FIRST ISSUE IN A 5-PART SERIES

THIRD ANNUAL

CONQUERING THE CANCER CARE CONTINUUM™

Good Manufacturing Practice

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I am very excited to announce our Third Annual *Conquering the Cancer Care Continuum* newsletter series. These publications will continue to address highly relevant topics in oncology management. The first issue focuses on current good manufacturing practice (cGMP) and includes articles written by a clinical oncology pharmacist, an oncology nurse practitioner, and a regulatory lawyer. These perspectives, based on the faculty's expertise and personal experience, explore a wide array of issues related to this topic, including regulation for the approval of novel drugs, the pros and cons of over-the-counter (OTC) supplements, and the importance of careful patient selection in clinical trials. Future issues in the series will discuss access to quality care, advances in side effect management, the impact of the Affordable Care Act on cancer care, and pediatric patient care.


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Patients often assume that if a drug or supplement can be purchased over the counter, there should be no concerns about safety, efficacy, or drug-to-drug interactions that could negatively impact their cancer treatment or personal health. It is common for patients with cancer to ask oncology nurses which OTC drugs can be used to diminish specific side effects caused by the chemotherapy they are receiving. There are also situations in which patients decide to self-medicate with OTC medications and neglect to inform their healthcare providers, assuming that their actions are safe. The challenge we face is that there is a lack of evidence-based research on most of these substances, and the existing data do not provide a definitive answer as to what is and is not acceptable for use in patients with cancer. Although, anecdotally, we may have some information on what has worked for other patients, scientific data are not usually available. Furthermore, even when there is confirmation through research that certain OTC options diminish treatment-related symptoms, we do not know whether these substances will have an impact on the metabolism of the cancer therapy being administered. Clinical trials of new or existing OTC supplements are so expensive that few or none can be justified in the current world of healthcare. All agents investigated within a clinical trial setting require the use of a New Drug Application, a regulatory complexity that has costs of its own.

Despite the lack of definitive information about OTC drugs and supplements, nurses must be prepared to make recommendations about their use in the outpatient setting. When nurses are considering a specific recommendation, they would be wise to consider the

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following questions. *What level of evidence-based research exists regarding the drug/supplement to date? Has this drug undergone investigation by the US Food and Drug Administration (FDA) as part of a clinical trial?* Additionally, nurses need to stop and think twice before making recommendations. Given that not all OTC agents fall under the auspices of the FDA, there is risk that a patient may experience untoward side effects or drug reactions; he or she may also potentially lose the benefit he or she is receiving from his or her cancer therapy. If cGMPs are in place, however, there is a higher likelihood that an agent has been evaluated for safety, which may increase a provider's comfort level in recommending it to patients.

We need to be diligent in staying abreast of what the FDA is doing, and we need to know which federal laws are associated with drug manufacturing.

Clinical oncology pharmacists are also in a pivotal position to counsel patients and need to rely on cGMPs. They, too, interact with cancer patients every day and need to be aware of clinical trials for which patients may be eligible at specific points in time. Some patients may express that they want to try "everything," hoping for a miracle to happen by participating in a phase 1 clinical trial. Others who are very ill may want to leave as part of their personal legacy the decision to participate in a phase 1 clinical trial that may benefit the next generation of patients dealing with the same disease. Pharmacists are also involved in identifying later-stage trials that may be helpful to patients. They are directly involved in educating patients regarding various study designs as well as teaching about various investigational drugs. What pharmacists cannot do is guarantee the patient that the novel agent has been manufactured in accordance with cGMP. Additionally, the benefits of cGMP are not consistently followed globally. Drugs produced in one country may not be as highly regulated as they are in the United States. This results in inconsistent drug contents that may pose a danger to patients. We also know that patients will order drugs online and may or may not tell their oncology providers what they are taking and how they obtained it.

