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BUSINESS, CONSUMER SERVICES AND HOUSING AGENCY
DEPARTMENT OF CONSUMER AFFAIRS
GOVERNOR EDMUND G. BROWN JR.

To: Board Members

Subject: Agenda Item X - Federal Food and Drug Administration's Draft Guidance Documents – Discussion and Consideration, including Whether to Submit Board Comments, regarding:

1. Insanitary Conditions at Compounding Facilities
2. Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act
3. Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act

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Attachment 1

Background:
In recent months, the FDA has released multiple guidance documents regarding compounding and outsourcing duties and regulation. The guidance documents are instructional in that they reflect enforcement priorities the FDA pursues during inspections.

The FDA notes in each of these documents that the guidance documents "do not establish legally enforceable responsibilities. Instead, the guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited."

At its August 31 meeting, the Enforcement Committee discussed several of the guidance documents which contain proposed elements for FDA regulation. The committee determined that comments should be submitted on the guidance documents and asked board staff to draft comments for the board to review and approve at its next meeting.

At this meeting:
The board's executive officer Virginia Herold is attending the FDA's *50 –State Meeting on Compounding* on September 20-21. At the board meeting Ms. Herold will provide an update on the discussion concerning these guidance documents.

Attachment 1 contains copies of the FDA Guidance Documents.

Attachment 1

Insanitary Conditions at Compounding Facilities

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Sara Rothman (CDER) at 301-796-3110.

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

August 2016
Compounding and Related Documents

Insanitary Conditions at Compounding Facilities

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
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Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
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August 2016
Compounding and Related Documents

Contains Nonbinding Recommendations

Draft — Not for Implementation

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Guidance for Industry[1]

Insanitary Conditions at Compounding Facilities

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 it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Under section 501(a)(2)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act), a drug is deemed to be adulterated "if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health."[2] Drug products prepared, packed, or held under insanitary conditions could become contaminated and cause serious adverse events, including death.

Under sections 503A and 503B of the FD&C Act, compounded human drug products can qualify for exemptions from specified provisions of the FD&C Act if certain conditions are met. However, neither section 503A nor section 503B provides an exemption from section 501(a)(2)(A) of the FD&C Act. Drugs prepared, packed, or held (hereinafter referred to as "produced") under insanitary conditions are deemed to be adulterated, regardless of whether the drugs qualify for exemptions set forth in sections 503A or 503B of the Act.[3] Any drug that is produced under insanitary conditions is adulterated under the Act, including compounded human and animal drugs; repackaged drug products; compounded or repackaged radiopharmaceuticals; and mixed, diluted, or repackaged biological products. The policies described in this guidance document specifically address pharmacies, Federal facilities, physicians' offices (including veterinarians' offices), and outsourcing facilities that compound or repackage human or animal drugs (including radiopharmaceuticals); or that mix, dilute, or repackage biological products. For purposes of this guidance, we refer to such entities as "compounding facilities."

[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 and the Center for Veterinary Medicine at the Food and Drug Administration.

[2] Insanitary conditions are conditions that could cause a drug to become contaminated with filth or rendered injurious to health; the drug need not be actually contaminated. A drug that is actually contaminated with any filthy, putrid, or decomposed substance is deemed to be adulterated under section 501(a)(1) of the FD&C Act.

FDA is issuing this guidance to assist compounding facilities in identifying insanitary conditions so that they can implement appropriate corrective actions. This guidance is also intended to assist State regulatory agencies in understanding some examples of what FDA considers to be insanitary conditions that could cause a drug to become contaminated or rendered injurious to health.

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.

II. BACKGROUND

A. Public Health Risk of Insanitary Conditions

FDA has investigated numerous outbreaks of infections and deaths found to be the result of drug products that were contaminated because they were produced under insanitary conditions. Most notably, in 2012, injectable drug products produced by a compounding facility and shipped across the country caused a fungal meningitis outbreak that resulted in more than 60 deaths and 750 cases of infection. FDA has investigated numerous other serious adverse events, including deaths, associated with contaminated drug products produced by compounding facilities, and it is likely that such adverse events are underreported.

Since the 2012 fungal meningitis outbreak, FDA has identified insanitary conditions at many of the compounding facilities that it has inspected, and numerous compounding facilities have voluntarily recalled drug products intended to be sterile and temporarily or permanently ceased sterile operations as a result of those findings. However, FDA does not inspect the vast majority of compounding facilities in the United States because they generally do not register with FDA unless they elect to become outsourcing facilities.[4] Therefore, FDA is often not aware of these facilities and potential problems with their drug products, or conditions and practices, unless it receives a complaint, such as a report of a serious adverse event or visible contamination. It is critical that compounding facilities avoid the presence of insanitary conditions and identify and remediate any insanitary conditions at their facilities before the conditions result in drug contamination and patient injury.

