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Acute Care
ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

As approval of medical cannabis spreads state by state, product labeling improvements are a must

Problem: Anecdotal support, public opinion, and state laws in the US are outpacing scientific research involving medical marijuana, more professionally known as medical cannabis. Medical cannabis differs from the street product in that the plant must be reliably grown and handled in a manner that resembles good manufacturing practices. This allows growers to assay and establish the products' contents with the intent of passing that information on to dispensaries and patients. However, lack of federal regulation has allowed for heterogeneity of state programs, yielding a wide variety of cannabis formulations, products, flashy strain names, and patient safety concerns.

For example, the use of strain (or brand) names is prevalent, but studies have shown that there are genetic inconsistencies among products with the same strain name.[1-4] Furthermore, the lack of consistency in state cannabis labeling requirements, along with the lack of involvement of healthcare professionals, has given rise to labeling practices that risk patient safety. Thus, it is difficult for dispensaries to provide patients with products that are clearly labeled, which is a critical component for safe and reproducible effects.

Components of Medical Cannabis

Cannabis sativa has many phenotypes (strains) that include hundreds of chemicals (cannabinoids) produced in varying amounts based on the strain and growing conditions. As a comparison, think of all the varieties and tastes of apples, including regional varieties, crab apples, and genetic hybrids such as "grape-apples." The two most notable cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD), although cannabis has many other physiologically active molecules whose effects are not fully understood.

THC is associated with psychoactivity (or psychotoxicity), including euphoria, relaxation, pain relief, anxiety, and memory impairment. The psychoactive effects tend to be dose limiting, and taking too much can make patients feel uncomfortable. When talking to patients, it is helpful to describe the psychoactive effects as impairment or intoxication and to caution that it might cause light-headedness and postural hypotension, increasing the risk of falls. THC has been associated with cannabis use disorder, while CBD has not.

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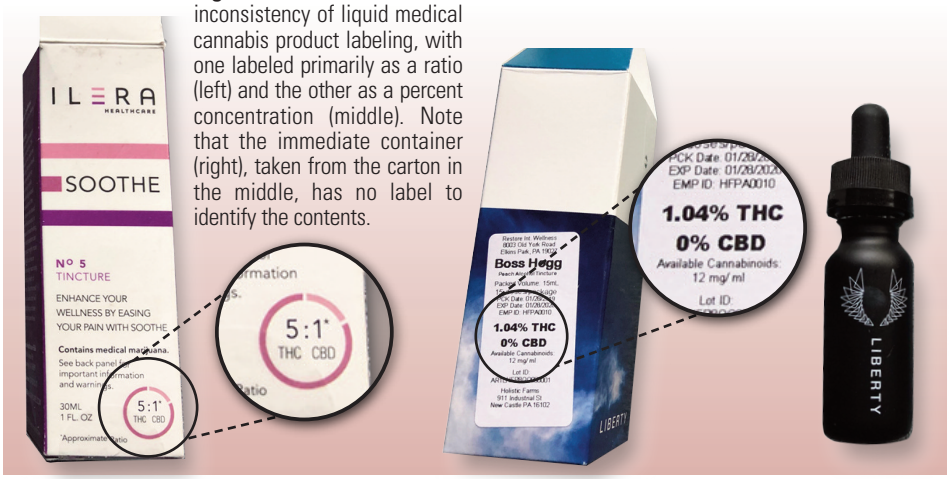

Figure 1. Photo illustrates inconsistency of liquid medical cannabis product labeling, with one labeled primarily as a ratio (left) and the other as a percent concentration (middle). Note that the immediate container (right), taken from the carton in the middle, has no label to identify the contents.

Sidebar: Example of labeling issues with medical cannabis

The following report provides an example of the difficulty healthcare providers might encounter during medication reconciliation in determining a patient's dose of medical cannabis taken at home due to the absence of label standards.