We rely on government agencies to ensure the safety of our drugs. Ensuring safety of compounded sterile products was thought to be managed relatively well, at least through consumers' eyes, until a serious incident was uncovered in October 2012, when a compounding pharmacy failed to maintain a sterile technique and an outbreak of fungal meningitis occurred. This resulted in loss of trust in such specialty pharmacies. During that time, the FDA advised healthcare providers to discontinue using products manufactured by a specific compounding pharmacy and recalled all of the products it had manufactured. Though the Centers for Disease Control and Prevention was able to track down the source of this outbreak and stop the pharmacy chain from continuing to disperse these drug preparations, 751 people developed meningitis, of whom 64 died. This serious incident brought about the need for more scrutiny, and a new regulation was enacted in November 2013: the Drug Quality and Security Act. This act provided a major revision in the compounding of human drugs. It splits compounders into 2 categories—traditional compounders and outsourcing facilities. It is hoped that this law will increase the safety of drug manufacturing.

Many of us take drug manufacturing for granted to some degree. However, this is a serious mistake. We need to be diligent in staying abreast of what the FDA is doing, and we need to know which federal laws are associated with drug manufacturing. We also must be aware of which regulations and research are associated with OTC drugs and supplements before making recommendations to our patients, especially while they are receiving cancer treatment. ■

Good Manufacturing Practice: A Nurse's Perspective

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As a nurse practitioner and a researcher whose focus is on supportive care in cancer, many of my patients and their caregivers look to me for answers to their questions regarding over-the-counter (OTC) supplements and prescription drugs used to treat various disorders. Oftentimes, patients seek my opinion concerning appropriate OTC and prescription drugs for treating such conditions as peripheral neuropathy. One of the most common questions I receive is: *What over-the-counter drugs can I take to treat my peripheral neuropathy symptoms?*

Beth Faiman, PhD(c), MSN, APRN-BC, AOCN

The answer to this question is not an easy one. By all means, I am aware of the multiple OTC and prescription drug trials conducted in various tumor types over the last 2 decades in the area of peripheral neuropathy prevention and treatment. Of the existing oral OTC supplements used to treat this condition,[1-4] many are obtained easily but none have been clearly shown to decrease neuropathy symptoms in patients with cancer who are undergoing chemotherapy. OTC supplements are appealing to patients, as many of these agents are readily available and relatively inexpensive compared with prescription medications. But what monitoring practices are in place for clinical trials designed to investigate the safety and efficacy of new OTC supplements and prescription drugs? Should nurses and clinicians be concerned that most OTC supplements are not regulated by the US Food and Drug Administration (FDA)?

According to the FDA, the definition of a drug—whether OTC or prescription—is any substance "… intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease…."[4] Clinical trials of new or existing OTC supplements are costly to conduct because FDA trials are heavily regulated. Enhanced regulation leads to increased costs—with the purpose of protecting the clinical trial participants.

All agents investigated within clinical trials, and that are intended to treat disease or mitigate symptoms, require the use of a New Drug Application (NDA) and investigational new drug (IND) process. In addition, all drug trials within the United States must adhere to the governmental FDA Code of Federal Regulations (CFR) Title 21 regulations.[5] Unfortunately, important and potentially pivotal drug trials, which are costly to perform, are not conducted because of limited funding or a lack of qualified researchers and personnel to carry out the studies.

Current good manufacturing practice (cGMP) is an essential component of new drug research, and ensures the quality and consistency of each compound through a variety of processes covered under CFR Title 21 regulations.[5-7] The CFR Title 21 regulations outline personnel, equipment, facilities, and manufacturing considerations for drug trials. Additional areas include drug processing, packaging, labeling, and distribution of the drugs, all of which are carefully monitored. Identity, strength, and drug purity are also confirmed by following cGMP.

How do cGMPs impact nursing practice? It is within the scope of practice for nurses to recommend OTC drugs in the outpatient setting. When approached with the question of which OTC supplement or prescription drug is best to take to mitigate a particular symptom, I first consider the following: (1) the level of evidence and (2) whether the drug was investigated under the auspices of an FDA-regulated trial.

Should nurses and clinicians be concerned that most over-the-counter supplements are not regulated by the US Food and Drug Administration?

I have firsthand knowledge of the importance of cGMP and the role played by the FDA in a recent clinical trial[8] in which I held the NDA/IND. This randomized trial evaluated the use of a readily available OTC agent for the treatment of cancer-related neuropathy symptoms. Through my experience, I observed that the

strict nature of clinical trials is magnified further when an NDA/IND is requested. Aware of the rigorous processes and controls of FDA-regulated trials with a focus on drug safety and consistency of a compound, I looked to see if OTC and prescription drugs were evaluated in this manner in this particular trial.