In addition, to protect the public health, it is critical that both FDA and State regulatory agencies take appropriate action when compounders produce drugs under insanitary conditions. Based on its inspections, FDA determines whether compounding facilities produce drugs under insanitary conditions in violation of section 501(a)(2)(A) of the FD&C Act, and if so, the Agency may initiate regulatory action. However, compounding facilities that are not registered with FDA as outsourcing facilities are primarily overseen by the States and, as explained above, generally are not routinely inspected by FDA. Therefore, FDA encourages State regulatory agencies to assess during inspections whether compounding facilities that they oversee engage in poor practices,

[4] *See* section 503B of the FD&C Act.

including those described below, and if so, to take action, as appropriate, consistent with State laws and regulations, and to contact FDA.

III. POLICY

Section III.A of this guidance describes examples of conditions that would be considered insanitary conditions under section 501(a)(2)(A) of the FD&C Act. FDA has observed each of these conditions in one or more of the compounding facilities it has inspected. **These are only examples and are not an exhaustive list. Other conditions not described in this guidance may be considered insanitary**.

Section III.B of this guidance describes procedures that compounding facilities should employ to ensure that they do not have insanitary conditions and that they are capable of producing sterile drug products, and section III.C describes actions that compounding facilities should take if they identify insanitary conditions at their facilities. Finally, section III.D of this guidance describes potential FDA regulatory actions if insanitary conditions are not adequately corrected.

FDA intends to consider the entire set of conditions at the facility, including whether the facility engages in the procedures described in section III.B, when prioritizing regulatory action against a compounding facility for producing drugs under insanitary conditions.

A. Examples of Insanitary Conditions[5]

1. Insanitary Conditions Applicable to the Production of Sterile and/or Non-Sterile Drugs

Although maintaining sterility is not a requirement for non-sterile drugs, non-sterile drugs can become contaminated with microorganisms of a type or at a level that can cause patient harm. Non-sterile aqueous solutions are particularly susceptible to microbial growth if contaminated. Contamination may also include non-viable filth and the presence of unintended drug components. The following are examples of insanitary conditions that are applicable to both sterile and non-sterile drug production.

- Vermin (e.g., insects, rodents) observed in production areas or areas immediately adjacent to production.
- Visible microbial contamination (e.g., bacteria, mold) in the production area.
- Non-microbial contamination in the production area (e.g., rust, glass shavings, hairs).
- Handling beta-lactam, hazardous, or highly potent drugs (e.g., hormones) without providing adequate containment, segregation, and cleaning of work surfaces, utensils, and personnel to prevent cross-contamination.
- Production of drugs while construction is underway in an adjacent area without adequate controls to prevent contamination of the production environment and product.

[5] For definitions of some of the terms used in this section, refer to United States Pharmacopeia (USP) Chapter <797>.

2. Insanitary Conditions in a Sterile Operation

a. Aseptic Practices

- Putting on gowning apparel improperly, in a way that may cause the gowning apparel to become contaminated. This includes, for example, gowning in non-classified areas, gowning apparel touching the floor, or putting on sterile gloves improperly (e.g., touching the outside of a glove with bare hands).
- Failing to disinfect or change gloves frequently enough given the nature of the operations to prevent contamination.
- Engaging in aseptic processing wearing non-sterile gloves. This could contaminate the critical area.[6]
- Engaging in aseptic manipulations with exposed hands, wrists, legs, hair, or mouth, for example.
- Performing aseptic manipulations outside of an International Organization for Standardization Class 5 (ISO 5) area.
- Exposing unprotected sterile product, including stock solutions, to lower than ISO 5 quality air (e.g., removing it from the ISO 5 area without a robust and intact container closure system).
- Engaging in aseptic processing after leaving the cleanroom and re-entering from a non-classified area without first replacing gowning apparel (e.g., sterile gloves, gowns, mask, foot covers). Movement of personnel in and out of the cleanroom without regowning may bring contaminants from the non-classified areas into the cleanroom.
- Moving quickly in the vicinity of open containers or instruments (e.g., needles). While conducting aseptic manipulations, ISO 5 airflow must be unidirectional to protect the product from contaminating particles. Quick movement of personnel disrupts the airflow and increases the risk of bringing lesser quality air into the ISO 5 area.
- Conducting aseptic manipulations or placing equipment/supplies in an area that blocks the movement of first pass air around an open container, whether before or after it is filled with sterile product. If unidirectional air over the critical surface is blocked, the area is no longer protected. If it is blocked by personnel conducting aseptic manipulations, contamination on personnel, particularly on exposed skin, could be introduced to the critical area.
- Using a non-sterile tool or manually contacting the inner surface of the container or closure. For example, during manual stoppering (e.g., hand stoppering), personnel touching the top of open containers, or the lower side or bottom of closures. This could contaminate the drug in the vials.
- Touching equipment or other surfaces (e.g., walls, telephone, floors) located outside of the ISO 5 area with gloved hands and then proceeding with aseptic manipulations without changing or sanitizing gloves.