A hospitalized patient reported taking medical cannabis at home to ease her pain and help her sleep. She removed a dropper bottle from her purse and showed the healthcare provider the cannabis liquid, which had a wrap-around label on it (**Figure 1**). The label noted that the product was a "330 mg tincture" and listed the contents as a "hybrid" with a "1:10" ratio. Patient directions for use were NOT included on the label.

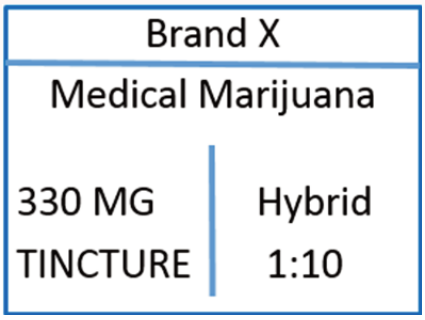

Figure 1. Wrap-around label on a dropper bottle of cannabis liquid (with the commercial name redacted and replaced with Brand X).

When the patient was asked the dose she takes daily, she said half a dropperful at bedtime and that the bottle contained a 30-day supply. The dropper had 0.5 mL and 1 mL calibrations.

So how much THC and CBD did the patient take with each dose? The label does not list a volume corresponding to the "330 mg" tincture, making it difficult to determine the mg per mL concentration. Per the patient's verbal recall of her daily dose of half a dropperful (0.5 mL), the healthcare provider might multiply each 0.5 mL dose by the

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CBD is not psychoactive, and preclinical data suggests it has anti-inflammatory, analgesic, anti-nausea, antiemetic, antipsychotic, anxiolytic, and antiepileptic properties. Patients may take escalating doses of CBD because they do not feel any cognitive impairment. Common side effects include headache, diarrhea, restlessness, and/or somnolence.

Both THC and CBD may interact with other medications. Examples include interactions with epilepsy medications and warfarin. While the dose of THC is directly correlated with cognitive and motor function effects, the dose of CBD may be more predictive of the magnitude of possible drug interactions.

Dosage Forms

There are a variety of medical cannabis dosage forms, producing different pharmacokinetic and pharmacodynamic effects. Common formulations include capsules and liquids for oral use, vaporized products (extracts and raw flower), sublingual drops, transmucosal adhesives, topical creams/ointments, transdermal patches, and suppositories.

Nonstandard, Confusing Labeling

All state laws require products to be assayed and labeled by the grower, and ideally verified by an accredited third-party lab, for at least the two major cannabinoids currently of interest, THC and CBD. While the total cannabinoid content must be listed on the label, only THC and CBD individual quantities must be expressed on the label. The amounts of these two cannabinoids are clinically relevant for managing patients' symptoms. However, the way these components are expressed on labels is not standardized (**Figure 1**, page 1) and can lead to errors.

Ratio expressions. The two primary cannabinoids are often expressed as a ratio of either THC:CBD or CBD:THC. So, the first problem is that no international or national standard exists governing which cannabinoid is listed first when presented as a ratio, and most state regulations do not dictate a formal convention. The order of components in the ratio may differ between growers and even within a grower's product line, causing confusion when determining which product to use. Look-alike product labeling (**Figure 2**), particularly within a grower's product line, has also been reported, leading to confusion between products containing different ratios of THC and CBD.

Percent concentrations. In addition to (or in place of) ratio expressions, some products are labeled with the percent concentration. This makes it difficult for staff in dispensaries and patients to calculate the amount of THC and/or CBD in the product. For example, would you be able to easily identify the amount of THC and/or CBD in 0.5 mL of a 0.037% product, especially if the mg/mL amount is not clearly listed? With some products, the mg amount of each primary ingredient can be found on container labels, which is preferred for dosing and consistency but could still cause confusion in patients who are more familiar with ratio expressions. It is critical to know the actual mg amount of each primary component, especially THC, which is most likely to elicit clinical and/or adverse effects. But too often, the mg amount of a liquid product is listed without a corresponding volume, preventing the ability to determine the concentration. And again, there is no standard. The **Sidebar** (right column, page 1) provides an example of this problem along with several other labeling issues.

