

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

List of Bulk Drug Substances that can be used to Compound Drug Products in Accordance with Section 503A of the Federal Food, Drug, and Cosmetic Act

Docket No. FDA-2016-N-3464

Preliminary Regulatory Impact Analysis
Initial Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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I. Introduction and Summary

Compounding pharmacies combine, mix, or alter a drug or components of a drug to create a medication tailored to the needs of an individual consumer. Compounded drug products are exempt from certain provisions of the Food, Drug, and Cosmetic Act (FD&C Act) if they meet the conditions set forth in section 503A of the FD&C Act, including the requirements for premarket approval of new drug products, and current good manufacturing process (CGMP) requirements. Among the conditions to qualify for the exemptions in section 503A are that any bulk drug substances used in the compounded drug product either be the subject of and comply with an applicable U.S. Pharmacopeia (USP) or National Formulary (NF) monograph if such a monograph exists and the USP chapter on pharmacy compounding; or if such a monograph does not exist, are a component of an FDA-approved drug product. In addition, under section 503A of the FD&C Act, pharmacies may compound drug products using bulk drug substances that are not the subject of an applicable USP or NF monograph or a component of an approved drug product only if they appear on a list developed through regulations issued under section 503A(c) (503A Bulks List). No such codified list currently exists. The proposed rule identifies bulk drug substances that we propose to place on the 503A Bulks List, and also identifies bulk drug substances that we have evaluated and propose not to place on the 503A Bulks List. This proposed rule would begin the process of creating the 503A Bulks List, which will continue on a rolling basis. Until we make a final determination about a drug substance that we are evaluating, we intend to follow our interim policy as described in guidance.¹

¹ Our guidance “Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act” provides more specific information on our intent to take regulatory action during our review of bulk substances.

In the proposed rule, we describe the criteria that we propose to use when evaluating bulk drug substances being considered for inclusion on the 503A Bulks List. These include:

1. The physical and chemical characterization of the substance;
2. Any safety issues raised by the use of the substance in compounded drug products;
3. The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and
4. Historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature.

Using these criteria, we reviewed 10 bulk drug substances. Based on our review, and our consultation with both the Pharmacy Compounding Advisory Committee (PCAC) and the United States Pharmacopoeia Convention, Inc. (USP), we propose to put six of the substances on the 503A Bulks List. This proposed rule would allow them to be used to compound drug products under the exemptions provided by section 503A of the FD&C Act. Because we believe that pharmacy compounders currently prepare these drugs, we do not anticipate that the rule would have an economic impact for those six substances. However, we ask for comments on whether the rule may have such an impact. Drug products compounded with the four bulk drug substances that we propose not to include on the 503A Bulks List would not meet the conditions of section 503A of the FD&C Act and therefore drug products compounded using those bulk drug substances would not be eligible for the exemptions from the FD&C Act provided by that section. In general, pharmacy compounding and sale of drugs compounded using such substances, would continue to be unlawful if the proposed rule is finalized, and may be subject to enforcement action. It is possible, however, that these four substances could be made available in

a more limited manner under an investigational new drug (IND) application where applicable requirements are met. For these four bulk drug substances, silver protein mild, piracetam, oxitriptan, and tranilast, we present a qualitative discussion of potential impacts of the proposed rule.

Although this proposed rule affects only 10 bulk drug substances, we continue to evaluate other bulk drug substances for inclusion on the 503A Bulks List. These bulk drug substances will be the subject of separate rulemakings.

Throughout our regulatory impact analysis, we use the following terms:

- “Pharmacy” or “pharmacies” refers to pharmacies compounding under 503A of the FD&C Act
- “Bulk drug substance” as referenced in this proposed rule means active pharmaceutical ingredient as defined in 21 CFR 207.1(b)
- IND application refers to an application for expanded access to investigational drugs for treatment use covered in 21 CFR 312.300 -312.320

II. Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We have developed a comprehensive Economic Analysis of Impacts that assesses

the impacts of the proposed rule. We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because we find little evidence that a substantial number of small entities would be affected by the proposed rule or that the economic impact on each affected small entity would be significant, we propose to certify that the proposed rule would not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

A. Market Failure or Other Social Purpose Requiring Federal Regulatory Action

Compounded drug products, including drugs compounded using these bulk drug substances, have not gone through the rigorous approval process required to determine if a new drug product is safe and effective, and can be consistently manufactured to applicable quality standards. Although drug products compounded using these bulk substances generally may not be lawfully marketed, we have stated in an interim guidance our intention not to take regulatory action while we review substances nominated with sufficient evidence to evaluate them, provided we do not identify significant safety issues with drugs compounded using the bulk drug

substances. There is evidence that pharmacies sell at least some drug products compounded with these bulk drug substances. The availability of drugs compounded using these bulk drug substances may lead consumers to believe these compounded drugs are safe and effective. They may, therefore, make choices they would not make if they were better informed.