[6] A *critical area* is an area designed to maintain sterility of sterilized materials. Sterilized product, containers or closures, and equipment may be exposed in critical areas. The ISO 5 area is the critical area, and the terms are used interchangeably throughout this guidance.

- Storing open sterile vials within the critical area without protective cover longer than needed for the process of filling drug product. The longer a vial is open to the environment, the greater the risk of contamination.
- Failure to disinfect container closure systems of sterile drug components immediately prior to opening for use.

b. Equipment/ Facilities

- Actionable microbial contamination of the ISO 5 area or in adjacent areas.
- Cleanroom with unsealed, loose ceiling tiles.
- ISO classified areas with difficult to clean (e.g., porous), particle-generating, or visibly dirty (e.g., rusty) equipment or surfaces such as shelving, floors, walls, doors, window sills, and ceilings. For example, wood is both difficult to clean and particle-generating.
- Classified areas and segregated production areas surrounding the ISO 5 area that contain dust-collecting overhangs (e.g., utility pipes or ledges, such as windowsills).
- ISO 5 area open to the surrounding cleanroom with minimal or no physical barriers separating it from non-aseptic activities (e.g., non-aseptic weighing materials, gowning, container labeling).
- ISO 5 area open to non-classified rooms (segregated production area). Lower quality air from the surrounding room entering the ISO 5 area increases the risk of introducing microbial contamination into drug products being manipulated.
- A facility designed and/or operated in a way that permits poor flow of personnel or materials, or allows the influx of poor quality air into a higher classified area. Examples include:
  - materials flow into the ISO 7 area directly from an unclassified area;
  - air return located next to the high efficiency particulate arrestance (HEPA) filter rather than near the floor;
  - an air vent between classified and unclassified areas;
  - a door opened between the unclassified area and the ISO 8 anteroom while the door between the ISO 7 and ISO 8 areas is also open;
  - inadequate pressure differentials between areas of higher quality air and lower quality air.
- A lack of HEPA-filtered air, or inadequate HEPA filter coverage or airflow, over the area to which sterile product is exposed.
- HEPA filters that are not sealed around each perimeter to the support frame. The air entering the cleanroom must be HEPA filtered to remove airborne particles. If HEPA filters are not sealed, air that is not HEPA filtered could enter the cleanroom.
- The presence of sinks or drains in the cleanroom where the ISO 5 area is located. Sinks and drains are sources of microbial contamination.
- Use of non-sterilized or non-depyrogenated equipment (e.g., transfer tubing, temporary bulk containers). Use of such equipment can introduce or increase bioburden and endotoxins.
- Use of non-sterilized or non-depyrogenated final containers/closures. Use of such container/closures could contaminate the drug product after it has been sterilized.

c. Sterilization

- The "sterilizing filter" is not adequate to accomplish sterilization and is not pharmaceutical grade.
- Temperature and time conditions used for heat sterilization are not lethal to heat-resistant microorganisms.

d. Cleaning and Disinfecting

- Non-sterile disinfecting agents and cleaning pads or wipes are used in the aseptic processing areas, especially the ISO 5 area. Non-sterile cleaning and disinfecting items could spread microbial spores.
- No, improper, or infrequent, use of a sporicidal agent in the facility's cleanrooms and ISO 5 area.
- No disinfection of equipment and/or supplies entering the aseptic processing areas. Disinfection should occur at each transition from areas of lower quality air to areas of higher quality (e.g., from non-classified to first classified room, from anteroom to buffer room, from buffer room to ISO 5 area).
- Disinfectant contact time (also known as "dwell time") and coverage of the item being disinfected are insufficient to achieve adequate levels of disinfection. The use, including contact time, of commercially-obtained disinfectants should follow the manufacturer's instructions.

B. Identifying Insanitary Conditions

Certain procedures are critical to ensuring that compounding facilities do not have insanitary conditions that could compromise drug sterility and that they are capable of producing sterile drug products. FDA recommends that compounding facilities that produce drugs that are intended to be sterile routinely employ these procedures to help ensure that they can produce sterile products. A non-exhaustive list of such procedures follows.