Figure 2. A patient reported frequently confusing these products with different ratios of THC and CBD because the labels look so similar. Also note the bottle on the left contains a 10:1 ratio, and the bottle on the right contains a 1:1 ratio, but both are labeled as a 330 mg tincture.

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patient-reported 30-day supply in the bottle to obtain a presumed strength of 330 mg/15 mL, or 22 mg of cannabinoids/mL. Of course, this is an unreliable method of determining the mg/mL amount.

The label also does not specify whether the ratio of 1:10 is THC:CBD or CBD:THC. So how much THC is in each dose compared to CBD? Because the patient said she takes the product for pain and sleep, one might assume the primary cannabinoid is THC. In that case, 1:10 would signify CBD:THC, or 2 mg CBD and 20 mg of THC per mL of tincture based on the prior error-prone calculation. Based on the patient's self-reported dose of 0.5 mL, she appeared to be taking 10 mg of THC and 1 mg of CBD with each dose. However, when the patient's husband brought in the outer carton of the product the next day, it was clear that the presumed dosing information was incorrect. The dispensary label indicated that there was no CBD at all in the product, despite displaying a 1:10 ratio.

SAFETY briefs

Fasting during Ramadan and safe drug administration. Fasting during Ramadan, a month in the Islamic calendar, is one of the Five Pillars of Islam. This year, Ramadan begins the second week of May and ends the first week of June. During this time, Muslims who fast refrain from certain activities, including eating, drinking, and smoking from dawn until sunset. Their meals are before the break of dawn (suhoor) and at sunset (iftar). The Qur'an, the holy book for Muslims, states several exemptions from fasting, including if it is detrimental to one's health (e.g., diabetes, immunocompromised condition, pregnancy, the frail and elderly, children). However, many Muslims with medical conditions choose to fast during Ramadan, which may affect how they take their prescribed medications. Thus, healthcare professionals should be prepared to help these patients manage their medication regimens safely while fasting.

If patients decide to fast, they must be educated regarding the best time to take any oral medications that reach the stom-

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Labeling of the immediate container. For some liquid products and almost all vaporization cartridges, only the outer carton is labeled, and the immediate container (bottle or cartridge) is not labeled at all (**Figure 1**, page 1). If the carton is discarded or lost, the unlabeled product may be confused with something else.

Label contents. Certain dosage forms also lack important ingredient and label information. For example, the labeling of tinctures does not always include the alcohol content, and frequently the term tincture is misapplied to products that do not contain alcohol. Transdermal patches often do not include key information such as onset and duration of effect, delivered dose, and cautions about possible systemic effects. It should also be mentioned that there are terpenes present in essential oils of the marijuana plant that give it its fragrance, which are also physiologically active molecules that have been known to have clinical effects—from anxiolytic to anti-inflammatory effects, and more.[5] Product assays will sometimes list plant terpenes, but not all states require this.

Safe Practice Recommendations: To promote patient safety, labeling standards are needed for medical cannabis products, at the very least to specify THC and CBD contents and concentrations accurately in metric units, and healthcare providers need to know how to interpret the label information. Because ratio expressions are predominantly used today, medical cannabis products must conform to some type of labeling convention to signify whether THC or CBD is listed first in a ratio expression. However, we are not convinced that ratio expressions should be used at all given the potential for errors as seen with other medications previously expressed this way (e.g., **EPINEPH**rine 1:10,000), which is now prohibited on most medication labels.

The common practice of expressing concentrations as percentages, without a total volume or the mg amount per mL, introduces significant risk of error when calculating the dose, especially one based on a nonstandard serving size. Clearly mandating the expression of strengths and concentrations of the THC and CBD contents in metric units (e.g., mg, g, mg/mL) would provide the safest communication to both patients and healthcare providers. Additionally, all immediate product containers should be labeled, not just the outer packaging.