Before proposing to place a bulk drug substance on the 503A Bulks List, we conducted a limited evaluation of the substance using the criteria identified in the proposed rule. Even a limited evaluation of a substance by us would include more information than the average consumer would likely have. As we have an advantage in understanding the risks and benefits of drug products, there is an information asymmetry between us and the average consumer. This rule may address this information asymmetry in two ways. First, by taking regulatory action, we can prevent consumers from taking certain compounded drugs that consumers might have avoided if they were fully informed.

Second, this rule would provide more information to consumers and thus reduce the information asymmetry. Placing or not placing a substance on the 503A Bulks List serves as a signal to the consumer of our limited assessment of the risks and benefits of a drug product compounded from the bulk drug substance. This signal may help to correct false impressions consumers may have had about the risks and benefits of drug products compounded from the bulk drug substances. Consumers would be less likely to believe that drugs compounded using these substances are safe and effective based solely on their availability. Thus, consumers may respond and substitute an FDA-approved drug or an OTC monograph product, potentially improving their health outcomes.

Consumers often decide whether or not to take drug products containing these substances on the advice of a physician. If their physicians are already knowledgeable about these bulk

substances, any signal provided by the 503A Bulks List may have less effect on consumer decisions and health outcomes.

B. Affected Firms and Substances

Although the proposed rule addresses 10 bulk drug substances, we expect no impact on the compounding pharmacies that compound drug products with the 6 substances proposed for inclusion on the 503A Bulks List. If made final, the proposed rule would directly affect compounding pharmacies that wish to compound drug products with the 4 bulk drug substances that would be excluded from the list—silver protein mild, piracetam, oxitriptan and tranilast. The proposed rule could also affect manufacturers of these 4 bulk drug substances, wholesalers who distribute these substances, and repackagers of these substances who supply compounders. Even though the demand for these bulk drug substances by compounding pharmacies would likely be greatly reduced, some demand may remain from those who take drug products made from these substances under an IND application. However, we don't have data on the number of firms that the proposed rule could affect. We welcome comment on the number and types of firms that would likely be affected, and the expected impact of the proposed rule on these firms.

We have very limited information about the amount of the 4 bulk drug substances currently used in compounded drug products in the United States. There is little evidence from internet searches that compounding pharmacies use silver protein mild in compounded drug products in the United States. Although internet searches suggest that drug products compounded from bulk oxitriptan exist, we do not have information on the amount or value of oxitriptan currently used in compounded drug products in the United States.

In 2014, our import entry data shows that bulk piracetam imports for human use had a reported value of \$2,400. Assuming no domestic production of bulk piracetam, this would

represent the total value of this active ingredient prior to distribution and compounding. The accuracy of the import value, however, depends on the value reported by importers. Even with reporting inaccuracies, the magnitude of the import value suggests a low demand for piracetam. Furthermore, at the February 2015 Pharmacy Compounding Advisory Committee meeting, a firm that nominated piracetam for the 503A Bulks List reported that it sold just \$13,000 worth of bulk piracetam in 2014. This wholesale value also suggests that the market for drug products compounded from piracetam is small.

Of the four bulk drug substances evaluated and not proposed for inclusion on the 503A Bulks List, tranilast appears to be the most widely compounded. Through internet searches, we found many pharmacies offering compounded tranilast products. In 2014, about \$127,000 of bulk tranilast was reported in our import entry data. The accuracy of the value of imports depends on the reporting of the value by importers; this value excludes any domestic production of bulk tranilast.

For each of the four bulk drug substances that we propose not be placed on the 503A Bulks List, we request detailed information about the quantity and value of these substances currently used in compounded drug products in the United States.

