Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Compliance/OUDLC

July 2016
Compounding and Related Documents

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or the Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed in the title page.

I. INTRODUCTION AND SCOPE

To qualify for exemptions under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act), a drug product must be compounded by a licensed pharmacist or physician who does not compound regularly or in inordinate amounts any drug products that are essentially copies of a commercially available drug product, among other conditions. This guidance sets forth the FDA's policies regarding this provision of section 503A, including the terms *commercially available*, *essentially a copy of a commercially available drug product*, and *regularly or in inordinate amounts*.[2]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research, in consultation with the Office of Regulatory Affairs at the Food and Drug Administration.

[2] This guidance does not apply to drugs compounded for use in animals, to biological products subject to licensure in a biologics license application, or to repackaged drug products. For proposed policies pertaining to compounding drug products from bulk drug substances for use in animals, see FDA's draft guidance, *Compounding Animal Drugs from Bulk Drug Substances*. For proposed policies pertaining to mixing, diluting, and repackaging biological products, see FDA's draft guidance, *Mixing, Diluting, and Repackaging Biological Products Outside the Scope of an Approved Biologics License Application*. For proposed policies pertaining to repackaged drug products, see FDA's draft guidance, *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities*.

All FDA guidances are available on the FDA guidance web page. FDA updates guidances regularly. To make sure you have the most recent version of a guidance, always consult the guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

A. Section 503A of the FD&C Act

Section 503A, added to the FD&C Act by the Food and Drug Administration Modernization Act in 1997 and amended by the Drug Quality and Security Act in 2013, describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to qualify for exemptions from the following three sections of the FD&C Act[3]:

- Section 501(a)(2)(B) (concerning current good manufacturing practice (CGMP) requirements)
- Section 502(f)(1) (concerning the labeling of drugs with adequate directions for use)
- Section 505 (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs))

One of the conditions that must be met for a compounded drug product to qualify for the exemptions under section 503A of the FD&C Act is that it must be compounded by a licensed pharmacist or a licensed physician that "does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product."[4]

The statute further states that "[t]he term 'essentially a copy of a commercially available drug product' does not include a drug product in which there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug."[5]

A complete list of the conditions that must be met for a compounded drug product to qualify for the exemptions in section 503A appears in the FDA's guidance, *Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act*.

B. Compounding, Generally

Compounded drug products serve an important role for patients whose clinical needs cannot be met by an FDA-approved drug product, such as a patient who has an allergy and needs a medication to be made without a certain dye, an elderly patient who cannot swallow a pill and needs a medicine in a liquid form that is not otherwise available, or a child who needs a drug in a strength that is lower than that of the commercially available product. Drug products for identified individual patients can be compounded by licensed pharmacists in state-licensed

[3] In addition, under section 581(13) of the FD&C Act, the term "product," for purposes of pharmaceutical supply chain security requirements, does not include a drug compounded in compliance with section 503A.

[4] See section 503A(b)(1)(D).

[5] See section 503A(b)(2).

pharmacies and Federal facilities and by licensed physicians operating under section 503A of the FD&C Act. Drug products can also be compounded by outsourcing facilities under section 503B of the FD&C Act for identified individual patients pursuant to prescriptions or for distribution to health care practitioners without first receiving a prescription.[6] Both sections 503A and 503B restrict compounding drug products that are essentially a copy of a commercially available drug product (section 503A) or an approved drug product (section 503B).

C. Risks Associated with Compounded Drug Products

Although compounded drugs can serve an important need, they also pose a higher risk to patients than FDA-approved drugs. Compounded drug products are not FDA-approved, which means they have not undergone FDA premarket review for safety, effectiveness, and quality. In addition, licensed pharmacists and licensed physicians who compound drug products in accordance with section 503A are not required to comply with CGMP requirements. Furthermore, FDA does not interact with the vast majority of licensed pharmacists and licensed physicians who compound drug products and seek to qualify for the exemptions under section 503A of the FD&C Act for the drug products that they compound because these compounders are not licensed by FDA and generally do not register their compounding facilities with FDA. Therefore, FDA is often not aware of potential problems with their compounded drug products or compounding practices unless it receives a complaint such as a report of a serious adverse event or visible contamination.

