Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B 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DRAFT GUIDANCE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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TABLE OF CONTENTS

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or the Agency) on this topic.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

For a drug product compounded by an outsourcing facility to qualify for the exemptions under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act or Act), it must not be "essentially a copy of one or more approved drug products,"[2] and must meet the other conditions in section 503B.[3] This guidance sets forth the FDA's or policies concerning the *essentially a copy* provision of section 503B.[4]

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.

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[1] This guidance was 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] See section 503B(a)(5).

[3] See section 503B(a)(11).

[4] 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 For proposed policies pertaining to compounding drug products from bulk drug substances for use in animals, see FDA's draft guidance *Compounding Animal Drugs from Bulk Drug Substances*.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*.

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II. BACKGROUND

A. Section 503B of the FD&C Act

In 2013, the Drug Quality and Security Act created a new section 503B of the FD&C Act, which describes a new category of compounders called *outsourcing facilities*.[5] Section 503B of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility to qualify for exemptions from the following three sections of the FD&C Act:

- 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))
- Section 582 (concerning drug supply chain security requirements).

In contrast to drug products compounded under section 503A of the FD&C Act, drug products compounded by outsourcing facilities under section 503B cannot qualify for exemption from current good manufacturing practice (CGMP) requirements in section 501(a)(2)(B) of the FD&C Act. Outsourcing facilities are also subject to FDA inspections according to a risk-based schedule, specific adverse event reporting requirements, and other conditions that help to mitigate the risks of the drug products they compound.

One of the conditions that must be met for a compounded drug product to qualify for the exemptions under section 503B of the FD&C Act is that "the drug is not essentially a copy of one or more approved drugs."[6] Section 503B(d)(2) defines *essentially a copy of an approved drug* as —

- A drug that is identical or nearly identical to an approved drug, or a marketed drug not subject to section 503(b) and not subject to approval in an application submitted under section 505, unless, in the case of an approved drug, the drug appears on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing (section 503B(d)(2)(A)); or
- A drug, a component of which is a bulk drug substance that is a component of an approved drug or a marketed drug that is not subject to section 503(b) and is not subject to approval in an application submitted under section 505, unless there is a change that produces for an individual patient a clinical difference, as determined

[5] See Pub.L. No.113-54, §102(a), 127 Stat. 587, 587-588 (2013). Under section 503B(b), a compounder can elect to register with FDA as an outsourcing facility. Section 503B(d)(4) defines an *outsourcing facility* as a facility at one geographic location or address that is engaged in the compounding of sterile drugs; has elected to register as an outsourcing facility; and complies with all of the requirements of section 503B. An outsourcing facility is not required to be a licensed pharmacy, although compounding must be by or under the direct supervision of a licensed pharmacist. In addition, an outsourcing facility may or may not obtain prescriptions for identified individual patients.

[6] See section 503B(a)(5).

by the prescribing practitioner, between the compounded drug and the comparable approved drug (section 503B(d)(2)(B)).

A compounded drug product only qualifies for the exemptions in section 503B if it is compounded by an outsourcing facility that compounds all of its drugs, both sterile and non-sterile, in accordance with all of the conditions of section 503B.[7] A complete list of the conditions that must be met for a drug product to qualify for the exemptions in section 503B appears in the guidance *For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B 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 for a patient who has an allergy and needs a medication to be made without a certain dye contained in an FDA-approved drug product, or an elderly patient or a child who cannot swallow a pill and needs a medicine in a liquid form that is not available in an approved product. Drug products for identified individual patients can be compounded by licensed pharmacists in State-licensed pharmacies and Federal facilities and by licensed physicians operating under section 503A of the FD&C Act.[8] Drug products can also be compounded by outsourcing facilities for identified individual patients pursuant to prescriptions or for distribution to health care practitioners without receiving prescriptions. Sections 503A and 503B restrict compounding drug products that are essentially copies of commercially available (section 503A) or approved drug products (section 503B).

