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COMMENTARY

Food and Drug Administration Restrictions on Drug Compounding: Needed Medications are Going to Disappear: A Call for Intervention

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Abstract

Drug compounding is undergoing a sea change as the Food and Drug Administration (FDA) is imposing restrictions on what ingredients can be compounded and whether they may be held in the physician's office for multiple uses as well as limiting interstate shipments. The FDA has been subjecting ingredients that have historically been an important part of medical practice to a monograph style review, resulting in rejection of ingredients in favor of approved drugs, even those for which a US Pharmacopeia dietary supplement monograph exists. The article describes the encroachment by the FDA on the practice of medicine and efforts by the American Association of Naturopathic Physicians, the Integrative Medicine Consortium, and the International Academy of Compounding Pharmacists to address problems of access to needed medications.

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Food and Drug Administration Is Changing Rules on Access to Compounded Medications

Drug compounding is undergoing a sea change as the Food and Drug Administration (FDA) is asserting jurisdiction and imposing restrictions on what ingredients can be compounded, whether they may be held in the physician's office for multiple uses, limiting whether specialty pharmacies can ship products interstate, and increasing inspection activity. These and other restrictions are threatening access to compounded medications, drugs that have historically played a critical role in treating and supporting patient care across the broad spectrum of conventional, integrative, and naturopathic medicine.

Curtailing the use of compounded medications is a direct interference in state-authorized medical practice, a boundary that the FDA has previously recognized as both a limit on its jurisdiction and its competence. The FDA, in this instance, is plainly staking out new territory on both fronts, interfering with medical practice by openly finding that physicians cannot be trusted to make decisions about these compounds and not only pre-empting medical decision making but also state pharmacy practices such as allowing in-office use. The FDA is requiring that ingredients that are not a component of an approved drug or subject of a USP drug monograph go through a monograph-style review, heavily stilted toward rejecting them in favor of a requirement to only use approved pharmaceuticals.

These changes jeopardize patient care and have alarmed the medical and pharmacy communities across all specialties. Representatives of more than 40 professional associations have been in regular attendance at FDA "listening" sessions attempting to address serious problems that this has created with access to medications, a problem that will become much more pronounced in the next few years as the regulatory process moves forward. The American Association of Naturopathic Physicians (AANP) and the Integrative Medicine Consortium (IMC) are working with the author to file a citizen petition (See Sidebar, "Getting Involved") with FDA seeking relief from ingredient determinations we see as scientifically indefensible and made without compliance with administrative rules. The International Academy of Compounding Pharmacists (IACP) is actively seeking a legislative fix for some of the most damaging aspects of the FDA's efforts.

Compounding Pharmacies Are Important for Integrative Care

Compounding, in some instances, may simply be done to allow use of active ingredients without preservatives or allergenic substances, convert into a different route of administration such as for topical use, or by an intravenous route to assist patients with digestive disorders or to achieve therapeutic levels systemically. Or it may be to provide drugs that are simply otherwise unavailable.

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These products are used to treat a significant variety of conditions, including digestive disorders such as colitis, chronic bacterial and viral infections, anemia and vitamin deficiencies, ophthalmologic conditions, Parkinson's disease, migraine, hepatitis, diabetes, chronic fatigue, asthma, arthritis, and other autoimmune disorders. They can be used as part of procedures, such as in anesthesia, or adjunctively, such as therapies to mitigate the side effects of chemotherapy. In other cases, compounded ingredients may simply offer functional benefits such as antioxidant or anti-inflammatory effects. They are essential for millions of patients. Critical drugs that are a key part of integrative practice, such as glutathione, *N*-acetyl cysteine, and a-lipoic acid are under review and likely to be withdrawn from the list of what can be compounded, joining those recommended for removal and only awaiting final administrative action in the coming months and years.[i]

Compounding Is Not Without Risk: The Origins of FDA's Initiative

As with any health care process, compounding is not without risk, particularly when abused. In September of 2012, a meningitis outbreak affecting more than 800 patients, of whom 76 died, was traced to the New England Compounding Center (NECC). Although compounding is intended for the creation of small doses in response to patient need, NECC was criminally engaged in large-scale manufacture and the knowing shipment of contaminated injectable products. NECC owners and pharmacists were sentenced to lengthy prison terms[1] and Congress set about to enhance safety by creating larger scale "outsourcing facilities" subject to current Good Manufacturing Practices to produce compounded drugs needed in high volumes, particularly where sterility is required. Congress created these so-called "503B" facilities by adding that section to Food, Drug and Cosmetic Act (FDCA, or "the Act") with the passage of The Drug Quality & Security Act (PL 113-54; DQSA) in 2013.