FDA has investigated numerous serious adverse events associated with compounded drug products that were contaminated or otherwise compounded improperly, including the adverse events associated with the 2012 fungal meningitis outbreak in which contaminated injectable drug products resulted in more than 60 deaths and 750 cases of infection. FDA has also identified many pharmacies that compounded drug products under insanitary conditions whereby the drug products may have been contaminated with filth or rendered injurious to health and that shipped the compounded drug products made under these conditions to patients and health care practitioners across the country, sometimes in large amounts.

D. Compounded Drugs That Are Essentially Copies of Commercially Available Drug Products

Section 503A provides exemptions from new drug approval, labeling with adequate directions for use, and CGMP requirements of the FD&C Act, so that drug products can be compounded as customized therapies for identified individual patients whose medical needs cannot be met by commercially available drug products. The restrictions on making drugs that are essentially copies ensure that pharmacists and physicians do not compound drug products under the exemptions for patients who could use a commercially available drug product. Such a practice would create significant public health risks because patients would be unnecessarily exposed to

[6] Section 503B of the FD&C Act describes the conditions that must be met for a human drug product compounded by an outsourcing facility to qualify for exemptions from sections 505, 502(f)(1), and 582 (concerning drug supply chain security requirements) of the FD&C Act. The conditions applicable to outsourcing facilities are discussed in separate guidances applicable to those facilities.

drug products that have not been shown to be safe and effective and that may have been prepared under substandard manufacturing conditions. FDA has investigated serious adverse events in patients who received contaminated compounded drugs when a comparable approved drug, made in a facility subject to CGMP requirements, was available.

In addition to these immediate public health risks, section 503A's limitations on producing a drug product that is essentially a copy of a commercially available drug product protects the integrity and effectiveness of the new drug and abbreviated new drug approval processes that Congress put in place to protect patients from unsafe, ineffective, or poor quality drugs. Furthermore, sponsors may be less likely to invest in and seek approval of innovative, life-saving medications if a compounder could, after a drug is approved, compound "substitutes" that have not had to demonstrate safety and effectiveness and are not produced in accordance with CGMP requirements or labeled with adequate directions for use.

Sponsors might also be less likely to seek approval of an ANDA for a generic drug if compounders were permitted to compound drugs that are essentially copies of commercially available drugs without going through the ANDA process. An ANDA must include data to demonstrate that the drug has the same active ingredient and is bioequivalent to an approved drug. FDA also conducts a premarketing inspection of proposed manufacturing facilities before approving the application.

The copies restriction also protects FDA's drug monograph process. FDA has an ongoing process for evaluating the safety and effectiveness of certain over-the-counter (OTC) medications, and if the Agency determines that an OTC drug meets certain conditions and is generally recognized as safe and effective, it will publish a final monograph specifying those conditions. Products that comply with a final monograph may be marketed, but manufacturers are required to meet CGMP standards. Restrictions in section 503A prevent compounders from producing drugs without having to comply with monograph standards, or CGMP requirements.

III. POLICY

As stated above, to qualify for the exemptions under section 503A of the FD&C Act, a drug must be compounded by a licensed pharmacist or a licensed physician that does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product.[7] In other words, a compounded drug product is not eligible for the exemptions in section 503A if it is both 1) essentially a copy of a commercially available drug product, and it is 2) compounded regularly or in inordinate amounts. Accordingly, and as discussed below, when evaluating whether a drug product meets the condition in section 503A regarding essentially copies, FDA intends to determine first whether a compounded drug product is *essentially a copy of a commercially available drug product*, and if it is, FDA intends to determine second whether the drug product was compounded regularly or in inordinate amounts.

[7] See section 503A(b)(1)(D).

FDA's policies with regard to the terms (1) *commercially available drug product*, (2) *essentially a copy of a commercially available drug product*, and (3) *regularly or in inordinate amounts*, are as follows:

A. Commercially Available Drug Product

For purposes of this guidance, a drug product is commercially available if it is a marketed drug product.

We do not consider a drug product to be commercially available if

- the drug product has been discontinued and is no longer marketed[8]) or
- the drug product appears on the FDA drug shortage list in effect under section 506E of the FD&C Act.[9] A drug "appears on the drug shortage list in effect under section 506E" if the drug is in "currently in shortage" status (and not in "resolved" status) in FDA's drug shortage database.