C. Compounded Drugs that are Essentially Copies of Approved Drug Products

Although compounded drugs can serve an important need, they also pose a higher risk to patients than FDA-approved drugs. Drug products compounded by outsourcing facilities in accordance with the conditions of section 503B are exempt from FDA drug approval requirements and the requirement to be labeled with adequate directions for use. Because they are not FDA-approved, they have not undergone FDA premarket review for safety, effectiveness, and quality. Although outsourcing facilities must comply with CGMP requirements and are inspected by FDA according to a risk-based schedule, their drugs also lack a premarket inspection and finding of manufacturing quality that is part of the drug approval process. Because they are subject to a lower regulatory standard, drugs compounded by outsourcing facilities should only be distributed to health care facilities or dispensed to patients to fulfill the needs of patients whose medical needs cannot be met by an FDA-approved drug.

[7] See sections 503B(a)(11) and 503B(d)(4)(A)(iii).

[8] Section 503A of the FD&C Act describes the conditions that must be met for a human drug product compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to qualify for exemptions from sections 501(a)(2)(B), 502(f)(1), and 505 of the FD&C Act. The conditions applicable to compounders seeking to operate under section 503A are discussed in separate guidance documents applicable to these entities.

The restrictions on compounding drugs that are essentially copies of approved products ensure that outsourcing facilities do not compound drug products under the exemptions in section 503B for use in patients who could use an approved product. Compounding copies of these products would unnecessarily expose patients to drug products that have not been shown to be safe and effective.

In addition to these immediate public health risks, section 503B's prohibition on producing a drug product that is essentially a copy of an approved drug product protects the integrity and effectiveness of the new drug and abbreviated new drug approval processes. Sponsors would be less likely to invest in and seek approval of innovative, life-saving medications if an outsourcing facility could, after a drug is approved, compound "substitutes" that may be less expensive because they have not gone through the drug approval process.

Sponsors would also be less likely to seek approval of an ANDA for a generic drug if outsourcing facilities were permitted to compound drugs that are essentially copies of approved 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. Section 503B's restrictions on producing a drug product that is essentially a copy of an approved drug product protect the integrity of both the new drug and the abbreviated new drug approval processes.

D. Compounded Drugs that are Essentially Copies of Unapproved Non-Prescription Drug Products

The definition of *essentially a copy of an approved drug* in section 503B(d)(2) also refers to drug products that are not subject to section 503(b) (i.e., non-prescription drug products) and that are not subject to approval in an application submitted under section 505. Congress did not provide exemptions under section 503B for such drugs, which ensures that outsourcing facilities do not compound unapproved over-the-counter drug products under the exemptions in section 503B. Such products may be produced only under the same requirements that apply to other drug manufacturers. Section 503B also protects FDA's drug monograph process. FDA has an ongoing process to evaluate the safety and effectiveness of over-the-counter (OTC) medications, and if the Agency determines that an OTC drug meeting certain conditions is generally recognized as safe and effective, it will publish a final monograph specifying those conditions. Compounding copies of such drug products would undermine the process that drug manufacturers must comply with, which includes a set of specific regulatory requirements that limit the formulation of the drug product, and both the content and format of its labeling.

III. POLICY

Under section 503B(a)(5) of the FD&C Act, a compounded drug must not be essentially a copy of one or more approved drugs.

A. Definition of *Essentially a Copy of an Approved Drug*

The definition of *essentially a copy of an approved drug* has two components, specified in sections 503B (d)(2)(A) and 503B(d)(2)(B) of the Act. Section 503B (d)(2)(A) applies to a compounded drug that is "identical or nearly identical" to an approved drug or an unapproved non-prescription drug. All other compounded drugs are evaluated under section 503B (d)(2)(B). FDA applies these provisions as depicted in the diagrams in Appendices A and B.

The definition of *essentially a copy of an approved drug* in section 503B(d)(2) addresses both drug products approved under section 505 and marketed drug products that are not subject to section 503(b) and that are not subject to approval in an application submitted under section 505.

For purposes of this provision:

- *Approved drug* means a drug product that is approved under section 505 of the FD&C Act and does not appear on the list described in subsection 503B(a)(4) of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective.
- *Marketed drug not subject to section 503(b) and not subject to approval in an application submitted under section 505* means any non-prescription drug product marketed without an approved application.[9] We refer to these products as *covered OTC drug products* throughout the remainder of this guidance document.
- 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), as indicated in FDA's drug shortage database.[10]

In the discussion that follows, in subsection 1, we explain how we intend to apply the definition of *essentially a copy of an approved drug* in section 503B(d)(2) when the compounded drug is compared to an approved drug, and then in subsection 2, we explain how we intend to apply this definition when the compounded drug is compared to a covered OTC drug product.