C. Costs of the Proposed Rule

Although we lack sufficient data to quantify the potential costs of the proposed rule, we describe the possible impact of excluding each of the four substances from the 503A Bulks List. As noted previously, some of the substances could be made available under an IND application. Compounding pharmacies and wholesalers who may have previously handled the bulk drug substance would no longer do so, and would incur some administrative costs to learn about the rule and to train staff about its requirements. We estimate that each affected firm would spend

from 1 to 2 hours on administrative costs. The average hourly wage for a pharmacist in 2014 equals about \$57, or \$114 including 100 percent overhead. Thus, each affected firm would incur administrative costs that range from \$118 to \$235. We request comment on the potential administrative costs of the proposed rule. We request comment on any additional costs that firms may incur in response to the establishment of criteria to evaluate the bulk substances.

For each of the four substances we propose not to include on the 503A Bulks List, there is a potential private cost to certain producers. Manufacturers, wholesalers, repackagers and compounders may lose profits they earn from selling the substances or from drug products compounded from these four substances. Loss of profits would depend on the amount of these substances currently used to compound drug products, how profitable they are, and whether producers can compound alternative products in response to the proposed rule. In many cases, these lost profits would be transfers, such as lower costs to consumers and to other entities. We note when these costs may be transfers, and discuss other transfers in the section on distributional effects.

The cost to consumers and payers would vary depending on the difference in the price of drug products compounded with these four substances and the price of alternative treatments. Consumers or payers may incur costs if they pay more for alternative treatments than they currently do for products compounded with the affected substances. Conversely, they would have a cost savings if they pay less for alternative treatments than for drug products compounded with these substances.

If final, the effect of the proposed rule on pharmacies, consumers, and payers would also depend on the willingness of sponsors to hold an expanded access IND for a drug product made from the bulk drug substance. Consumers may continue to have access to drug products made

from the substances that we propose to not to put on the list if there is a sponsor willing to hold an expanded access IND and the substance can meet the criteria for expanded access. There are many requirements for accessing drugs under an IND. The drug must treat a serious or life-threatening disease, no satisfactory alternative exists, an investigator must submit an IND and have it approved, and locate a facility willing to supply the drug. We request comment on the likelihood of a sponsor submitting an IND for one of the affected substances.

To submit an IND, an investigator (who often is the physician of the patient) must obtain informed consent, have a written protocol, obtain Institutional Review Board (IRB) approval, submit Form 3926 to the FDA, and agree to submit additional annual and other reports to the FDA. The estimated time to fill out Form 3926 for a physician is 45 minutes. The mean hourly wage in 2015 for physicians and surgeons was \$107.10.² Allowing for 100% overhead, the cost of filling out one form would be \$160.64 per form. Individual INDs require one form per patient. We request comment on the number of patients that would be likely to seek access to drug products containing the affected bulk substances under an IND. We request comment on whether investigators would be likely to submit individual INDs. We also request detailed comment on the expected costs of submitting INDs for drug products containing the affected substances, including costs of obtaining IRB approval and developing protocols. We request comment on whether investigators would be likely to pursue INDs for intermediate-size patient populations, and on how the costs of submitting INDs for larger populations would compare with submitting INDs for individuals.

² Bureau of Labor Statistics. "May 2015 National Industry-Specific Occupational Employment and Wage Estimates," NAICS 621100 - Offices of Physicians. http://www.bls.gov/oes/current/naics4_621100.htm

To access a drug under an IND, the investigator and patient must find a facility willing to supply the drug. We request detailed comment on the upfront and ongoing costs of supplying these drugs under an IND and how those costs would affect the prices consumers pay. We also request comment on whether suppliers would be willing to complete necessary steps to supply drug products containing the affected bulk substances under an IND.

Consumers receiving such a drug under an IND could only receive the drug for treatment under conditions described in the IND, and must be informed that the drug they receive is not an approved product. They would receive information about the known benefits and risks of the drug. The sponsor would also be required to monitor the consumer for adverse events from the drug. If there were an IND that included one of the affected bulk substances, consumers may continue to take a drug compounded with that substance, potentially reducing the size of any costs or cost savings to consumers or payers as a result of the rule.

We request data and welcome comments on the impact of the proposed rule on the market for these four bulk drug substances. We also welcome comment on the likelihood that sponsors would submit an IND application for drug products made from these bulk drug substances.

D. Distributional Effects

Many of the economic impacts of the proposed rule would be distributed between consumers and producers. For example, if consumers switch from a drug compounded from one of the affected substances to an alternative therapy, pharmacies compounding with the affected substances could earn less profit on that substance, but providers of alternative therapies could see an increase in profit.