1. Conduct routine[7] environmental monitoring, including a) nonviable airborne particulate sampling; b) viable airborne particulate sampling; c) personnel sampling (including glove fingertip sampling); and d) surface sampling, including but not limited to equipment, work surfaces, and room surfaces. Environmental monitoring provides information on the quality of the aseptic processing environment and, if problematic, the compounding

[7] For compounding facilities that are not registered with FDA as outsourcing facilities, see USP Chapter <797>. For outsourcing facilities, see FDA's draft guidance, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* ("interim CGMP draft guidance"). Once final, this guidance will represent FDA's current thinking regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until FDA promulgates CGMP regulations that are more specific to outsourcing facilities.

This interim CGMP draft guidance states that outsourcing facilities should conduct environmental monitoring of the ISO 5 area at least daily. FDA recommends that compounding facilities that are not registered as outsourcing facilities also conduct daily environmental monoitoring during operations.

facility should promptly identify potential routes of contamination and perform corrective actions.

2. Certify the ISO 5 area every six months. If the ISO 5 area is not certified every six months or does not pass all certification requirements, there is no assurance that the ISO 5 area is working properly (e.g., generating unidirectional ISO 5 airflow). Smoke studies should be conducted as part of the certification to assess the airflow patterns necessary to maintain unidirectional flow from areas of higher air quality (e.g., ISO 5) to areas of lower air quality (e.g., ISO 7) to prevent microbial contamination of the sterile drug products during processing. Conducting smoke studies under dynamic conditions helps to ensure that unidirectional airflow is maintained while personnel are working in the ISO 5 area.

3. Measure pressure differentials during operations to help ensure proper airflow (i.e., from areas of higher quality air to adjacent areas with lower quality air).

4. Conduct media fill studies to closely simulate aseptic production operations incorporating, as appropriate, worst-case activities and conditions that provide a challenge to aseptic operations.

C. Corrective Actions

A compounding facility should immediately assess the impact of insanitary conditions on drug products produced, which should include an evaluation of how widespread the insanitary conditions are and over what period of time the conditions existed.

The compounding facility also should determine whether to cease production of drug products until the conditions have been corrected and initiate a recall of all potentially affected lots on the market.

For example, FDA considers the following insanitary conditions to be particularly serious, and if any one of these conditions exists, FDA strongly recommends that a compounding facility immediately initiate a recall of purportedly sterile drugs and cease sterile operations until the condition(s) have been corrected:

- Vermin (e.g., insects, rodents) observed in ISO 5 areas or in immediately adjacent areas.
- Visible microbial contamination (e.g., bacteria, mold) in the ISO 5 area or in immediately adjacent areas.
- Non-microbial contamination in the ISO 5 area (e.g., rust, glass shavings, hairs).
- Performing aseptic manipulations outside of the ISO 5 area.
- Exposing unprotected sterile product, including stock solutions, to lower than ISO 5 quality air (e.g., removing it from the ISO 5 area without a robust and intact container closure system).
- Cleanroom areas with unsealed, loose ceiling tiles.

- Production of drugs while construction is underway in an adjacent area without adequate controls to prevent contamination of the production environment and product.
- Consistent and frequent pressure reversals from areas of less clean air to areas of higher cleanliness.
- The "sterilizing filter" is not adequate to accomplish sterilization and is not pharmaceutical grade.
- Temperature and time conditions used for heat sterilization are not lethal to heat-resistant microorganisms.

If a compounding facility decides to initiate a recall, it should notify its local FDA District recall coordinator as soon as the decision to recall is made.[8] The compounding facility should also notify the applicable State regulatory body in the State(s) to which the facility ships drugs, consistent with State laws and guidance.

In addition to the immediate actions recommended above, if a compounding facility has insanitary conditions, it should undertake a comprehensive assessment of its operations, including, as applicable, facility design, procedures, personnel, processes, materials, and systems, and should consider consulting a third party with relevant drug production expertise to conduct this comprehensive evaluation and to assist in implementing appropriate corrective actions.

Compounding facilities producing purportedly sterile drug products under insanitary conditions should not rely on a passing sterility test as an indication of sterility assurance because microbial contamination, when present, is not uniformly distributed within a batch and may not be identified by a sterility test. Furthermore, compounding facilities must correct all insanitary conditions at their facility,[9] regardless of whether the drugs pass a sterility test.[10]

D. Regulatory Action

If a compounding facility produces drugs under insanitary conditions, the facility and responsible individuals may be subject to Federal regulatory actions including, but not limited to, a warning letter, seizure of product, and/or injunction. FDA may also recommend that the facility initiate a recall of some or all of its drugs and cease operations until the insanitary conditions have been adequately addressed. In addition, the applicable State regulatory agency may pursue regulatory action against the facility under applicable State authorities.