1. Application of the "Essentially a Copy" Definition in Section 503B(d)(2) When the Compounded Drug Is Compared to an Approved Drug (see Appendix A)

a. Compounded drugs that are identical or nearly identical to an approved drug (section 503B(d)(2)(A))

Under section 503B(d)(2)(A), a compounded drug is essentially a copy of an approved drug if the compounded drug is identical or nearly identical to an approved drug unless the approved drug appears on the drug shortage list in effect under section 506E at the time of compounding, distribution, and dispensing.

[9] This includes unapproved OTC drugs whether they are marketed under FDA's OTC Drug Monograph Review program or outside the monograph system.

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

i. Identical or nearly identical (Appendix A, box 1)

FDA intends to consider a compounded drug product to be identical or nearly identical to an approved drug if the compounded drug product and the FDA-approved drug have the same:

- active ingredient(s),
- route of administration,
- dosage form,
- dosage strength, and
- excipients.[11]

A compounded drug product that has all of these characteristics in common with an FDA-approved drug product is essentially a copy of an approved drug, unless the approved drug appears on FDA's drug shortage list at the time of compounding, distribution, and dispensing. If a compounded drug product is identical or nearly identical to an approved drug that is ***not*** on FDA's drug shortage list at the time of compounding, distribution, and dispensing, the compounded product is essentially a copy and an outsourcing facility may not produce it under section 503B.

In establishing this policy, FDA considered the following. Under section 503B(d)(2)(A), the identical or nearly identical compounded product cannot be exempted from the copying restriction by a prescriber determination that there is a change to the compounded product that produces a clinical difference for an individual patient. Compounded products meeting the criteria outlined above are not expected to contain changes from an approved drug that would produce such a difference.

A compounded drug that is identical or nearly identical to an approved drug is not considered essentially a copy if the approved drug is in shortage at the time of compounding, distribution, and dispensing.[12] In such a case, the outsourcing facility can compound the drug provided that it complies with the other conditions of 503B. It is important to patients and prescribers that compounded drugs prepared to address a shortage closely resemble the drug in shortage, and for that reason, the statute seeks to allow compounders to compound drugs that are as close as possible to the drug in shortage.[13] A compounded drug product with the characteristics described in our policy would be the same as the approved drug in several important respects. The active ingredient is the substance in a drug product that is intended to furnish pharmacological

[11] In some cases, information about the excipients contained in an approved drug is not publicly available and not known to the outsourcing facility. In such cases, FDA does not intend to consider whether the compounded drug has the same excipients that the approved drug is labeled to contain in determining whether a compounded drug is identical or nearly identical to an approved drug.

[12] *Distribution* means that a compounded human drug product has left the facility in which the drug was compounded. Distribution includes delivery or shipment to a physician's office, hospital, or other health care setting for administration and dispensing to an agent of a patient or to a patient for the patient's own use.

[13] See footnote 11.

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. Dosage form is the way of identifying the drug in its physical form, and route of administration describes the way a drug is administered to the body. Inactive ingredients (also known as "excipients") may include preservatives, dyes, and flavorings. The dosage strength of a drug product indicates the amount of the active ingredient that is present in each dosage.

If the outsourcing facility compounds a product that differs on one or more of these characteristics, we generally would not consider the product to be identical or nearly identical. As described below, if the compounded drug product is not considered identical or nearly identical under section 503B(d)(2)(A), it would then be evaluated under section 503B(d)(2)(B).