Dramatic Reduction in Permitted Ingredients and Interstate Access

Although Congress did not change the provision governing traditional, small pharmacy compounding under §503A of the Act, the FDA has taken this as an opportunity to completely rewrite the regulatory structure of how physicians access and use compounded drugs, including a wholesale resetting of what ingredients are permitted for traditional §503A compounding and the standards by which ingredient approvals are determined. The FDA has imposed an uncertain and burdensome ingredient nomination process that places the responsibility on the professions and small pharmacies to submit monograph levels of evidence and use data for an FDA analysis that is slowly and inexorably leading to denials of numerous drugs that have a long history of safe use.[1] Of the 49 nominated ingredients that have been reviewed thus far, fully 70% have been rejected.

Even ingredients that have been accepted for use reveal the open biases in the agency and its selected members of the Pharmacy Compounding Advisory Committee (PCAC) with which it reviews ingredients. 2,3-dimercaptopropane-1-sulfonate (DMPS) was accepted for listing, but only because it is the sole effective agent for the treatment of arsenic poisoning. Its use in mercury detoxification was roundly denounced for the use of "presumed" amalgam toxicity.[2] Fortunately, once an item is listed, the FDA may not restrict the indications for which it used, just as with any other "off-label use."

The FDA can, however, limit the route of administration, so approved ingredients may be limited to topical or oral use. Most of the nominated ingredients that are slated for removal from the market are in fact dietary supplements subject to a USP dietary supplement monograph. Congress instructed the FDA to accept "applicable" USP monographs as a basis for compounding.[3] According to 21 USC §353b(a)(3), "… if an applicable monograph exists under the United States Pharmacopeia, the National Formulary, or another compendium or

Getting Involved

Supporting the Citizen Petition:

More than 195 supporters have contributed funds to support the citizen's petition, an administrative filing raising that raised detailed challenges to the issues with ingredient approvals presented in this article along with many other legal, clinical, and public health policy difficulties created by the FDA's revision of compounding practice. For more information, please visit https://www.youcaring.com/patientswhobenefitfromcompoundedmedications-687276/.

If you are a health care or patient organization or health care provider interested in cosigning this petition, please contact director@aznma.org (Baron Glassgow, executive director, Arizona Naturopathic Medical Association) working on behalf of both the American Association of Naturopathic Physicians and the IMC.

Supporting HB 2871:

For more information on HB 2871 and what you can do to encourage its passage, please see the International Academy of Compounding Pharmacists Web page at http://www.iacprx.org/page/AdvocacyHR2871/.

i. Commonly used drugs have been recommended for removal from the market and will become unavailable in the next few years, such as MS, chondroitin sulfate, curcumin, *Aloe vera* 200:1 freeze dried, D-ribose, and acetyl-L-carnitine, *Germanium sesquioxide*, rubidium chloride, doxy-D-glucose, alanyl-L-glutamine, gluteraldehyde, glycyrrhizin, domperidone, quinacrine hydrochloride, and *Boswellia*. Other important ingredients still under review and at high risk of rejection include glutathione, α-lipoic acid, methycobalmin, and quercetin. These products will remain available as over-the-counter dietary supplements, though these cannot be used in compounding. The fact that the FDA considers they have insufficient demonstrations of safety and effectiveness to allow even physician prescribing suggests another congressional fight over dietary supplements may be pending.

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pharmacopeia recognized by the Secretary for purposes of this paragraph, the bulk drug substances each comply with the monograph."[4] But FDA has refused to accept listing in the USP dietary supplement compendium as a sufficient basis for compounding.[4] This has left these ingredients subject to the nomination and approval process in which FDA conducts reviews that are highly critical of industry data. Ingredient nominations are being refused placement on the positive bulk list simply because there is an approved drug available for the same indication, the proposed indication is a serious disease or from concern that use of a compounded drug would delay treatment. Although these standards have bearing on OTC medications, they are remarkable and unprecedented standards to apply to items prescribed in the judgment of a treating physician.