Knowledge of cGMPs is imperative when one evaluates the risks and benefits associated with the use of OTC supplements and prescription drugs by patients.

Should nurses and clinicians be concerned that not all OTC agents are regulated by the FDA? The short answer is "yes". Taking any drug is associated with risks. OTC drugs can interact with other medications, may lead to increased side effects, and can contain chemicals that are not consistent among lots. Yet, if cGMPs are in place, compounds can be safely evaluated and recommended to patients. Patients should be reminded to report the use of all OTC supplements to their providers.

Nurses play a critical role in the care of patients. Knowledge of cGMPs is imperative when one evaluates the risks and benefits associated with the use of OTC supplements and prescription drugs by patients. Future research will be required for many available drugs, thus elucidating the safety and efficacy of both OTC and prescription medications. ■

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Good Manufacturing Practice: A Pharmacist's Perspective

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JR is a 43-year-old man with a primary hepatocellular carcinoma. He was diagnosed 6 months ago with metastatic disease and today has been told that there are no remaining conventional treatment options available for the management of his cancer. To look at this patient is to see a young man who seems to be otherwise healthy, a man who continues to work full time, to travel, and to be an active husband and father. Only his distinct yellow skin coloration betrays him and reveals to all who see JR that his liver is failing and, in the absence of some treatment that can slow his disease, will result in his demise in the weeks to come. JR's menu of options is more limited than ever. He can choose to accept the finality of hospice care or take a chance on an unproven investigational therapy in the setting of a clinical trial.

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This is a scenario that is repeated every day in oncology practices around the world. As a clinical oncology pharmacist in a community practice setting, I am intimately involved in the treatment planning and decision-making process for our patients and am routinely called upon to evaluate clinical trial options for patients like JR. For some patients, the hope of a miracle cure becomes the driving force behind their desire to receive an investigational drug. For others, it is their sense of benevolence, their recognition that while they may not receive much benefit, they may be helping future patients with the same type of cancer. The strict inclusion and exclusion criteria for late-phase clinical trials often exclude patients with end-stage disease due to their organ failure or short life expectancy. However, phase 1 trials of the most unproven novel agents will sometimes (but not always) welcome these patients. For healthier patients, a later-phase clinical trial may be an appropriate option that allows them the potential to live longer.

One of our duties as oncology practitioners is to scrutinize every available option in order to ensure to the best of our ability that these novel agents and their corresponding studies are reasonable and safe for patients. This is not always an easy task, especially when patients are referred to a site in another town or state. The concerns of both patients and practitioners may cause hesitation as we ask what standards are in place to ensure that the maxim "do no harm" will apply to these already fragile patients, as they are thrust into a world of a new oncologist, a new large academic medical center, and an unapproved treatment option.

Fortunately, many of the assurances related to novel drug agents and their evaluation in clinical trials come via the US Food and Drug Administration (FDA)'s investigational new drug (IND) process and current good manufacturing practice (cGMP), as outlined in the Code of Federal Regulations (CFR) Title 21. This highly regulated procedure ensures that prior to beginning studies, the manufacturer or sponsor must submit an IND application that includes chemistry, manufacturing, and control information, which the FDA reviews to determine whether or not the new drug possesses the properties and reasonable safety to permit treatment of human subjects. Unlike the case of drugs that are ready to enter phase 2 or 3 trials, it is recognized that phase 1 agents may be manufactured on a small scale, and thus are not held to the same high standards. As such, cGMP rules for phase 1 drugs relate mainly to the manufacturer's written procedures, policies, and protocols; appropriately controlled and maintained equipment; the manufacturing environment; and assurance of data quality recorded and reported by the manufacturer.[1] In addition to these fundamental elements of safety, drugs produced in larger quantities in traditional manufacturing facilities for the express purpose of use in later-phase clinical trials must adhere to more stringent provisions for drug processing, packaging, and labeling, as also

For healthier patients, a later-phase clinical trial may be an appropriate option that allows them the potential to live longer.

outlined in CFR Title 21. While there exists variance in the rules for the manufacturing of drugs at various stages of development, a common theme is ensuring patient safety beyond the inherent risks of drug toxicity and uncertain efficacy associated with any medication.

A review of the FDA's database of warning letters reveals that even with the best of intents, these regulations are violated from time to time.

