A SUPPLEMENT TO

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

Compounding Conundrums: What the Future Holds

ISSN: 1545 9616

February 2020 • Volume 19 • Issue 2 (Supplement)

Funding Acknowledgment:
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Compounding Conundrums: What the Future Holds

EDITORIAL

ORIGINAL ARTICLE

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To Compound or Not to Compound

Leon H. Kircik MD

Icahn School of Medicine at Mount Sinai, New York, NY; Indiana University Medical Center, Indianapolis, IN; Physicians Skin Care, PLLC Louisville, KY; DermResearch, PLLC, Louisville, KY; Skin Sciences, PLLC, Louisville, KY

Leon H. Kircik MD

In-office compounding, once part and parcel of dermatologic practice, has become increasingly controversial—and confusing. As a result of legitimate public health concerns, FDA scrutiny began with compounding facilities. Unfortunately, regulatory focus has shifted to compounding by individual physicians in their offices, especially to dermatology practices. Without doubt, compounding remains necessary in certain instances, and we, as dermatologists, are actively seeking to protect our right to compound needed drug formulations in our offices. Some treatments simply are not there for us on the market in their final applicable forms, either because the required active or combination of actives are not available or because a certain vehicle base is not provided. Additionally, some of the drugs we use for in-office procedures are only available via compounding.

While in-office compounding is a time-honored practice that ought to be protected, the reality is that most dermatologists would prefer to have access to appropriate final formulations that would reduce the need to compound. There are many benefits to finished product, not the least of which is convenience for the physician and the patient. Finished formulations offer consistency of concentration and dose, as well as reliable efficacy and safety. Finished formulations also offer shelf-stability in practice-friendly packaging, meaning that practices don't need to maintain as much inventory of raw active drugs and excipients, which may expire before they are used up.

Consider the case of cantharidin, which has been used for some time as an effective in-office treatment for molluscum, one of the most challenging pediatric presentations in the dermatology clinic. As detailed in the pages ahead, the status of cantharidin has changed recently so that it is now listed as a 503B category 1 agent, indicating that it may only be available in bulk orders with overwhelming amount of bureaucratic paperwork requirements. For most dermatology practices, this is simply not practical, since most of the product would likely expire before it is used to treat patients as well as meeting regulatory requirements, which are impossible to comply with in our fast-paced practices.

Additionally, while many dermatologists have successfully offered cantharidin treatment in their offices in the past, there has been concern about appropriate dosing. Administration of cantharidin at too low a concentration may impair efficacy, while too high a concentration may elicit a robust blistering response that may cause not only unnecessary discomfort for patients but also unwanted medical legal headaches for us.

This is a situation where the availability of an FDA-approved formulation for in-office use would be beneficial to physicians and patients. In fact, VP-102 topical cantharidin 0.7% film solution is currently pending approval by the FDA for the treatment of molluscum contagiosum after completion of phase 3 studies in the pediatric population. If approved, this novel film solution would obviate concerns about access, since the formulation would be readily available to be used in our offices. Additionally, a branded formulation offers the guarantee of consistency in the concentration of active, a known vehicle base, a consistent delivery technique, and documented clinical experience in rigorous, randomized, controlled trials for its efficacy and safety.

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As we continue to monitor FDA action with regards to drug compounding, it is important that we as dermatologists advocate for our rights as physicians and for the needs of our patients. We must preserve our right to compound appropriately in the clinic when an alternative is not available. At the same time, we do recognize that branded formulations provide a tremendous benefit to us and our patients, not the least of which are consistency, hence, efficacy and safety in addition to convenience. As the regulatory landscape shifts and the market place evolves, we continue to optimistically watch innovation in the drug space. The development of novel branded formulations of time-tested drugs like cantharidin will be a welcome addition to our treatment armamentarium.

DISCLOSURE

Leon H. Kircik MD has received compensation for his editorial support from JDD and has served as a consultant for Verrica.