Ensuring that all inactive ingredients, especially additives, in a product are included in the labeling is critical to mitigate allergic reactions to dyes and flavoring agents. Drug-drug binding interactions can result from the product's vehicle (e.g., sesame oil) and other herbal products (e.g., melatonin) that are sometimes added. This information could be provided on a side panel to avoid clutter on the primary display panel.

The US Food and Drug Administration (FDA) approved a single cannabidiol product, **EPIDIOLEX** (Greenwich Biosciences) in June 2018 for the treatment of seizures associated with Lennox-Gastaut and Dravet syndromes in patients age 2 and older. It is available by prescription only. However, for all other forms of medical cannabis, healthcare providers interacting with patients should clearly communicate that these products are not approved by FDA for any medical conditions; thus, therapy is considered investigational, and safety, including reproducibility of response between products, is not fully understood. Further, CBD-only products that are routinely sold on the internet and in retail establishments have not been evaluated by FDA for potency, purity, or safety. There are many reports of CBD-only products containing either no detectable CBD, or significantly more CBD than is on the label. Based on studies, approximately 1 in 5 CBD-only products contains detectable amounts of THC, putting patients unknowingly at risk of impairment as well as testing positive on urine drug screens for THC.[6,7]

ISMP and FDA would like to learn more about labeling and packaging problems or other practice issues with medical cannabis. Please report all hazards, close calls, and errors with medical cannabis to the ISMP National Medication Errors Reporting Program

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ach, particularly if drug absorption can be affected by food intake. As a general rule, medications that are dosed once or twice daily can be taken before or with the morning meal (suhoor) and/or with or after the evening meal (iftar). A physician will need to assess the risk vs. benefit profile of medications that require three or more daily doses and determine the safest administration plan, including the possibility of switching to a slow-release or once daily medication. Patients should be advised to consult a pharmacist if they have questions.

Because each Islamic school of teaching may differ regarding which routes of medication administration nullify the fast, specifically ask your patients what routes of administration are acceptable for use without breaking their fast. For example, some schools of teaching may allow administration of eye and ear drops, nasal sprays, asthma inhalers, skin creams, transdermal patches, or subcutaneous injections while fasting, whereas others may not.

For patients with diabetes who choose to fast, dose modifications for insulin or other antidiabetic medications may be necessary. Blood glucose testing should occur throughout the day, and patients should be instructed to break the fast for a blood glucose level less than 70 mg/dL or greater than 300 mg/dL, for symptoms of hypoglycemia or hyperglycemia, or if acute illness occurs. Additional suggestions for managing medications for fasting patients with diabetes, cardiovascular disease, gastrointestinal health issues, or renal disease can be found at: www.ismp.org/ext/252. Also, examples of handouts for patients with diabetes can be found at: www.ismp.org/ext/253 (English) and www.ismp.org/ext/254 (Arabic).

HIGH-ALERT

A mitoMYcin-mitoXANTRONE mix-up.

A patient with goblet cell cancer of the appendix and carcinomatosis presented to the operating room for cytoreduction and hyperthermic intraperitoneal chemotherapy with mitoMYcin. However, while processing the order, pharmacy staff selected mitoXANTRONE from the shelf and dispensed the drug in a brown overwrap believing it was light-sensitive mitoMYcin. With the brown overwrap, it was not immediately recognized that the drug was

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(ISMP MERP, www.ismp.org/MERP), and ISMP will forward the reports to FDA. Look for more about medication safety issues with medical cannabis (e.g., duplicate therapy, drug interaction checking, managing hospitalized patients who use medical cannabis at home) in subsequent newsletters throughout the year.

*ISMP thanks **Christine Roussel**, PharmD, BCOP, Director of Pharmacy at Doylestown Hospital in PA, for providing this article.*

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Payer-driven biosimilar requirements: New risks in patients with cancer and chronic diseases

PROBLEM: With the advent of biosimilar drugs, payers are often determining which biosimilars are to be administered to outpatients treated in hospitals and clinics. Manufacturers' rebates are largely driving these decisions. This would be analogous to determining which manufacturer's generic drug can be dispensed based on the patient's insurance. If this were the case, organizations would need to stock payer-specific generics and ensure that the right generic was dispensed to the right patient. For example, this would require stocking 5 different acetaminophen products for 5 different payers.