Outsourcing facilities seeking to compound drugs under this provision should also take note that other provisions of the FD&C Act contain requirements for drug product formulation and packaging that are important for patient safety. In particular, drug products compounded in accordance with section 503B remain subject to adulteration and misbranding provisions of the FD&C Act including, but not limited to, section 501(b) (concerning drug products that are recognized in an official compendium and whose strength differs from, or whose quality or purity falls below, the standards set forth in such compendium) and section 502(g) (concerning drug products that are recognized in an official compendium and that are not packaged and labeled as prescribed therein).

ii. Compounded drugs that are identical or nearly identical to an approved drug on FDA's drug shortage list after the shortage is resolved (Appendix A, box 2)

As explained above, under section 503B (d)(2)(A), a compounded drug is not essentially a copy of an approved drug if the approved drug appears on FDA's drug shortage list at the time of compounding, distribution, and dispensing. However, FDA recognizes that there may be circumstances in which a drug product is in shortage when the outsourcing facility compounds the drug, but the shortage is resolved before the outsourcing facility distributes it. FDA does not intend to take action against an outsourcing facility for filling orders that it received for a compounded drug that is identical or nearly identical to an approved drug that was on FDA's drug shortage list at the time that the outsourcing facility received the order, provided the drug also appeared on the FDA drug shortage list within 60 days of the outsourcing facility distributing or dispensing the drug.[14]

[14] An outsourcing facility may not be able to predict when a drug shortage will be resolved, and the facility may have orders for a compounded drug in-house that were in progress when the drug was removed from FDA's drug shortage list (e.g., the outsourcing facility may have compounded a drug while it was in shortage, but the shortage ended while the outsourcing facility awaited the results of sterility testing before release). This policy provides some regulatory flexibility when an outsourcing facility fills orders that it received for a compounded drug while the drug was in shortage. FDA may take regulatory action, however, if an outsourcing facility continues to fill new orders for the compounded drug after the approved drug is removed from FDA's drug shortage list, or if it continues to fill orders more than 60 days after the drug has been removed from FDA's drug shortage list.

b. Compounded drugs that contain a bulk drug substance that is a component of an approved drug (see Appendix A, boxes 3 and 4)

Under section 503B(d)(2)(B), a compounded drug product is essentially a copy of an approved drug if a component of the compounded drug product is a bulk drug substance[15] that is also a component of an approved drug, unless there is a change that produces for an individual patient a clinical difference, as determined by the prescribing practitioner, between the compounded drug and the comparable approved drug.

i. Using the same bulk drug substance (Appendix A, box 3)

If a component of the compounded drug is a bulk drug substance that is also a component of an approved drug, the compounded drug product is essentially a copy of an approved drug and cannot be compounded under section 503B, unless there is a prescriber determination of clinical difference, as described below.[16] This provision applies to a compounded drug whether it was compounded from bulk drug substances or from drugs in finished form.

ii. Prescriber determination of clinical difference (Appendix A, box 4)

If an outsourcing facility compounds a drug, the component of which is a bulk drug substance that is a component of an approved drug, there must be a change that produces a clinical difference for an individual patient as determined by the prescribing practitioner. If an outsourcing facility intends to rely on such a determination to establish that a compounded drug is not essentially a copy of an approved drug, the outsourcing facility should ensure that the determination is on the prescription or order (which may be a patient-specific prescription or a non-patient specific order) for the compounded drug.

FDA is aware that a health care practitioner who orders a compounded drug from an outsourcing facility for office stock will not know the identity of the individual patients who will receive the compounded drug at the time of the order. In that case, the outsourcing facility should obtain a statement from the practitioner that specifies the change between the compounded drug and the comparable approved drug and indicates that the compounded drug will be administered or dispensed only to a patient for whom the change produces a clinical difference, as determined by the prescribing practitioner for that patient. Such assurances should be provided by a person able to make the representation for the health care practitioner.

[15] Title 21, section 207.3(4) of the Code of Federal Regulations defines the term *bulk drug substance* to mean "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 a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances."

[16] FDA expects that if a compounded drug has the same bulk drug substance as an approved drug, the two drugs have the same active ingredient.

For example, a hospital may need an FDA-approved drug combined with a particular diluent in infusion bags to administer to patients during surgery. The pharmacy manager for the hospital could order the compounded drug from an outsourcing facility and document on the order that the compounded drug will only be administered to patients for whom the prescriber determines that this formulation will produce a clinical difference from the comparable approved drug. Similarly, a physician who regularly treats patients with an allergy to an inactive ingredient in a particular approved injectable drug product could order a compounded version of the drug for office use from an outsourcing facility provided that he or she includes a statement on the order that removing the particular inactive ingredient produces a clinical difference for his or her individual patients and that he or she will provide the drug only to patients with that particular clinical need.