In addition to the pending removal of numerous ingredients from use, FDA initiatives are undermining access to compounded drugs by preempting the majority of states that allow physicians to keep available supplies on hand, so-called office use. The FDA is also broadly interpreting restrictions in the DQSA on interstate sales in a manner that could curtail interstate dispensing from specialty compounding pharmacies, even though they are the only available supplier of some bulk ingredients in the entire country.

The Citizen's Petition: Addressing Poor Public Health Policy Underlying Ingredient Denials

The responses of the health care community to these changes have been robust. The American AANP and the IMC have filed extensive comments with the agency are working with the author to file a Citizen Petition with FDA seeking relief from ingredient determinations we see as scientifically indefensible and made without compliance with administrative rules.

Filing a citizen petition is the next administrative step in seeking a change in policy. The agency is required to respond to the petition within 180 days; expectations for prompt and significant revisions are not high but aligned with other congressional and political pressures on the agency may provide some important policy changes. The citizen petition is required to preserve the right to take additional legal actions; if not filed, then legal challenges to the agency become unavailable. Filing is anticipated mid-summer of 2018.

Although components of approved drugs and ingredients listed in USP drug monographs may continue to be compounded, this left more than 425 ingredients without authorization. The FDA requested ingredient nominations and developed criteria and a means to review them with a PCAC. The nomination process, entered into by AANP, IMC, IACP, and many other physician and pharmacy organizations, required busy physicians, pharmacists, and their organizations to nominate and submit extensive data supporting each ingredient. More than 350 of these nominations were denied as having insufficient information and are currently illegal to compound. Those that the FDA deemed as having sufficient nomination support at the moment are subject to a safe harbor[5] and may be compounded until the ingredients are published for notice and comment in the federal register, a process that is proceeding slowly. Only 5 ingredients have been published for prohibition from use thus far,[ii] and the removal of these ingredients from the allowed bulk ingredient list will not be enforced until the final rule is published, which is expected in August 2018. The agency expects to start rolling out proposed groups of approximately 10 withdrawn ingredients in the Federal Register at a time for comment, with a final rule disallowing use to follow a few months later. The process will be ongoing for the next several years. Even now, however, overzealous FDA inspectors have been citing pharmacies for compounding products that are planned for withdrawal but are currently under a safe harbor.

The FDA is obligated to publish the criteria by which it is reviewing nominated ingredients, but instead the FDA published only 4 topic areas as a guide to their reviews. Rather than publish the actual criteria in use for comment, these give only general notice that the agency would balance findings regarding physical characterization, safety, effectiveness, and history of use. In actual practice, the FDA is using specific criteria in its briefing documents since the ingredient approval process began in 2014. Actual FDA practice has presumed that if an ingredient is nominated for a specific indication for which an approved drug exists, the nominated ingredient will be denied for even minimal safety risks, rejected ingredients in part from a concern that its use by a physician could unnecessarily delay treatment with an approved medication or even, among others, because the indication the ingredient is proposed to treat is "serious." Another criteria that the FDA has imposed is a higher threshold requirement that ingredients demonstrate effectiveness against disease, when the ingredient may simply have appropriate functional uses.[6] Drugs, by definition, include those used solely for functional purposes. Yet nominators of ingredients are being told that uses such as antioxidant and anti-inflammatory are not sufficient and evidence of effectiveness against disease is required. Congress intended that traditional compounding practice not be disturbed, but the FDA is remaking the industry to follow the new drug approval process even though compounding, when not abused, has historically worked well.

The FDA appears to be avoiding publication for comment of the actual criteria it is using, because it is not defensible from a legal, scientific, or policy perspective.

ii. The only ingredient decisions published for notice and comment thus far are positive listings for brilliant blue G, approval for topical use only for thymol iodine and cantharidin and denials for use of silver protein mild, piractem, tranilast, *N*-acetyl glucosamine, and oxitriptan (5-HTP). See "List of bulk drug substances that can be used to compound drug products in accordance with §503A of the Federal Food, Drug, and Cosmetic Act," Notice of Proposed Rulemaking (NPRM), issued on December 16, 2016.