There may also be distributional effects for payers. Some compounded drug products are reimbursed by private payers. The proposed rule could create transfers between payers and pharmacies. If consumers switch to alternative therapies as a result of the proposed rule, and those therapies are more or less costly to payers than the compounded drug products that consumers were taking, there may be a transfer between payers and consumers. If consumers stop using products with these bulk drug substances without substituting an alternative therapy or suffering ill effects, payers may pay less, resulting in a transfer from consumers and pharmacies to payers. We request comment and data on the potential distributional effects of the proposed rule on private payers.

E. Cost to Government

There may be economic effects of the proposed rule on government payers, but these effects are uncertain. Government payers may pay less if there is a reduction in reimbursement for compounded products that include these bulk drug substances. Government payers might pay more if consumers switch to more costly alternative products covered by government payers.

F. Summary of the Annualized Costs of the Rule

We lack data on the scope of the current use of drug products compounded from the substances at issue and the number of firms affected by the proposed rule, which are necessary to quantify the total potential costs of the proposed rule. Potential costs include administrative costs, additional costs for consumers and payers if alternative therapies are more costly than the affected compounded drug products, and a potential loss of producer surplus if producers use additional resources in response to the exclusion of some substances from the 503A Bulks List.

G. Potential Benefits of the Proposed Rule

The benefits of the proposed rule are unquantified; we include a qualitative discussion of potential benefits. Establishing criteria for the review of bulk substances may help with consistency in review. It may also signal to nominators the type of supporting information that they need to include with their nominations for the 503A Bulks List, potentially allowing nominators to use their resources more efficiently. We request comment on any potential benefits of establishing criteria.

Because the proposed rule may remove certain compounded drug products from the market (except through an IND), we discuss potential alternatives available to consumers. FDA-approved alternatives and drugs marketed under an OTC monograph exist for many of the drug products compounded using the four bulk drug substances not proposed for inclusion on the 503A Bulks List. Consumers who switch to more effective or safer treatments may experience better health outcomes than they currently experience with the compounded drug products. Consumers not currently taking a compounded drug product may also benefit by avoiding potential future risks associated with the bulk drug substances not proposed for inclusion on the 503A Bulks List and losses associated with purchasing ineffective products compounded from these bulk drug substances.

As discussed previously, we expect that few consumers currently use drug products compounded from bulk silver protein mild. This substance has been used to treat conjunctivitis and by ophthalmologists as a preoperative chemical preparation of the eye. However, a number of FDA-approved anti-infective agents for ophthalmic use exist and have been shown to be both safe and effective. Also, as noted in the preamble of the proposed rule, the use of silver protein mild declined dramatically after the introduction of FDA-approved ocular anti-infectives.

Consumers appear to have used compounded oxitriptan to treat insomnia and depression. There is limited evidence that drug products compounded from this substance can effectively treat depression; there are many safe and effective alternative treatments on the market approved to treat depression. Consumers who switch to alternative treatments, therefore, may experience more effective treatment for their depression. The use of oxitriptan to treat depression has raised significant safety issues. Based upon its mechanism of action, concomitant use of oxitriptan with antidepressant drugs could result in serotonin syndrome, a serious and life-threatening drug interaction. Unlike drugs approved to treat depression, however, compounded drugs are not required to include labeling that would adequately warn physicians and consumers of safety risks.

Consumers have historically used piracetam products to treat a variety of disorders related to cognitive impairment, including Alzheimer's disease. Data from a well-controlled clinical trial show that piracetam failed to demonstrate efficacy for mild cognitive impairment, a condition which frequently precedes Alzheimer's disease. Studies of the efficacy of piracetam for other indications have been inconclusive. However, people with mild cognitive impairment may receive more effective treatment with FDA-approved alternatives than with compounded piracetam products.

By not including tranilast on the proposed 503A Bulks List, some adverse events may be avoided. A large trial of tranilast found evidence that the substance causes significantly elevated liver enzymes at higher doses. [Ref. 1] As noted previously, consumers may benefit from the avoidance of adverse events associated with taking a compounded product. Choosing a safer and more effective alternative product could improve health outcomes. For example, tranilast has been compounded for several indications, including eczema, psoriasis, or scar treatment, and oral

and intranasal formulations have also been available from compounding pharmacies. FDA-approved drugs are available for these indications. Tranilast is also used in the treatment of keloids and hypertrophic scars, conditions for which there are no FDA-approved drugs or biologics. During the June 2015 Pharmacy Compounding Advisory Committee meeting, one nominator asserted that other treatments for keloids and hypertrophic scars are “caustic, invasive, and expensive.” In these cases, the proposed rule may create a negative benefit for consumers who can’t obtain topical tranilast products under an IND program.