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Compounding in Dermatology Update

Vlatka Agnetta MD,[a] Abel Torres MD JD MBA,[b] Seemal R. Desai MD,[c] Adelaide A. Hebert MD,[d] Leon H. Kircik MD[e]
[a]University of Florida, Gainesville, FL
[b]Department of Dermatology, University of Florida, Gainesville, FL
[c]Innovative Dermatology, Plano, TX; Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX
[d]UTHealth McGovern Medical School, Houston, TX
[e]Icahn School of Medicine at Mount Sinai, New York, NY; Indiana University Medical Center, Indianapolis, IN; Physicians Skin Care, PLLC, Louisville, KY; DermResearch, PLLC, Louisville, KY; Skin Sciences, PLLC, Louisville, KY

INTRODUCTION

Medication compounding is defined as any alteration, mixing, or combining of two or more ingredients that make the drug more specific to the needs of the patient.[1] Compounded medications are used widely in patient care to meet their individual medical needs and maximize treatment outcomes. The Food and Drug Administration (FDA) and the United States Pharmacopeia (USP) have been the leading organizations in creating the official rules and guidelines on drug compounding.

Ever since an outbreak of fungal meningitis in 2012 from contaminated steroid injections causing multiple deaths, safety in medication compounding has been a major source of concern resulting in a series of new compounding rules, regulations, and guidelines set by the regulating agencies. These new standards were developed with the intention to maximize medication safety. Between 2012 and today, there have been multiple revisions and changes to the rules reflecting a very complex and dynamic issue on medication compounding.

While patient safety should and has always been the primary focus of the health providers, the FDA, and the USP, these strict and constantly changing complex rules pose many challenges to health practitioners when planning the treatment plan for their patients. Limitations to compounding particular medication mixtures can restrict treatment options leaving patients and providers with few or no good treatment alternatives and ultimately negatively affecting patient care.

The Food and Drug Administration (FDA) and United States Pharmacopeia (USP)

The FDA is the government agency that generates the official federal regulations for medication and food safety. It was established after the US Congress passed a set of federal laws called the Food Drug and Cosmetic Act (FDCA), which formed a legal framework for the FDA to operate within. Compounded medications are currently not approved for traditional distribution by the FDA because they do not ordinarily undergo a rigorous pre-market safety and quality process. Instead, the FDA now mandates that compounding must be done by a licensed pharmacist, a licensed physician, or under direct supervision of a licensed pharmacist in an outsourcing facility.[1]

By contrast, the USP is not a government agency, but rather a private organization that existed prior to the FDA and has had a tremendous historic as well as present role in medication safety and public health. The USP also publishes detailed information on all the drug products including their identity, quality, parity, and potency. The FDA carefully evaluates and usually adopts USP recommendations in developing and updating new federal regulations. Thus, the FDA minimum standards closely parallel the USP standards. USP general chapter <797> contains detailed information on sterile medication compounding, responsibilities, requirements, and facilities to properly compound and store these medications.[2] These chapters define standards with the intent to minimize potential risks and maximize product safety.

Federal Regulations

The FDA initially created section 503A, which refers to so-called "traditional pharmacies". These traditional pharmacies have been the main source of medication compounding in the past. They are licensed, regulated, and inspected by the states based on state statutes.[3] Nevertheless, they have to follow the minimum federal regulations set by the FDA.

After the 2012 incident of contaminated steroid injections causing an outbreak of fungal meningitis, the US Congress passed the Drug Quality and Security Act (DQSA). This act amended Section 503A of the Federal Food, Drug, and Cosmetic Act (FDCA) mandating more strict regulations and oversight of medication compounding.[4] While 503A traditional pharmacies can still compound the medications, they are much more restricted with the new regulations. They can only compound and dispense a compounded medication for an individual patient's specific prescription for up to a 30-day supply. The FDA is allowed to inspect 503A traditional pharmacies if any allegations of "manufacturing" without receiving a specific prescription arise.[3] In-office compounding falls under the 503A category when a licensed physician is the one who is compounding the medication. If the medication is not an FDA approved product or listed in the USP or National Formulary monograph as noted below, the drug needs to appear on FDA's 503A bulks list. Additionally, 503A also regulated in-office compounding.