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The agency is obligated to define a standard that provides guidance to the public, professions, and a reviewing court; there are no standards contained with the published topic areas on which one could tell whether a given decision was consistent with the alleged criteria, leaving room for the agency to make arbitrary and capricious decisions. Many of these criteria directly discount the education and training of physicians, such as rejecting an ingredient that might "unnecessarily" delay treatment with an approved medication even though the patient is clearly under a physician's care. The FDA has limitations in law against invading the practice of medicine and has had a long-standing policy against doing so, but it is moving to require physicians use drugs approved for specific diseases rather than compounded drugs even when those choices are not clinically sensible.

Fruits of the FDA Ingredient Review Process: 2 Striking Examples

The FDA proposes denying approval for compounding a widely sold dietary supplement, oxitriptan (5-HTP),[6] in large part because it presumes a naturally occurring physiologic substance with a history of safe use must demonstrate that it does not have the same side effects as synthetic pharmaceuticals with a different mechanism of action merely because they each treat the same diagnostic category. Per 21 UC §321(g), "The term *drug* means … (b) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (c) articles (other than food) intended to affect the structure or any function of the body of man or other animals ..."[6] The FDA's policy is that physicians should be required to use the synthetic pharmaceutical option known to have these side effects for the ironic justification that the physiologic ingredient "might" have these same effects. Furthermore, the FDA ignores the history of safe use in its calculus, the involvement of trained physicians who know and follow the patients for whom they are prescribing, that 5-HTP can be obtained as a dietary supplement and used without the benefit of physician oversight and has been used without any reasonable concern of significant risks. Nor has the FDA evidenced any consideration that there exists an entire field of nutraceutical compounding in which patients are prescribed custom formulations of nutrients.

Based on FDA's actual criteria, the dietary supplement methylsulfonylmethane (MSM) is pending rejection for arthritis management in large measure because of 4 cases of bleeding or elevated international normalized ratio (INR). The agency believes that the availability of a COX-2 inhibitor, a drug carrying a black box warning for risk of heart attack and stroke, is such a clear choice that physicians should be denied MSM as a treatment option in favor of the COX-2 inhibitor. Physicians have been able to make informed choices with their patients as part of their practice of medicine, free of FDA's bias that a drug that has gained its approval must be superior no matter the extent of damage and death that drug has wrought. That MSM or other ingredients rejected may merely be prescribed as an adjunctive to, and not a replacement for approved medications, is a consideration entirely absent in the FDA's application of its criteria. A process that leads to decisions so at odds with reason and the public health is clearly arbitrary and capricious and one the citizen's petition asks FDA to reconsider.

Reviewing the Reviewers: The FDA Approach to Ingredient Approvals

The proposition that there is an approved product for an indication by no means suggests that patients have available a complete resolution of their illness. The proposition that no other solutions are needed or that nominated ingredients do not have a demonstrable role to play is clearly not an assumption that can be drawn. Such a demonstration is not a requirement for a new drug application; research for new drugs in virtually all areas continue despite available products, and there is no rationale for imposing this unusual threshold on compounded products.

Not surprising, the PCAC findings have been inconsistent, and in some cases the existence of an approved treatment for an indication has been a basis for denial; in other cases, the committee has voted to allow a drug to be available as an alternative treatment.[7] For example, compare the transcript rom the PCAC meeting on June 23, 2016, afternoon session, at 138 (member explaining basis for recommendation to approve tea tree oil was to allow another alternative to be available) while declining other nominations, such as domperidone, because an approved drug allegedly was already available.[7] There is no discernable rationale for these distinctions, and the citizen's petition argues that this had led to decisions that are inconsistent, arbitrary, and capricious.

Restricting compounded drugs based on whether there are already available drugs by indication is troubling as proper treatment cannot be simplistically determined by broad diagnostic categories. In the pending case of MSM, a search of arthritis in *DSM-10* yields not only osteoarthritis and rheumatic conditions but a variety of related inflammatory and other disorders. Diagnosis is a matter of taxonomy with limited predictive power as to what medications will work, even within the same precise diagnosis let alone the broad categories that the FDA is applying.