Many outsourcing facilities compound non-sterile drugs in addition to sterile drugs.[17] All drugs compounded by an outsourcing facility must be compounded in accordance with section 503B, including the prohibition on compounding drug products that are essentially copies of approved drug products in order for any of them to qualify for the exemptions provided in section 503B.[18] For example, a hospice may need a compounded liquid formulation of a drug that is only approved in capsules to treat elderly patients who cannot swallow capsules. The pharmacy manager for the hospice could order the compounded drug from an outsourcing facility and document on the order that the liquid formulation produces a clinical difference for hospice patients who are unable to swallow capsules and that the compounded drug will be dispensed only to a patient whose prescribing practitioner determines that the liquid formulation will produce this clinical difference for the patient.

FDA does not believe that a particular format is needed, provided that an order for office stock (i.e., not patient-specific) clearly identifies the relevant change and the clinical difference produced for patient(s), as determined by the prescriber. For example, the following would be sufficient:

- "Liquid form, compounded drug will be prescribed to patients who can't swallow tablet" (if the comparable drug is a tablet)
- "Dilution for infusion solution to be administered to patients who need this formulation during surgery" (if the comparable drug is not available at that concentration, pre-mixed with the particular diluent in an infusion bag)
- "1 mg, pediatric patients need lower dose" (if the comparable drug is only available in 25 mg dose)

[17] An entity that *only* compounds non-sterile drugs does not meet the statutory definition of an outsourcing facility in section 503B(d)(4) of the FD&C Act. The definition states, in part, that an outsourcing facility "is engaged in the compounding of sterile drugs" (section 503B(d)(4)(i)).

[18] Under section 503B(a)(11), a compounded drug can qualify for the exemptions from section 503B only if all of the facility's compounded drugs are compounded in accordance with section 503B.

An order that only identifies the product formulation, without more information, would not be sufficient to establish that the determination described by section 503B(d)(2)(B) has been made.

Many outsourcing facilities also compound drug products based on prescriptions for identified individual patients. The following are examples of statements on a patient-specific prescription that could be used to document the prescriber's determination that a compounded drug has a change that produces a clinical difference for a particular patient:

- "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)
- "150 mg drug X in 120 ml cherry-flavored Syrup USP, patient needs alcohol-free preparation (if the comparable drug is only available in formulations that contain alcohol)

However, if a prescription identifies only a patient name and product formulation, this would not be sufficient to establish that the determination described by section 503B(d)(2)(B) has been made.

Note also that the clinical difference identified on either a patient-specific prescription or order, or non-patient specific order, must be produced by the "change" between the outsourcing facility's product and the approved drug (i.e., a change in product formulation). Other factors such as a lower price are not sufficient to establish that the compounded product is not essentially a copy of the approved drug.

If a prescription or order does not make clear that the determination required by section 503B(d)(2)(B) has been made, the outsourcing facility may contact the prescriber or health care facility, and if the prescriber or health care facility confirms it, make a notation on the prescription or order that the prescriber has determined that the compounded product contains a change that produces a clinical difference for patient(s). The notations should be as specific as those described above, and the date of the conversation with the health care facility or prescriber should be included on the prescription or order.

FDA generally does not intend to question the determinations of clinical difference that are documented in a prescription or order as described above. However, we do intend to consider whether a prescription or order relied upon by an outsourcing facility to establish that a drug is not essentially a copy documents that the determination was made.

iii. Essentially a copy of one or more approved drug products

Under section 503B(a)(5), a compounded drug product must not be essentially a copy of **one or more** (emphasis added) approved drug products. When applying section 503B(d)(2)(B), FDA intends to consider a compounded drug product that has bulk drug substances that are components of one or more approved drugs to be essentially a copy of

an approved drug product, unless the prescribing practitioner determines that there is a change that produces a clinical difference for an individual patient between the compounded drug product and the comparable approved drug. For example, if there are two approved drug products that are tablets, one containing 5 mg of active ingredient A and the other containing 10 mg of active ingredient B and the outsourcing facility compounded a tablet that offered both active ingredients in the same dosage strengths, the compounded drug would be essentially a copy absent a prescriber determination of clinical difference.