Commercially available drugs are available on the market, and they are generally subject to FD&C Act requirements relating to approval, labeling, and CGMP requirements, and the copies restriction applies to all such drugs because section 503A is not intended to provide a means for compounders to produce compounded drugs exempt from the Act's requirements that are essentially copies of commercially available drug products.

B. Essentially a Copy of a Commercially Available Drug Product

1. What is Essentially a Copy?

FDA intends to consider a compounded drug product to be essentially a copy of a commercially available drug product if:

- the compounded drug product has the same active pharmaceutical ingredient(s) (API) as the commercially available drug product;
- the API(s) have the same, similar, or an easily substitutable dosage strength; and
- the commercially available drug product can be used by the same route of administration as prescribed for the compounded drug,

[8] FDA maintains a list of approved drug products that sponsors have indicated are not marketed in the discontinued section of the list of Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). See http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Specifically, the list includes approved drug products that have never been marketed, are for exportation, are for military use, have been discontinued from marketing and we have not determined that they were withdrawn for safety or effectiveness reasons, or have had their approvals withdrawn for reasons other than safety or effectiveness subsequent to being discontinued from marketing.

[9] See http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.

unless a prescriber determines that there is a change, made for an identified individual patient, which produces for that patient a significant difference from the commercially available drug product.

The limitations in section 503A(b)(1)(D) apply to the compounding of drug products that are *essentially* copies of a commercially available drug product – not only to drugs that are exact copies or even to drugs that are nearly identical. This is to ensure that compounders do not evade the limits in this section by making relatively small changes to a compounded drug product and then offering the drug to the general public without regard to whether a prescribing practitioner has determined that the change produces for the patient a significant difference. For example, Congress contemplated that a compounded drug may be essentially a copy of a commercially available drug if "minor changes in strength (such as from .08% to .09%) are made that are not known to be significant . . ." for the patient for whom the drug was prescribed.[10]

a. Same API

With regard to the characteristics listed above, an API is the substance in a drug product that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or function of the body.[11] When a compounded drug product offers the same API as a commercially available drug product, in the same, similar, or easily substitutable dosage strength and for use through the same route of administration, we generally intend to consider such a drug product *essentially a copy,* unless a prescriber determines that there is a change, made for an individual patient, that will produce a significant difference for that patient.

We recognize that, for some patients, a drug product that has the same API, strength, and route of administration may include a change that produces a significant difference for a particular patient. For example, a drug product compounded without a particular inactive ingredient may produce a significant difference for a patient who has an allergy to the inactive ingredient in the commercially available drug product. However, for other patients, this change may produce no difference at all. Congress did not intend for compounders to use, for example, the fact that some patients may have allergies as a basis to compound a drug without the inactive ingredient for other patients who do not have the allergy under the exemptions in section 503A (i.e., without meeting requirements for premarket approval, labeling with adequate directions for use, or CGMP requirements).[12] In the context of compounding and consistent with the statute, we intend to consider such a drug essentially a

[10] U.S. House. Food and Drug Administration Modernization Act of 1997*, Conference Report* (to Accompany S. 830). (105 H. Rpt. 399).

[11] Section 503A refers to bulk drug substances. A *bulk drug substance* is defined as any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances (21 CFR 207.3(4)).

[12] *See* note 10.

copy, unless a prescriber determines that there is a change that will produce a significant difference for the patient for whom it is prescribed.

b. Same, Similar or Easily Substitutable Strength

FDA generally intends to consider two drugs to have a similar dosage strength if the dosage strength of the compounded drug is within 10% of the dosage strength of the commercially available drug product.