Are cGMP regulations sufficient? As oncology providers, it is our duty to question the likely value of each and every drug and combination regimen that we prescribe for our patients. While we are trained to adhere to clinical practice guidelines and make evidence-based decisions, at times it is the art of medicine and the associated gut instinct that allows us to personalize therapy when a clear and concise course of action is uncertain. Whether we elect to pursue a clinical trial with a novel agent or an unconventional combination of commercially available drugs, there is some comfort in knowing that cGMP rules exist to ensure that the drugs our patients receive are unadulterated, contain the expected active ingredients and excipients, and have been prepared in a properly maintained facility.

Because I am a pharmacist involved in conducting all phases of clinical trials, it is often my responsibility to educate patients on a study's design and, most importantly, the investigational drug itself. Frequently I am asked, *Would you recommend this drug (or this study) for a family member?* While I can read the medical literature, seek to understand the mechanism of action and likely toxicities of a novel agent, and share with patients results from earlier studies, I cannot personally attest to the composition of the drug product that they take orally or receive intravenously. It is precisely for this reason that I am thankful that a regulated process exists precisely for this purpose. Even still, mistakes occur and unsafe medications cause harm by reaching patients every year. A review of the FDA's database of warning letters reveals that even with the best of intents, these regulations are violated from time to time. Fortunately, the number of identified cGMP issues is small, and when issues are identified, the FDA has the authority to shut down the production facility and recall adulterated medications. The consequences for endangering the public by violating these rules are often severe, which should also provide some confidence in the safety of the drugs that we prescribe. Overall, the system works more times than not, and I feel confident in the quality of the drugs that my patients receive either from commercial sources or as part of a clinical trial.

In conclusion, it is important to recognize that the benefits of cGMP are not standardized around the world. Drugs produced in other countries may not be as highly regulated, resulting in inconsistent drug contents, among other issues. As pharmacists, we are often referred to as the drug therapy experts, and as such, I think it is safe to say I speak for my peers by suggesting that these are some of the many reasons why the general public should seek to avoid drugs that are produced in locales where high standards are the exception rather than the rule and the safety of drug products cannot be ensured. In the United States, cGMP at a minimum provides some assurance that the drug production process is safe, well maintained, and regulated at a high level. ■

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Ensuring Safety of Compounded Sterile Products: A New Regulatory Framework

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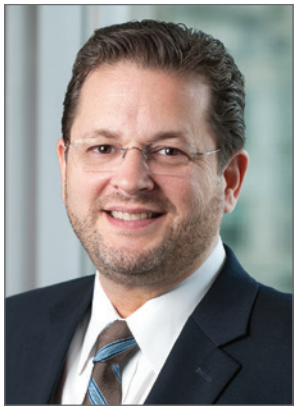
Confusion over the rules governing drug compounding has been an issue for many years. However, concerns about the safety and quality of compounded sterile products (CSPs), spurred by an outbreak of fungal meningitis infections that occurred in October 2012, have led to a fundamental change in the regulatory framework.[1]


Daniel A. Kracov, JD

In that month, the US Food and Drug Administration (FDA) advised healthcare providers to cease using products manufactured by New England Compounding Center (NECC) of Framingham, Massachusetts, and NECC recalled all of its compounded products.[2] These steps were taken as a consequence of a multistate outbreak of fungal meningitis and other infections among patients who received contaminated injectable products manufactured by NECC.[2] According to the Centers for Disease Control and Prevention, a total of 751 people developed infections, with 64 fatalities.[3]

In part due to the NECC crisis, new legislation was enacted in November 2013: the Drug Quality and Security Act (DQSA). Title I of the DQSA, known as the Compounding Quality Act (CQA) (section 102), addressed problems caused by earlier amendments to the Federal Food, Drug, and Cosmetic Act (FDCA) that were found to be unconstitutional by the US Supreme Court in 2002, and created ambiguity as to FDA authorities. The CQA expands upon those provisions to create a new regulatory construct for the regulation of compounding.[4,5]

Under the CQA, state boards of pharmacy will continue to oversee and regulate the practice of pharmacy, including traditional pharmacy compounding (ie, compounding pharmacies that manufacture specific products upon receipt of a prescription for an individual patient or in anticipation of prescriptions based on a documented history of prescribing for individual patients). However, a new category of outsourcing facilities, created by the CQA and regulated by the FDA, is essentially an intermediate form of drug manufacturer between traditional compounding pharmacies and pharmaceutical manufacturers that produce FDA-approved drugs.[5]