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"In-office" compounding refers to sterile medication preparation by the physician or medical staff in the outpatient clinic setting. Some examples of in-office compounding used in dermatology is buffering lidocaine with sodium bicarbonate, diluting triamcinolone with normal saline or sterile water, or reconstituting botulinum toxin with normal saline. As of 2018, the states that allow for compounding of sterile drugs for in-office use in limited quantities in the absence of patient-specific prescriptions are the following: Arizona, California, Colorado, Kansas, Michigan, Nevada, New Hampshire, Oregon, South Carolina, Tennessee, and Virginia. Connecticut, Florida, Idaho, Indiana, and Maryland only allow compounding of non-sterile drugs in limited quantities.[5] Some criticized studies have indicated that sterile drugs administrated through injection are more susceptible to contamination if compounded in the physician offices/clinical setting than in the pharmacy setting when in controlled environments. This has been the basis for many states developing very stringent in-office compounding criteria. In fact, many states have prohibited in-office compounding.[4]

When Section 503A was amended, a new Section 503B was created. This new section refers to "outsourcing facilities", which are a new compounding entity registered with the FDA and must meet the Federal manufacturing standards and undergo regularly scheduled routine inspections. These 503B outsourcing facilities can compound small or large amounts of sterile and non-sterile medications without needing patient-specific prescriptions. They do not have to be a licensed pharmacy, but compounding has to be performed under the direct supervision of a licensed pharmacist. These facilities can sell the medication to medical providers. 503B outsourcing facilities can operate across state line and they do not require prescriptions.[3] Unlike 503A facilities, the 503B outsourcing facilities must comply with the current good manufacturing practices (cGMP).[3] Since these new compounding pharmacies must follow a more rigorous regulatory pathway, they are considered safe and appropriate for compounding by the FDA. However, there are less of these facilities in the US, making access difficult. Also, it is usually not cost-effective for them to compound small amounts and thus they often require bulk compounding for products ordered. This can make access to their medication for patients and physicians too costly. As of September of 2019, there were about 76 FDA registered 503B outsourcing facilities in the US.[6] Office use compounding can fall under either the 503A or 503B regulations.

In contrast to "in-office" compounding, the term "office use" compounded medications refers to using medications in the physician's office that have been compounded in an appropriate compounding pharmacy/facility. Some examples of such medication use in dermatology are topical anesthetics preparation (LET, TAL, BLT), cantharidin and other viral wart treatments, aluminum chloride, etc. 503A pharmacies are able to compound these medications in small quantities and sell them to physicians offices thus making them cheaper and more accessible, but they can only be obtained with a patient-specific prescription. 503B outsourcing facilities can provide these compounded medications for office use, but this often means that the medication needs to be ordered in much larger quantities that will likely not be used before the medication expiration date or they may be more difficult and costly to obtain.[4]

State Regulations

All states have the authority to regulate their pharmacies. As stated earlier, each state regulatory body has to, at a minimum, follow the federal regulations for minimum standards in medication safety and compounding. These include the FDA regulations and the current Good Manufacturing Practices (cGMP) related to compounding. In addition to the FDA minimum standards, each state can include additional state specific and more stringent regulation rules. States usually create or enforce these rules either through the state pharmacy boards or the state medical boards.

Most states adopt the USP standards and guidelines to establish their minimum standards even if higher than the FDA regulations. Each state can make its own additional rules stricter than the USP guidelines and the variation seems to be somewhat arbitrary, likely due to different interpretations of the USP guidelines.

States that currently require full compliance with USP general chapter <797> are the following: Arizona, Connecticut, Delaware, Florida, Georgia, Hawaii, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Montana, Nevada, New Hampshire, New Mexico, North Carolina, North Dakota, Ohio, Oklahoma, South Carolina, Tennessee, Utah, Vermont, Virginia, Washington, West Virginia, and Wyoming.[5]

States that have "equivalent quality standards" (meaning that state requirements on sterile compounding practice are equivalent to or stricter than the USP <797> requirements) are: Wisconsin, Texas, South Dakota, Rhode Island, New Jersey, Nevada, Missouri, Illinois, California, Colorado, and Arkansas.[5]

Alabama, Alaska, District of Columbia, Idaho, NewYork, Oregon, and Pennsylvania require other quality standards. Kansas is the only state that doesn't require quality standards.[5]