With regard to the concept of easily substitutable strength, in some cases, the same or similar dosage strength can be achieved by administration of fractional or multiple doses of a drug product. For example, if FDA-approved Drug X tablets have a dosage strength of 25 mg and a patient needs 50 mg of Drug X, FDA would generally consider a compounded Drug X 50 mg tablet to have an easily substitutable strength because the patient could take two Drug X 25 mg tablets to achieve the required dose.

c. Same Route of Administration

Route of administration is a way of administering a drug to a site in a patient (e.g., topical, intravenous, oral).[13] In general, FDA does not intend to consider a compounded drug product with the same API and similar or easily substitutable strength to be essentially a copy of a commercially available drug product if the compounded drug product and the commercially available drug product have different routes of administration (e.g., if the commercially available drug product is oral and the compounded drug product is topical). However, if the compounded drug product has the same API and similar or easily substitutable strength as the commercially available drug product and the commercially available drug product can be used (regardless of how it is labeled) by the route of administration prescribed for the compounded drug, FDA generally intends to consider the compounded drug to be essentially a copy of the commercially available drug. In this case, the compounded drug product generally would not produce a significant difference for an identified individual patient relative to the commercially available drug product.

For example, if the commercially available drug is an injectable drug sold in a vial that is labeled for intra-muscular use, but the drug also can be drawn from the vial by a smaller needle for subcutaneous administration, a compounded drug product with the same API and similar or easily substitutable strength prescribed for sub-cutaneous administration would generally be considered to be essentially a copy, unless the prescriber documents on the prescription that the compounded drug product produces a significant difference for the identified individual patient.

Same Characteristics as Two or More Commercially Available Drug Products

[13] See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071667.htm.

FDA intends to consider a compounded drug product to be essentially a copy of a commercially available drug product if the compounded drug product contains the same APIs as two or more commercially available drug products in the same, similar, or easily substitutable strength and if the compounded drug product and the commercially available drug products have the same route of administration, unless there is documentation as described in section III.B.2. Such drug products present the same kinds of concerns as drug products that have a single API and in some respects may be more dangerous because of the potential for unintended drug interactions. For example, if drug X and drug Y are commercially available oral drug products, FDA intends to consider a compounded oral drug product that combines drug X and drug Y in strengths that are within 10% of the strengths of the respective commercially available products to be essentially a copy of the commercially available drug product, unless a prescriber determination of a significant difference has been documented.

2. Statement of Significant Difference

Pursuant to section 503A(b)(2) of the FD&C Act, a compounded drug product is not essentially a copy of a commercially available drug product if a change is made for an identified individual patient, and the prescribing practitioner has determined that the change will produce a significant difference for that patient. If a compounder intends to rely on such a determination to establish that a compounded drug is not essentially a copy of a commercially available drug product, the compounder should ensure that the determination is documented on the prescription.

FDA does not believe that a particular format is needed to document the determination, provided that the prescription makes clear that the prescriber identified the relevant change and the significant difference produced for the patient. For example, the following would be sufficient:

- "No Dye X, patient allergy" (if the comparable drug contains the dye)
- "Liquid form, patient can't swallow tablet" (if the comparable drug is a tablet)
- "6 mg, patient needs higher dose" (if the comparable drug is only available in 5 mg dose)

However, if a prescription identifies only a patient name and drug product formulation, this would not be sufficient to establish that the prescriber made the determination described by section 503A(b)(2). Note also that the significant benefit that the prescriber identifies must be produced by the change the compounder will make to a commercially available drug product (i.e., a change in drug product formulation). Other factors, such as a lower price, are not sufficient to establish that the compounded drug product is not essentially a copy of the commercially available drug product.[14]

[14] Congress noted that "where it is readily apparent, based on the circumstances, that the 'significant difference' is a mere pretext to allow compounding of products that are essentially copies of commercially available products, such compounding would be considered copying of commercially available products and would not qualify for the compounding exemptions if it is done regularly or in inordinate amounts. Such circumstances may include, for example, minor changes in strength (such as from .08% to .09%) are made that are not known to be significant or instances in which the prescribing physician is receiving financial remuneration or other incentives to write

If a prescription does not make clear that the prescriber made the determination required by section 503A(b)(2), or a compounded drug is substituted for the commercially available drug product, the compounder can contact the prescriber and if the prescriber confirms it, make a notation on the prescription that the compounded drug product contains a change that makes a significant difference for the patient. The notations should be as specific as those described above, and the date of the conversation with the prescriber should be included on the prescription.