2. Application of the "Essentially a Copy" Definition in Section 503B(d)(2) When the Compounded Drug Is Compared to a Covered OTC Drug Product (Appendix B)

a. Compounded drugs that are identical or nearly identical to a covered OTC drug product (section 503B(d)(2)(A)) (Appendix B, box 1)

Under section 503B(d)(2)(A), a compounded drug is not considered essentially a copy of an approved drug if it is identical or nearly identical to ***an approved drug*** that appears on FDA's drug shortage list at the time of compounding, distribution, and dispensing. The statute does not provide a similar exemption from the definition in section 503B(d)(2) if the compounded drug is identical or nearly identical to a ***covered OTC drug*** on FDA's drug shortage list. Therefore, FDA intends to apply the same policy described above in section III.A.1.a to OTC monograph drugs, with one exception.

If a compounded drug is identical or nearly identical to a covered OTC drug under section 503B(d)(2)(A), the compounded drug is essentially a copy of an approved drug, and the appearance of the covered OTC drug on FDA's shortage list does not change that result; the drug cannot be compounded under section 503B.[19] If the compounded drug is not identical or nearly identical to a comparable drug, it must be evaluated under section 503B(d)(2)(B), as described below.

b. Compounded drugs that contain a bulk drug substance that is a component of an covered OTC drug product (section 503B(d)(2)(B)) (Appendix B, box 2)

Under section 503B(d)(2)(B), a compounded drug product is essentially a copy and cannot be compounded under section 503B if a component of the compounded drug product is a bulk drug substance[20] that is also a component of a covered OTC drug, unless there is a change that produces for an individual patient a clinical difference, as determined by the prescribing practitioner, between the compounded drug and the comparable ***approved*** drug. A clinical difference between the compounded drug and an unapproved drug (such as a covered OTC drug) does not exempt the compounded drug from the definition in section 503B(d)(2)(B).

[19] The compounded drug would not be essentially a copy if it was also identical or nearly identical to an approved drug on FDA's drug shortage list, but this would be a very rare case.

[20] See footnote 15.

c. Essentially a copy of one or more approved drug products[21]

Under section 503B(a)(5), a compounded drug product must not be essentially a copy of **one or more** approved drug products. When applying section 503B(d)(2)(B), FDA intends to consider a compounded drug product that has bulk drug substances that are components of one or more approved drugs to be essentially a copy of an approved drug product unless the prescribing practitioner determines that there is a change that produces a clinical difference for an individual patient between the compounded drug product and the comparable approved drug. For example, if there are two approved drug products that are tablets, one containing active ingredient A and the other containing active ingredient B, and the outsourcing facility compounded a tablet that offered both active ingredients, the compounded drug containing active ingredients A and B would be essentially a copy absent a prescriber determination of clinical difference.

If a bulk drug substance is a component of a covered OTC drug *and* an approved drug, the bulk drug substance can be evaluated as a component of an approved drug, as described in section III.A.1 of this guidance.