Traditionally, state pharmacy boards only regulated pharmacists and compounding facilities. However, some states, like Ohio, have started to include physicians' offices under the board of pharmacy rules, putting more restrictions on the phy-

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sicians' offices. In 2017, the State of Ohio Board of Pharmacy passed a law requiring a "Terminal Distributor of Dangerous Drugs license" for any "person who is engaged in the sale of dangerous drugs at retail, or any person, other than a wholesale distributor or a pharmacist, who has possession, custody, or control of dangerous drugs for any purpose other than for that person's own use and consumption."[7] "Dangerous drug" refers to any medication that requires a prescription from a licensed provider.[8]

Another rule that seems to be highly variable from state to state is the timeframe during which in-office medication must be used after compounding. California, for example, mandates the use of such medication within one hour of compounding. Ohio has a 6 hours time limit. Both of which are much more strict than the current USP guidelines, which Florida currently follows. The most current USP guidelines require such compounds to be used within 12 hours of compounding if left at the controlled room temperature and will be discussed further in this article. This variation between states argues for a more uniform, evidence-based standard to be developed. The hope is that the upcoming USP update can help guide the state laws in such a way as to create a more uniform regulatory pathway and rules.[4]

FDA Compounding Lists/ Categories

Regardless of whether the medication is used topically, or by injection, the FDA has a list of bulk drug substances that may or may not be used for compounding. Under section 503A and 503B, this list allows for new nominations, additions, removal, and re-categorization of the medications on a periodic basis. In March of 2019, the FDA updated the list. Below, is the most updated list, but the reader is advised that it is subject to FDA changes and updates and should be revisited regularly for accuracy.

The FDA has put the bulk substances used in compounding into a list with three main categories based on their safety profile. Each category has a separate list for 503A and 503B compounding.

503A Bulk Criteria

Physicians and pharmacists compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) can only compound drug products from bulk drug substances meeting the following criteria:

(1) comply with the USP or National Formulary (NF) monograph if one exists, as well as the USP chapter on pharmacy compounding;
(2) if such USP or NF monograph does not exist, the bulk drug substances need to be components of FDA-approved drug products or
(3) if such USP or NF monograph doesn't exist and the bulk substance is not an FDA-approved drug product, the drug needs to appear on the FDA's 503A bulks list.[9]

503B Bulk Criteria

Currently, the outsourcing facilities operating under section 503B of the FD&C Act can only compound medication that includes a bulk drug substance if one of the two criteria are met:

(1) the bulk drug substance appears on the 503B bulks list of drug substances for which means that there is a clinical need
(2) the drug product compounded from a bulk drug substance appears on the FDA's drug shortage list at the time of compounding, distribution, and dispensing.[10]

Category 1: Bulk drug substances that may be eligible for inclusion because they were nominated with sufficient information for FDA to evaluate them, meaning they can be compounded.[11]

The 503A list of medications relevant to dermatology effective from the March 2019 update are: Aloe Vera, Capsaicin Palmitate, Coenzyme Q10, Glutathione, Glycolic Acid, Kojic Acid, Trichloroacetic Acid.[12] Cantharidin and squaric acid dibutyl ester were removed from the category 1 503A list on the most recent update, and remain on the category 1 503B list.

The 503B list of medications relevant to dermatology effective from the March 2019 update are: Adapalene, Aluminum Chloride Hexahydrate, Azelaic Acid, Benzocaine, Betamethasone Acetate, Betamethasone Dipropionate, Betamethasone Sodium Phosphate, Budesonide, Bupivacaine, Calcipotriene, Cantharidin, Clindamycin Phosphate, Clobetasol Propionate, Coal Tar Solution, Dapsone, Desoximetasone, Econazole Nitrate, Epinephrine, Fluconazole, Fluocinolone Acetonide, Fluocinonide, Hyaluronic acid sodium salt, Hyaluronidase, Hydrocortisone, Hydroquinone, Imiquimod, Itraconazole, Ivermectin, Ketoconazole, Lidocaine Hydrochloride, Metronidazole, Mometasone Furoate, Monosodium Glutamate, Mupirocin, Niacinamide, Oxymetazoline HCl, Phenol, Podophyllum, Polymyxin B Sulfate, Prilocaine, Proparacaine HCl, Salicylic Acid, Sodium Bicarbonate, Sodium Chloride, Sulfacetamide Sodium Monohydrate, Tacrolimus, Tazarotene, Terbinafine HCl, Tetracaine Hydrochloride, Tretinoin, Triamcinolone Acetonide, Triamcinolone diacetate, Urea, Vitamin D, Zinc Oxide.[13]

Category 2: Bulk drug substances that raise significant safety concerns, meaning they cannot be compounded.[11] Currently neither the 503A or 503B list of medications include any medications relevant to dermatology.