At the current time, pegfilgrastim (**NEULASTA**) has 2 biosimilars, pegfilgrastim-jmdb (**FULPHILA**) and pegfilgrastim-cbqv (**UDENYCA**). There is also **NEULASTA ONPRO**, which is delivered with an on-body injector, bringing the total to four products. The competition among the biosimilar and originator manufacturers for preferential status designation by payers has begun, and at least one payer has designated which pegfilgrastim product is to be administered to new patients to prevent febrile neutropenia.

While there are currently only 18 biosimilars approved in the US, there are 260 approved in international markets and 188 more in development.[1,2] The names of biosimilars combine a core name with a 4-letter distinguishing suffix presented in lowercase letters that is devoid of meaning, creating look- and sound-alike risks.[3] In 2019, cancer treatment is at center stage with the approval of multiple biosimilar products: ri**TUX**imab has 1 approved biosimilar, trastuzumab has 4 biosimilars, and bevacizumab has 1 biosimilar. If the current rebate-driven payer incentives designate which chemotherapy drug is to be given, this will significantly increase the complexity of the medication use process by adding steps to the already complex processes of checking chemotherapy medications.

Most electronic health records (EHR) contain chemotherapy regimens specific to the cancer diagnosis and stage of the disease. EHRs will need to add drug records for each biosimilar product, including the various dosages and common routes. Even without the biosimilars, health systems may already have multiple drug records in the EHR—for example, 2 for the pegfilgrastim products, 3 for ri**TUX**imab, 4 for bevacizumab, and 2 for trastuzumab. Physicians will need to ensure that the correct drug record is

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dark blue, and the patient inadvertently received mito**XANTRONE** during the procedure. The error was discovered when peritoneal tissues that were stained dark blue were observed, which is atypical when mito**MY**cin is used for this procedure. A search of the chemotherapy waste bucket revealed that mito**XANTRONE** was used in error. The patient was later discharged in stable condition but was unable to return for a repeat procedure using the correct medication due to her poor prognosis.

During investigation of the event, the pharmacy workflow system scanning process (DoseEdge by Baxter) was reviewed. Each drug in the workflow system has available routes assigned to it. When a drug is scanned with an ordered route that does not match the available routes, a "wrong route" error displays. The technology showed that the pharmacy technician had scanned the mito**XANTRONE** vials three times and received the same error message of "invalid route," as the mito**MY**cin had been prescribed by the intraperitoneal route, while mito**XANTRONE** is administered intravenously (IV).

DoseEdge displays only one validation error message at any given scan. "Invalid route" displayed because mito**XANTRONE** (instead of the intended mito**MY**cin) had been scanned, and intraperitoneal was not a route set up for this drug. A validation failure, like "invalid route" triggers a hard stop in the workflow and does not allow dose preparation to continue within DoseEdge. Since the workflow was stopped, a "wrong drug" alert did not occur, and the pharmacy team bypassed the IV workflow safety system. The technician was unfamiliar with mito-**XANTRONE**, so the dark blue color of the solution didn't put a halt to dispensing, either.

A request has been made to Baxter to revise the software so that identification of the wrong drug takes priority, although a "wrong route" message is also important and should immediately be investigated. Change in the expected appearance of a drug and unexpected workflow system error messages can be important clues for detecting potential medication errors and must be fully investigated. In situations where IV workflow system controls are

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selected based on the product determined by the patient's insurance. Since each chemotherapy and supportive care drug with one or more US Food and Drug Administration (FDA)-approved biosimilars will have multiple drug records, the risk of making a wrong-selection error is significantly increased. What if the regimen contains 3 drugs that all have biosimilars? Will the pharmacist also need to verify that each biosimilar has been correctly selected based on the payer's preference, in addition to making sure the correct regimen was selected at the right dose, route, and cycle number for the cancer diagnosis and stage? How will the drug inventory be labeled to ensure the right biosimilars are selected for compounding and dispensing based on the patient's insurance?