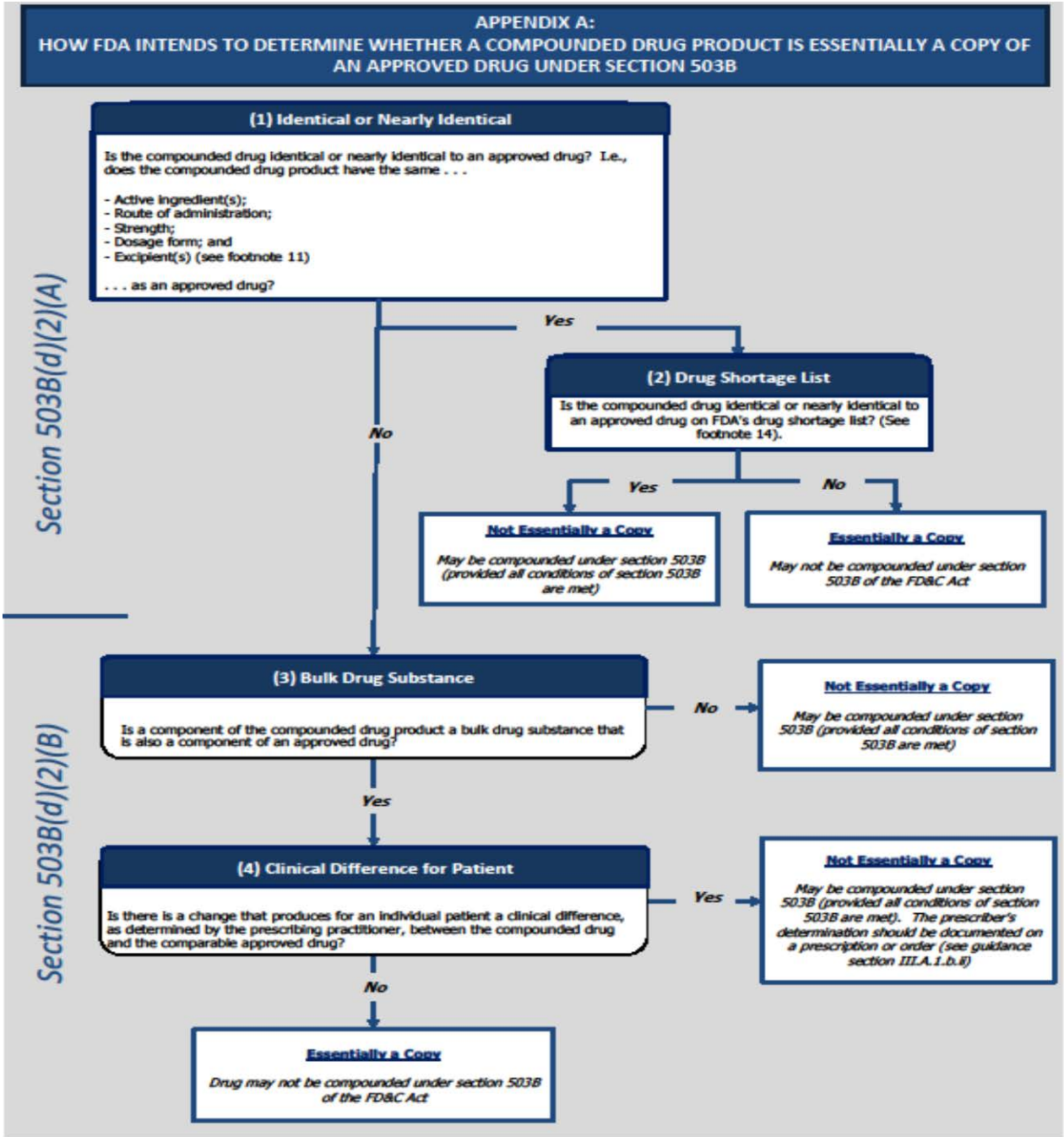
B. Recordkeeping

Outsourcing facilities should maintain records to demonstrate compliance with the essentially a copy provision in section 503B(a)(5). For example, where an outsourcing facility has compounded a drug that is evaluated under 503B(d)(2)(B) and a component of the compounded drug is a bulk drug substance that is a component of an approved drug, the outsourcing facility should maintain prescription or order records of a prescriber's determination of clinical difference as described above in section III.A.1.b.ii.