In denying 5-HTP in part because "there are multiple FDA- approved drug products available for the treatment of insomnia,"[7] the FDA fails to consider that benzodiazepines, hypnotics, sedatives, and over-the-counter options such as antihistamines all have well-known side effects that can include dependence, amnesia, dangerous hangover, and other adverse effects and which may be contraindicated because of conditions such as asthma, urinary retention, or concomitant use of opiates or other medications. The

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balancing of the approved therapies that are displacing the compounded ingredient does not even include the adverse effect profiles of the approved ingredients, an oversight that belies any balance in the process.

The assumption that an "effective" drug is available fulfills the need for a given condition is also a misuse of the term *effectiveness*. The case of MSM offers an important example of the difficulties with this reasoning with regard to the availability of approved medications for arthritis.[iii] Millions of arthritis suffers do not have adequate relief, and the fact that certain medications have demonstrated their effectiveness to the FDA's satisfaction sufficient to go to market by no means demonstrates that adequate treatment is available. This is due to individual differences in disease and response to medication, contraindications for use, medication conflicts, adverse reactions, or merely incomplete results. Many diseases are chronic, and approved drugs only ameliorate symptoms with partial success that varies wildly between patients. A drug may offer partial relief and be "effective," allowing it to go to market yet leave patients still suffering. Some drugs may only be offered to ameliorate symptoms while other to effect a cure, yet not even this distinction has made its way into the FDA's briefing discussions. To say that one or more effective drugs is available is by no means the same as saying that the disease is effectively treated. The latter proposition would startle the large population of arthritis sufferers.

For good reason, there is no such standard even for drugs seeking to be mass marketed under an NDA/IND application.[8] A pharmaceutical does not have to prove that it fills a treatment gap, nor even necessarily that it has a risk-benefit advantage. To impose such a standard on approved pharmaceuticals would remove large numbers of approved drugs from the market, and there is no rational basis for applying a stricter standard to compounded drugs. This is particularly obvious given that it is not even a standard required for OTC drug approval which, unlike compounded drugs, likely have no physician involved in treatment decisions. If nominated substances, such as MSM, can offer patients relief alongside other available treatments, then FDA's standards barring its use cannot amount to fair, reasonable, or compassionate health policy.

Furthermore, physicians may have informed reasons to approach an indication differently, such as attempting to resolve a functional cause found in that patient or according to a different school of medicine that seeks functional improvement rather than ongoing symptom management. This and other clinically significant differences are absent from FDA and PCAC's reasoning.

Many approved drugs demonstrate postmarket borderline effectiveness at best. Although no head-to-head comparison should be required, many rejected ingredients would in fact do well. Certainly, rejection of an ingredient merely for the existence of an approved drug for an indication is not only a baseless standard, but certainly cannot be grounded in mere approval for the mass-marketed drug. Approved drugs often have extremely high number needed to treat statistics, which conclusively demonstrates that approval does not mean a treatment void has been filled. Many of the largest-selling pharmaceuticals on the market show modest benefits at best and arguably outweighed by their risks. Studies of statin drugs, for example, show that 60 patients prescribed without known heart disease have to be on statins to prevent 1 heart attack and 268 must be on statins to prevent 1 stroke; no lives were seen as saved; the evidence of effectiveness is not overwhelming. Furthermore, 1 in 50 patients developed diabetes and 1 in 10 suffered muscle damage.[9] Based on this considerable evidence, patients on statin drugs are at least arguably more likely to be harmed than helped.[10]

Many approved pharmaceuticals with approved NDAs could not have survived the evident standard the FDA adopts in its final conclusion about MSM: The FDA acknowledged:

> The safety of MSM "consists mostly of non-serious adverse events, with the most common side effects consisting of gastrointestinal upset, fatigue, insomnia, and headache. However, there have been adverse events of concern reported in the literature that include increased blood pressure, increased effectiveness of anticoagulants, and elevated liver function tests. A search of the FAERS database showed **four** reports of either bleeding or increased INR. … Notably, there are a number of approved alternative treatments for osteoarthritis that have been demonstrated to be safe and effective (emphasis added with underscoring).[11]