It is not possible to offer comprehensive guidance about when a difference will be "significant" to an identified individual patient. FDA generally does not intend to question prescriber determinations that are documented in a prescription or notation. However, we do intend to consider whether a prescription or notation relied upon by a compounder to establish that a drug is not essentially a copy documents that the determination was made.

3. Documentation of shortage

If the drug was compounded because the approved drug product was not commercially available because it was on the FDA drug shortage list, the prescriber or compounder should include a notation on the prescription that it was on the drug shortage list and the date the list was checked.

4. Regularly or in Inordinate Amounts

A drug product is not eligible for the exemptions in section 503A if it is prepared by a pharmacist or physician who compounds "regularly or in inordinate amounts (as defined by the Secretary)" any drug products that are essentially copies of a commercially available drug product.[15] FDA interprets this to mean that to be compounded in accordance with section 503A, a drug product that is essentially a copy of a commercially available drug product cannot be compounded regularly – i.e., it cannot be compounded at regular times or intervals, usually, or very often. Nor can the amounts compounded be inordinate, in light of the purpose of section 503A.

Section 503A is intended to protect patients from the public health risks of providing compounded drugs to patients whose medical needs could be met by commercially available drug products and to protect the integrity and efficiency of the drug approval process. Under the statutory scheme, only very rarely should a compounded drug product that is essentially a copy of a commercially available drug product be offered to a patient. For example, a compounded drug product that has the same API, dosage strength, and route of administration as a drug product on FDA's shortage list would not be considered essentially a copy of a commercially available drug because a drug product is not considered *commercially available* if it is on FDA's drug shortage list. In addition, a compounded drug product is not essentially a copy of a

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prescriptions for compounded products." *See* the U.S. House. Food and Drug Administration Modernization Act of 1997*, Conference Report* (to Accompany S. 830). (105 H. Rpt. 399).

[15] See section 503A(b)(1)(D).

commercially available drug product if a prescriber has determined that the compounded drug has a change that produces a significant difference for a patient. We conclude, therefore, that a drug product that is essentially a copy of a commercially available drug product is compounded regularly or in inordinate amounts if it is compounded more frequently than needed to address unanticipated, emergency circumstances or in more than the small quantities needed to address unanticipated, emergency circumstances.

Once it has been determined that a compounded drug is essentially a copy of a commercially available drug product as described above, the following are examples of factors that may be the basis for concluding that it has been compounded regularly or in inordinate amounts:

- The compounded drug product amounts to more than a small number of prescriptions or a small percentage of the compounded drug products that a physician or prescriber prepares or provides to patients.
- The compounder routinely substitutes compounded drugs that are essentially copies of commercially available drugs upon receiving prescriptions for patients.
- The compounder offers pre-printed prescription pads that a prescriber can use to write a prescription for the drug product that is essentially a copy without making a determination that there is a change that will produce a significant difference for a patient.
- The compounded drug product is not compounded on an as-needed basis, but on a routine or pre-set schedule.

The foregoing list is not intended to be exhaustive. Other factors may be appropriate for consideration in a particular case.

To focus enforcement on the most significant cases, as a matter of policy, at this time FDA does not intend to take action against a compounder for compounding a drug product that is essentially a copy of a commercially available drug product regularly or in inordinate amounts if the compounder fills four or fewer prescriptions for the relevant compounded drug product in a calendar month.[16] Be aware that a prescription would not be considered to be for a drug that is essentially a copy of a commercially available drug product and would not be counted towards the four prescriptions if the prescription documents that the compounded drug product makes a significant difference for the patient as described above.

5. Recordkeeping

A licensed pharmacist or physician seeking to compound a drug product under section 503A should maintain records to demonstrate compliance with section 503A(b)(1)(D). For example, records should be kept of notations on prescriptions for identified individual patients that a prescriber has determined that the compounded drug has a change that produces a significant difference for the identified patient.

[16] For purposes of this policy, a prescription does not include additional refills. FDA intends to consider each refill of a prescription as an additional prescription.

Compounders under section 503A should also maintain records of the frequency in which they have compounded drug products that are essentially copies of commercially available drug products and the number of prescriptions that they have filled for compounded drug products that are essentially copies of commercially available drug products to document that such compounding has not been done regularly or in inordinate amounts.