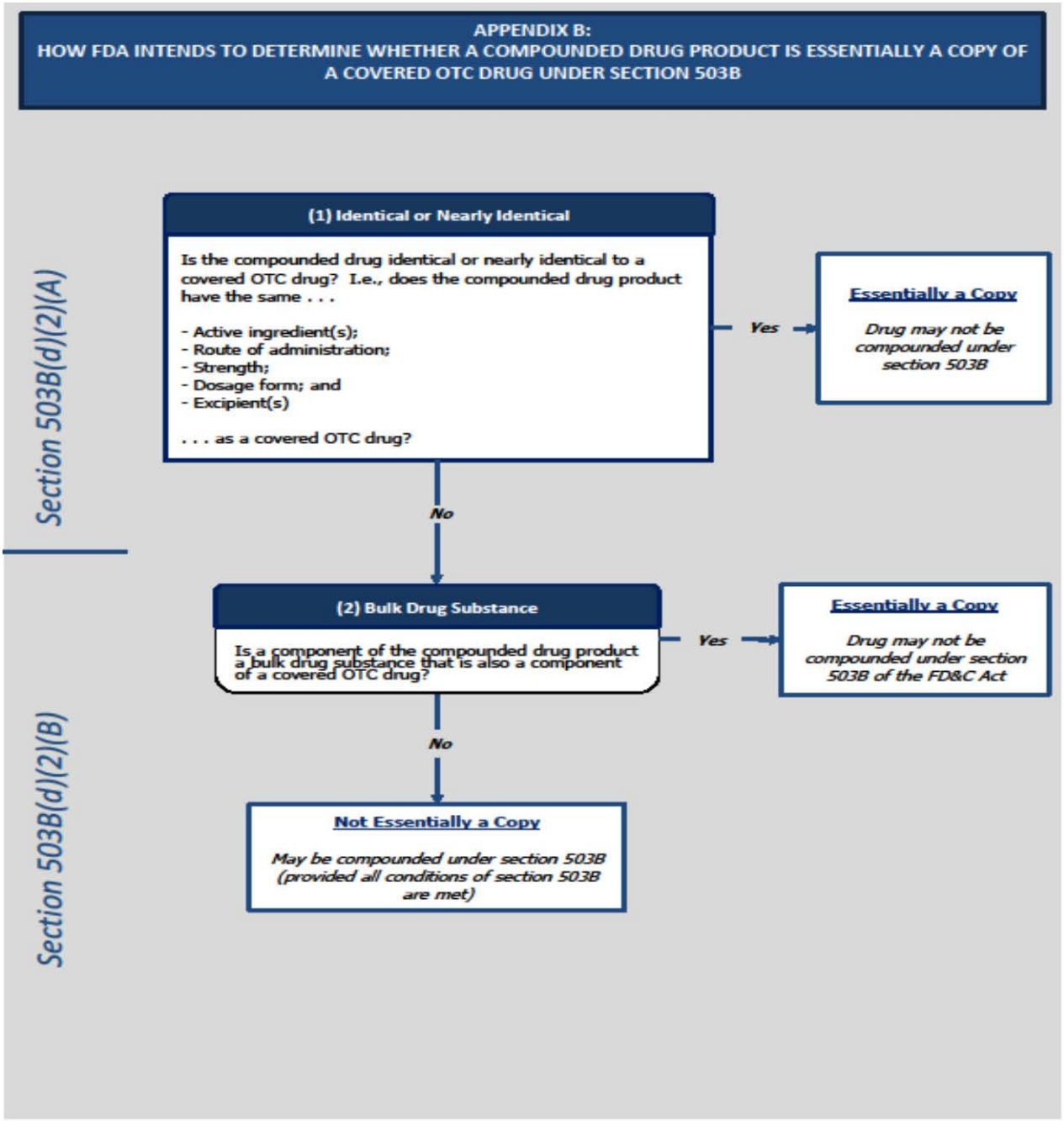
In addition, if the outsourcing facility compounded a drug that is identical or nearly identical to an approved drug product that appeared on FDA's drug shortage list, the outsourcing facility should maintain documentation (e.g., a notation on the order for the compounded drug) regarding the status of the drug on FDA's drug shortage list at the time of compounding, distribution, and dispensing.

[21] This scenario is not depicted in the diagrams in the appendices.

460 **APPENDICES A & B**



461
462


APPENDIX B:
HOW FDA INTENDS TO DETERMINE WHETHER A COMPOUNDED DRUG PRODUCT IS ESSENTIALLY A COPY OF A COVERED OTC DRUG UNDER SECTION 503B
Section 503B(d)(2)(A)
(1) Identical or Nearly Identical
Is the compounded drug identical or nearly identical to a covered OTC drug? I.e., does the compounded drug product have the same . . .
- Active ingredient(s);
- Route of administration;
- Strength;
- Dosage form; and
- Excipient(s)
. . . as a covered OTC drug?
Yes
Essentially a Copy
Drug may not be compounded under section 503B
No
Section 503B(d)(2)(B)
(2) Bulk Drug Substance
Is a component of the compounded drug product a bulk drug substance that is also a component of a covered OTC drug?
Yes
Essentially a Copy
Drug may not be compounded under section 503B of the FD&C Act
No
Not Essentially a Copy
May be compounded under section 503B (provided all conditions of section 503B are met)

463