To fairly do the risk-benefit balancing comparison the FDA claims it is doing, however, it would need to also weigh the safety and adverse effect profile of the approved drugs it claims occupy the territory. In the case of MSM, for example, the difficult safety profile of the approved COX-2 inhibitor, celecoxib (marketed as Celebrex), which has a black box warning[iv] based on potential damage that far exceeds the four bleeding or INR events, along with low rates of subjective symptoms that also show up in placebo study arms, referenced as possibly linked to MSM even when taking data limitations into account. And of course, physicians routinely address the of possible interactions with anticoagulants as part of their prescribing practice.

Implicit in the FDA's view is that products that have passed monograph review or clinical trials have demonstrated that they are safe and are therefore safer

iii. The FDA briefing document for MSM states that "[T]here appears to be, at best, a suggestion of possible efficacy in reducing pain based on differences in pain-related outcomes, in support of the use of MSM in patients with joint pain associated with OA. … Pain is a serious condition for which there are a number of approved alternative therapies. These alternatives have been shown to effectively treat OA pain."[7]

iv. Celebrex® black-box warning: Cardiovascular risk: NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see WARNINGS).

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alternatives. But this cannot be presumed to be the case, particularly in light of a fair comparison with the safety record of approved drugs. The FDA Adverse Event Reporting System (FAERS) shows that in 2017, there were 164 252 deaths and 906 941 serious incidents that were life threatening or resulted in hospitalization or disability, congenital anomaly, and/or other serious outcome[12] due either to medication errors or simply due to the intrinsic risks of the medication. The GAO has estimated that the FAERS system captures only 1% to 10% of all adverse reactions.[13] In 2010, there were 4.9 million visits to emergency rooms for drug-related emergencies, of which approximately 2.3 million visits were not due to abuse but from patients taking medications as prescribed.[14] The underreporting to FAERS is not only due to a lack of comprehensive reporting, but reported deaths generally cite the underlying disease even if a drug reaction was responsible for death. The drug approval process itself is not highly predictive of outcomes, because nearly 1 in 3 drugs approved in the past decade have had major safety issues after market approval.[15]

The drug approval process itself does not have a predictive track record clearly superior to the decades of safe use in the compounding industry. It certainly belies the idea that the literature review being conducted can correctly identify the appropriate cost-benefit relevant to the compounded medications being reviewed or justify the presumption that approved drugs are safer. By telling doctors they should prescribe a drug with a black box warning over a commonly and safely used dietary supplement, the FDA has taken a position that approved medications outweigh consideration of products with compounded medications with important historical uses.

HB 2871: IACP's Legislative Effort

The IACP, working with AANP, IMC, and numerous other professional medical associations, has been working to obtain congressional appropriations report language restricting the use of federal funds and instructing the FDA on its intent with regard to these and other issues as well as putting forward critical legislation in the form of HB 2871. This bill would provide that USP recognized dietary ingredients may be compounded and to allow state authorized office-use, among other legislative fixes.

Working with Representatives Morgan Griffith (R-VA) and Henry Cuellar (D-TX), the IACP has seen the introduction of the "Preserving Patient Access to Compounded Medications Act" (HR 2871), which would clarify congressional intent regarding key provisions of the DQSA. This bill would allow traditional compounding pharmacies to distribute compounded drugs for office-use without a prior patient-specific prescription in states that allow office-use compounding and would clarify the right to compound ingredients with USP dietary supplement as well as drug monographs. The meaning of these terms is discussed below.

Legislative Language to Address Office Use

The practice of "office-use" occurs when a pharmacist compounds and provides a batch of drugs allowing a physician to have it on-hand in anticipation of need, the pharmacy later receiving patient-specific prescriptions or documentation. A doctor may need to maintain a small supply in his or her office because it is unsafe or impractical to issue a traditional prescription or because it is needed for urgent care. A related issue in the supply chain is simply whether the pharmacist can make a sufficient supply to be able to cover expected scripts. The FDA has been more flexible about this "anticipatory" compounding and proposes that a pharmacist be able to create sufficient amounts to cover the scripts expected during the next 30 days based on ordering history. But the FDA has refused to yield any ground and intends to override state law where it allows for office use.