Category 3: Bulk drug substances nominated for bulk compounding without adequate support/evidence for their safety, meaning that they are restricted as not safe to compound at this time until additional safety information is gathered.[11]

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The 503A list of medications relevant to dermatology effective from the March 2019 update are: Hyaluronic Acid Sodium Salt, Papaya enzymes, White ointment.[12]

The 503B list of medications relevant to dermatology effective from the March 2019 update are: Aluminum chloride, Cidofovir, Coenzyme Q10, Collagenase, Desonide, Hyaluronidase, Kojic Acid, Miconazole nitrate, Nicotinamide, Nystatin, Resorcinol, Resveratrol, Retinoic Acid-All Trans, White ointment, White petrolatum.[13]

USP Compounding Lists/Categories

In June 2019, the USP published an update on General chapter 795, which applies to pharmaceutical compounding of non-sterile preparations and chapter 797, which applies to pharmaceutical compounding of sterile preparations. This update takes category 1 of the FDA bulk medications and recategorizes them into two different compounding sterile preparations (CSPs) based on the compounding conditions rather than the chemical compound properties themselves.[14]

Category 1: CSPs may be prepared in a segregated compounding area and therefore have a shorter beyond-use date (BUD). Category 1 CSPs can be used for up to 12 hours after the compounding if at controlled room temperature, and up to 24 hours after compounding if kept refrigerated.[14]

A good example relevant to dermatology that fits this category is the drawing up of lidocaine from a multi-purpose vial into smaller syringes and buffering it with sodium bicarbonate for local anesthesia. Thus far, there has been great variability between different states in formulating rules on how long the in-office lidocaine compounding can be used for. These rules have been based on some highly criticized studies that showed contamination was observed after a short period of time with in–office compounding. But the latter study ignored other substantive studies, such as that by Pete et al in 2016, that demonstrated safe medication use without micro-organisms or loss of medication properties even at four weeks after in-office compounding.[15] Thus far, the state rules on how long an in-office compounded injection can be used has varied greatly. One bright side to the anticipated recent USP updated guidelines is the hope that these most current USP guidelines will bring more guidance and uniformity to state rules.

Category 2 : CSPs must be prepared in a cleanroom environment and have a longer Beyond Use Date (BUD). Category 2 have more complicated and variable rules depending on whether the compounding was processed via aseptic vs sterile methods and depending upon the temperatures at which the compounding medication is stored afterwards. The BUD can vary from 24 hours to 90 days. Below is a table that summarizes the BUDs based on the CSP2 category (Table 1).[3,11] This category is not relevant to in-office compounding for dermatologists.[14]

In addition, a new USP General chapter 800 rule is expected to be implemented as of December of 2019. This rule refers to the safety guidelines in handling, compounding and administering hazardous medications listed on the National Institute for Occupational Safety and Health (NIOSH) website.[16]This list includes medications such as methotrexate and fluorouracil used in dermatology offices for intralesional injections. Current USP guidelines mandate using negative pressure rooms, chemotherapy gloves, and other special chemotherapy protective equipment for any type of handling and administration of these medications.[17] Although it may be too early at this time to know which state medical boards will implement this rule, many pharmacy state boards are planning to comply with it. This means that that any medical office or facility with a pharmacy license will be required to comply with its pharmacy state boards.

TABLE 1.