A requirement to use a payer-specific biosimilar would demand significant resources to procure and maintain separate inventory, as well as to prescribe, label, compound (depending on the medication), and dispense the right medication to the patient. Given the number of biosimilars expected to become available, these additional steps would significantly increase the risk of harmful medication errors. Furthermore, patients switched from one product to another due to payer decisions risk experiencing an immune reaction given that biosimilars are made from different living organisms, even though they are considered therapeutically equivalent. Also, billing errors are possible (each biosimilar has a different billing code), and if the wrong payer-specific biosimilar is administered, the health facility and patient would incur financial liability.

Safe Practice Recommendations: While the practice of payers making rebate-driven formulary decisions has been in place for many years, the scope has been primarily limited to self-administered drugs. In health systems, decision-making authority regarding the drugs used for patient care is defined by regulatory and accrediting agencies as part of the formulary process (**Table 1**). The question of whether payers should be able to direct health system formulary management needs to be addressed, not only from a regulatory and accrediting perspective, but more importantly from a patient safety perspective. The promise of biosimilars as a solution to rising drug costs cannot be realized at the expense of patient safety. Payers can achieve lower drug costs by allowing health systems to determine which biosimilars are available for patient use based on their formulary process and providing reimbursement regardless of which drug is selected.

*ISMP thanks **Rita Shane**, PharmD, Chief Pharmacy Officer at Cedars-Sinai Medical Center, and Professor of Medicine/Assistant Dean at the UCSF School of Pharmacy, for providing this article.*

Table 1. Regulatory/accrediting requirements for formulary decisions associated with the availability of medications

Agency	Reference	Excerpt
The Joint Commission (TJC)	Medication Management Standard MM.02.01.01	Members of the medical staff, licensed independent practitioners, pharmacists, and staff involved in ordering, dispensing, administering, and/or monitoring the effects of medications develop written criteria for determining which medications are available for dispensing or administering to patients. The hospital maintains a formulary, including medication strength and dosage.
Centers for Medicare & Medicaid Services (CMS)	Conditions of Participation 482.25(b)(9)	A formulary system must be established by the medical staff to assure quality pharmaceuticals at reasonable costs.

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2) Charting the global biosimilar pipeline 2018: biosimilars in development for a range of therapy areas from cancer and diabetes to ophthalmology and respiratory – ResearchAndMarkets.com. *BusinessWire.* June 15, 2018. www.ismp.org/ext/249
3) FDA. Nonproprietary naming of biological products: update guidance for industry. March 2019. www.ismp.org/ext/250

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bypassed, manual quality checks must be performed according to hospital policy. Also, ISMP has previously recommended tall man letters for both mito**XANTRONE** and mito**MY**cin. The FDA list includes mito**XANTRONE** but not mito**MY**cin, and the manufacturer's label for mito**MY**cin does not include tall man lettering with the drug name, while companies that sell mito**XANTRONE** do. In this case, the tall man letters on the label of mito**XANTRONE** did not help prevent the error.

Special Announcement

FREE ISMP webinar

On **June 20, 2019**, ISMP will present a **FREE** webinar thanks to support from Novartis on ***Back to the Basics: Preventing Administration of Neuromuscular Blocking Agents to Unventilated Patients***. Join our ISMP speakers as they describe key vulnerabilities with neuromuscular blockers that have led to errors and patient harm. The speakers will then define the best practices for safeguarding neuromuscular blockers and present targeted, national compliance data from associated surveys and self-assessment tools. Participants will be able to reflect on their level of compliance and make plans to implement strategies that will prevent this type of event from happening within their organization. For details, visit: www.ismp.org/node/1523.

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