Specifically, under new FDCA section 503B, drugs made by outsourcing facilities are exempt from new drug requirements, labeling, and track-and-trace requirements, presuming they are compounded by, or under the direct supervision of, a licensed pharmacist in a registered outsourcing facility and meet applicable requirements.[5] Outsourcing facilities are required to report biannually to the Secretary of Health & Human Services regarding drugs compounded in the facility and to submit adverse event reports. These facilities are also subject to a risk-based inspection schedule.[5] Compounders that do not register as outsourcing facilities can qualify as traditional compounders under section 503A of the FDCA. To the extent they otherwise fall outside these categories, they would be subject to all requirements in the FDCA that are applicable to conventional manufacturers.

The new legislation and its implications are directly relevant to oncologists, oncology nurses, oncology pharmacists, and other healthcare professionals who order, prepare, and administer injectable products for patient use. The CQA allows hospitals and other healthcare providers to evaluate novel strategies to obtain CSPs for their patients, including the use of outsourcing facilities that have registered with the FDA.

Providers of oncology care should know that, like pharmaceutical manufacturers, outsourcing facilities must comply with current good manufacturing practices (cGMPs). However, unlike pharmaceutical manufacturers, and assuming the product is not otherwise commercially available from a manufacturer, outsourcing facilities can produce specific CSPs without seeking FDA approval and without individual patient prescriptions, unlike traditional compounders. Thus, they can produce products in large quantities.

To date, the FDA has focused on producing guidance for outsourcing facilities related to registration with the agency and adherence to cGMP requirements: facility design, environmental monitoring, production and process controls, packaging and labeling, and complaint handling. Outsourcing facilities must also adhere to the following:

- Bulk substances used in manufacturing of CSPs must meet certain requirements and comply with the US Pharmacopeia and National Formulary monographs.
- Nonbulk ingredients must be safe and effective. Drugs withdrawn or removed from the market because of concerns about safety or effectiveness, or with demonstrable difficulties for compounding and/or safety concerns, cannot be used.[6]
- CSPs cannot be copies of 1 or more commercially available drugs. They must be distinct relative to FDA-approved drugs: change in dosage form, change in route of administration, or addition of ingredients. CSPs cannot compete directly with approved drugs.

The FDA is continuing efforts to inspect both traditional compounding and outsourcing facilities, and undoubtedly issues will arise in that context.

- If a risk evaluation and mitigation strategy (REMS) is in place for a given ingredient, outsourcing facilities must follow REMS controls and restrictions for CSPs that include the ingredient.
- CSPs made in an outsourcing facility must be labeled to indicate that they are compounded, and they must include the drug name, lot and batch number, dosage form, and strength.
- CSPs made by outsourcing facilities can be sold only by the facility, not marketed or distributed by other firms.

Cancer care providers should understand that the FDA is urging hospital systems and private payers to purchase CSPs from outsourcing facilities, rather than from traditional compounding pharmacies. Because registered outsourcing facilities are subject to cGMP, they will arguably better ensure patient safety. However, the costs associated with CSPs produced by registered outsourcing facilities have generated controversy. Various private plans have established barriers to CSP access in order to avoid paying outsourcing facilities' prices. Such pressures will only increase as more health systems accept capitated payments and implement other cost-containment approaches.

To date, over 55 CSP compounders are 503B-registered outsourcing facilities.[7] Oncology care providers are urged to review this FDA-updated list to learn whether their source of CSPs is registered. However, it is important to note that mere registration with the FDA does not indicate any agreement by the agency that the facility is in fact in compliance with the requirements for outsourcing facility status.

Implementation of the CQA will take time. The FDA is continuing efforts to inspect both traditional compounding and outsourcing facilities, and undoubtedly issues will arise in that context, which will result in further guidance. This will be an ongoing, active area for policy-making for several years. Additional drug-compounding–related issues on which the FDA is likely to opine relate to production of biologic injectable products, and distinctions between repackaging of sterile drugs and compounding. It behooves cancer care providers to keep abreast of these developments, because they directly affect the quality and safety of patient care. ■

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