Initially, some individual consumers may experience a loss of utility (i.e., disutility) if these four bulk drug substances are no longer compounded and they switch to a different drug that they perceive is not as beneficial as the compounded drug. For such consumers, the disutility would represent a negative benefit because they either forgo treatment or choose a treatment they regard as “second-best.” The loss of utility for some consumers may offset some of the benefits of the proposed rule to other consumers and to society. Nevertheless, we anticipate that by not including bulk drug substances for which there is little, if any, evidence of safety or effectiveness on the 503A Bulks List, the net social benefit of the proposed rule would be positive. We request detailed comment and data on potential benefits of the proposed rule.

H. Uncertainty

The market for compounded drugs is dynamic, and market forces may be changing the amount of these substances used in compounding and their profitability. For example, in 2014, Express Scripts announced that it would stop coverage of drug products compounded from about 1,000 bulk drug substances [Ref. 2]. We lack information about how such an action by a major payer might impact the market for the compounded drugs.

In the absence of specific data, we are uncertain about the current level of use of these substances in compounding drug products, the market for the bulk drug substances, and size of the markets for drugs compounded from these bulk drug substances. We lack information that would allow us to predict whether pharmacies and wholesalers would transition to producing alternative products and the costs associated with such a transition. We don't know how many consumers take drug products compounded using these bulk drug substances, which alternative therapies they would choose in the absence of products compounded using those bulk drug substances, or how much better or worse off they may be with those alternative therapies.

I. Alternatives Considered

One alternative considered for the proposed rule was to include tranilast on the 503A Bulks List for use only in topical, and not oral, compounded drugs. With no FDA-approved drug products indicated for the treatment of keloids and hypertrophic scars, a topical dosage form of compounded tranilast could provide a treatment option for consumers with these conditions. (There are other alternative therapies, however, including silicone gel sheeting, silicone gel, pressure garments, intralesional corticosteroid injections, bleomycin injections, surgery, 5-fluoruracil intralesional injections, and radiotherapy.) The alternative of allowing tranilast to be compounded for topical use may have less impact on profits, as fewer compounded products would be discontinued as a result of the proposed rule. However, given the lack of information available about the safety and efficacy of a topical form of tranilast and the possibility that absorption of topical tranilast could cause liver damage, it is uncertain that this alternative would have net positive benefits compared to the proposed rule.

J. Impact on Small Entities

The Regulatory Flexibility Act requires a Regulatory Flexibility Analysis (RFA) unless we can certify that the proposed rule would have no significant impact on a substantial number of small entities. The Small Business Administration (SBA) establishes thresholds for small entities by North American Industry Classification System (NAICS); the SBA considers small any entity below these thresholds. Firms affected by the proposed rule would fall into three major industries, NAICS 325412 Pharmaceutical Preparation Manufacturing, NAICS 424210 Drugs and Druggists' Sundries Merchant Wholesalers, and NAICS 446110 Pharmacies and Drug Stores. The thresholds for these industries are 750 employees for NAICS 325412, 100 employees for NAICS 424210, and annual sales of \$27.5 million for NAICS 446110.

We lack data on the number or size of manufacturers, wholesalers and compounding pharmacies that would be affected by the proposed rule. Moreover, we find little evidence of widespread use of the four bulk drug substances not proposed for inclusion on the 503A Bulks List. This suggests that the impact of the proposed rule would likely not be significant on small entities. Because we find little evidence that a substantial number of small entities would be affected by the proposed rule or that the economic impact on each affected small entity would be significant, we propose to certify that the proposed rule would not have a significant economic impact on a substantial number of small entities. We request detailed comments and data on the number of small entities that would be affected by the proposed rule, as well as data on the economic impact of the proposed rule on these small entities.

III. References

1. D. Holmes, M. Savage and J. LaBlanche, "Results of Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial," *Circulation*, vol. 106, no. 10, pp. 1243-1250, 2002.
2. E. Silverman, "Express Scripts Ends Coverage for 1,000 Compound Drug Ingredients,"

WSJ Pharmalot, 1 July 2014.