Category 2 CSPs[14]				
Preparation Characteristics		Storage Conditions		
Compounding Method	Sterility Testing Performed and Passed	Controlled Room Temperature (20°–25°)	Refrigerator (2°–8°)	Freezer (–25° to –10°)
Aseptically processed CSPs	No	Prepared from one or more nonsterile starting component(s): 1 day	Prepared from one or more nonsterile starting component(s): 4 days	Prepared from one or more nonsterile starting component(s): 45 days
		Prepared from only sterile starting components: 4 days	Prepared from only sterile starting components: 10 days	Prepared from only sterile starting components: 45 days
	Yes	30 days	45 days	60 days
Terminally processed CSPs	No	14 days	28 days	45 days
	Yes	45 days	60 days	90 days

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Topical Medications

Topical medications that are commonly used in dermatology pose a conundrum with a much lower safety risk for the patient than injectable medications. Nevertheless, they are still subject to the same compounding rules and regulations as injectables. Common examples of "office-use" compounded topical medications used by dermatologists include different preparations of pre-formulated numbing creams containing lidocaine, benzocaine and/or tetracaine, as well as compounded wart treatment formulations (eg, cantharidin), and aluminum chloride. 503A traditional pharmacies can make these formulations readily available in small amounts. However, there are several obstacles with 503A pharmacy topical compounding for dermatologists such as they require a patient-specific prescription. Yet, it may be unsafe to have a patient be in possession of medications that are intended for "in-office" physician supervised use. Since these are prescription-specific, it is also impractical and unsafe for an office to store these "in-office" use medications for each individual patient. In addition, topical compounding is also subject to the 503A bulk substances limitations and traditional pharmacies can't compound all topical prescriptions. Alternatively, physicians can acquire these compounded medications through 503B compounding facilities since they don't require a patient-specific prescription. The trouble is that these medications are often available only in large quantities that are very costly and wasteful if they cannot be used by their expiration date. In addition, there area also concerns about lack of GMP controls, lack of stability, and unpredicatable shelf life, and possible variability of concentration in different batches unlike an FDA approved product. Also, these facilities are far fewer and often less accessible, which can cause a significant delay in getting these medications in a timely manner. Thus, this has led to a cacophony of complaints of the impracticality and restriction for patient care of these new regulations.

Cantharidin is an example of the compounding conundrum. It was available briefly as a 503A category 1 medication for compounding and yet in March 2019 it was moved to the 503B category 1 list. The end result is that now access for patients to this drug is significantly restricted because 503B facilities will most likely sell it in bulk orders only. This is impractical since the average dermatologist doesn't need bulk supplies that will be costly and likely expire before they can be used in a cost-effective manner. This has resulted in physicians having to wait for a commercially available FDA approved formulation.

CONCLUSION

Medication compounding is an important part of medical treatments and has been used widely in many fields of medicine, especially dermatology. Patient safety is and should always be a primary concern in medication compounding. The rules and regulations mandated by the FDA, USP, and the individual states are constantly evolving and becoming more stringent.

While we must applaud the pursuit of safety, it needs to be recognized that this poses a challenge to in-office compounding and often deters the practitioners from continuing this practice due to fear of harsh penalties. As a result of this, many outpatient offices have decreased or eliminated in-office compounding. In addition, the 503B outsourcing facilities are not as readily accessible either physically or from a cost-effectiveness point of view as the 503A transitional pharmacies that are now even more limited in compounding. The American Academy of Dermatology (AAD) and other physician organizations have been actively working with the FDA, USP, and other policy-making government and non-government organizations to educate about the low risk office compounding and find the best solution to the compounding issues. In dermatology, intra-dermal anesthetics and steroid injections are widely used in everyday dermatology practice and often require dilution or mixing with a substance such as a buffer for an anesthetic in order to decrease pain with an injection. While injectable preparations are considered higher risk for adverse events and contamination than topical preparation, intra-dermal injections should be considered low risk when compared to intravenous, intra-articular, or intra-ocular injections since the side-effect profile is very different. Proper education on these low risk treatments such as topical treatments, intralesional steroid dilution, or lidocaine buffering is a key to understanding the risk benefit profile for our patients and demonstrates how these can be done safely and decrease the cost drastically. Certainly the current state of affairs is not in the best interest of our patients.

Amidst this regulatory chaos, the very first FDA-approved treatment for molluscum will be a welcome addition to our treatment armamentarium.

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AUTHOR CORRESPONDENCE

Leon H. Kircik MD
Email:..... wedoderm@yahoo.com

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