U.S. Court of Appeals for the Ninth Circuit. No. 01-344. Available at: «http://supct.law.cornell.edu/supct/html01-344.zs.html».
16. Code of Federal Regulations 820. Title 21, Part 820.
17. Code of Federal Regulations. Title 21, Part 314.420.
18. Code of Federal Regulations. Title 21, Part 207.
19. Code of Federal Regulations. Title 21, Part 216. Criteria set for submitting chemicals for compounding to the FDA.
20. Adams C, Cannell S. Women's beliefs about "natural" hormones and natural hormone replacement therapy. *Menopause.* 2000;8(6):433–440.
21. Drouet L. Venous thromboembolic pathology. New acquired risk factors or new data on acquired risk factors. *Arch Mal Coeur Vaiss.* 2001; 94(11 suppl):1318–1326.
22. Sitruk-Ware R. Progesterone in hormonal replacement therapy: new molecules, risks and benefits. *Menopause.* 2002;9(1):6–15.
23. Task Force Issues Caution on Combined Hormone Therapy [press release]. October 15, 2002. Agency for Healthcare Research and Quality, Rockville, Md. Available at: «http://www.ahrq.gov/news/press/pr2002/hrtrecpr.htm».
24. Kreilgaard M. Dermal pharmacokinetics of micro emulsion formulations determined by in vivo microdialysis. *Pharm Res.* 2001; 18(3):367–373.
25. Dimitrakakis C, Zhou J, Bondy CA. Androgens and mammary growth and neoplasia. *Fertil Steril.* 2002;77 (suppl 4):26–33.
26. Fausnight TB, Angelini BL, Gentile DA, Skoner DP. Case report of the efficacy of pharmacy compounded vs. FDA approved budesonide inhalation solution. *Ann Allergy Asthma Immunol.* 2001;79(1):1081–1206.
27. Shawn DH, McGuigan MA. Poisoning from dermal absorption of promethazine. *Can Med Assoc J.* 1984;130(11):1460–1461.
28. Smith JF. The incidence of topical steroid dilutions. *J Clin Hospital Pharm.* 1982;7(2):137–140.
29. Baudot S, Milpied B, Larousse C. Cutaneous side effects of ketoprofen gels: results of a study based on 337 cases. *Therapie.* 1998;53(2):137–144.
30. Offidani A, Cellini A, Amerio P, Simonetti O, Bossi G. A case of persistent light reaction phenomenon to ketoprofen? *Eur J Dermatol.* 2000;10(2):153–154.