This practice is authorized in the majority of states and was intended to be allowable under DQSA. Against strong opposition from physicians and pharmacy groups and even US Congress, the FDA has stated its intent to prohibit the practice nationally.[16] Given the persistent work of IACP, US Congress has directed the FDA via an appropriations report[17] to issue a final guidance that provides for office use in appropriate circumstances as well as allowing drugs compounded in anticipation of prescriptions for individual patients based on the history of previous orders. The FDA has nonetheless refused to change course. The FDA guidance for industry at this point is nonbinding, but it nonetheless sets forth a requirement that physicians may not use compounded medications for office use to treat patients. Instead, a physician must write a patient-specific prescription prior to receipt of each dose. What formerly could be treated in the same visit would now require a trip to the physician office for evaluation and diagnosis, a trip to the pharmacy to obtain the prescription or from a delivery service, and a follow-up visit to the physician office to administer the treatment. Even more critically, there are urgent situations in which drugs must be on hand but cannot be given per FDA's policy. Ophthalmologists, for example, need antibiotic ointments for infections and ethylenediaminetetraacetic acid for treating corneal ulcers, which they are having difficulty obtaining.

This causes delays in patient care and increased costs of care and of prescriptions, given that each prescription is made specific to the patient instead of available in bulk through the physician. There is an increased risk of noncompliance, of improper storage and handling, and decreased supply as some pharmacies have stopped providing some compounded drugs as a result. The office-use policy has been hotly contested and the community is attempting to work with the FDA on compromise solutions. When it will be actively enforced is unclear.

HB 2871 would amend the law to state that compounding of medications by a licensed pharmacist for office use to a patient in a clinical setting is permissible under §503A when done in accordance with state law.

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Legislative Language to Address USP Dietary Supplements Monographs

Most of the ingredients at issue would be allowed if FDA would accept ingredients for which there are USP dietary supplement monographs as a sufficient basis for compounding. Congress directed in the DQSA that the existence of any "applicable" USP monograph is sufficient, but FDA has rejected these monographs, thus disallowing an entire field of physician-guided therapeutic use of compounded nutraceuticals. HB 2871 makes it clear that a pharmacist may compound a drug product using bulk drug substances that complies with the monograph standards of the USP or National Formulary, including a dietary supplement monograph.

Legislative Language to Address Sales in Interstate Commerce: "Dispensing" or "Distribution"

Many ingredients are only available at highly specialized pharmacies. DMPS, for example, recommended by the FDA with PCAC approval for placement on the positive bulk ingredient list solely because of its singular role in treating arsenic poisoning, is only available from McGuff Compounding Pharmacy. Interstate shipment is thus a critical part of the supply line.

The DQSA limits interstate distribution to only 5% of a pharmacy's sales, which was seen as a way to curtail expansion into actual drug manufacture as occurred in the NECC tragedy. Although there are no limits on the amount that may be dispensed directly to an ordering physician or patient subject to a prescription order, the FDA is nonetheless interpreting the 5% limit to apply to all interstate sales, even direct dispensing on a prescription. This cap will make many important drugs unavailable.

HB 2871 defines *distribute or distribution* to clarify that those terms do not include the act of dispensing a compounded drug product in accordance with §503A. The bill also defines *dispense* to mean the act of the drug product leaving the facility in which it was compounded for delivery to a patient, patient's agent, or health care facility (including a hospital, physician's office, or other health care setting) pursuant to a valid prescription order for an identified patient.

Conclusion

The FDA's approach to compounding is a case study in a bureaucratic overreaction that threatens to do more harm than the original problem it was intended to solve. The FDA repeatedly cites the NECC tragedy as justification for its wholesale resetting of compounding practice, but there is no nexus between the criminal production of methylprednisolone acetate (MPA) and the removal of scores of needed ingredients from the market or prohibitions from office use. Ironically, pharmacies can still compound preservative-free MPA. Physicians are facing the loss of important drugs and nutraceuticals and the freedom to access them in their office. It is important to be aware of these changes, and to help educate the FDA about the value of these medications.

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