[8] *See* the FDA guidance, *Product Recalls, Including Removals and Corrections*.

[9] *See* section 501(a)(2)(A) of the FD&C Act.

[10] USP Chapter <71> concerning sterility testing states, "these Pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by validation of the sterilization process or of the aseptic processing procedures."

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

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July 2016
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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

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Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act

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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*.

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 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.

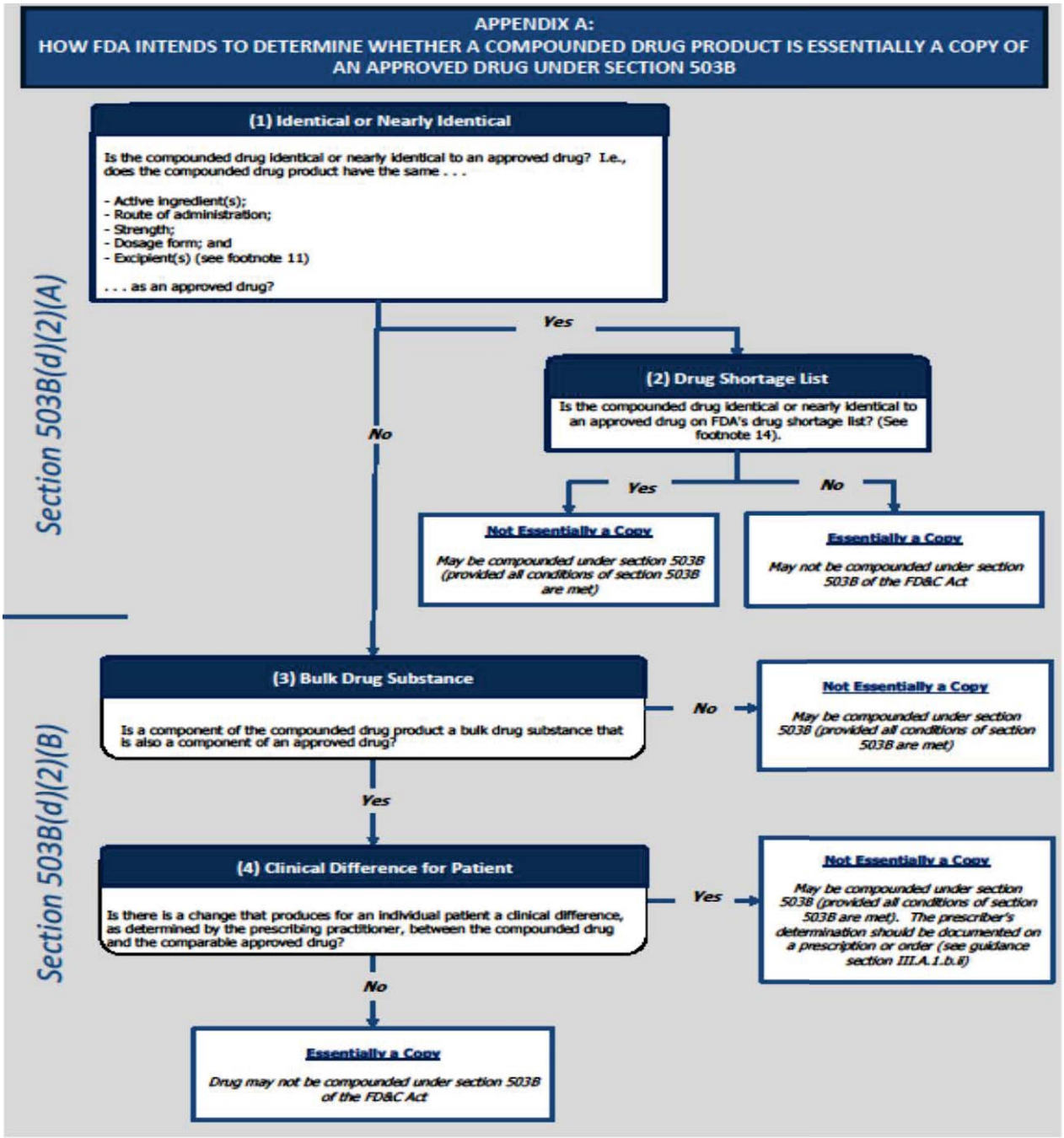
B. Recordkeeping

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**



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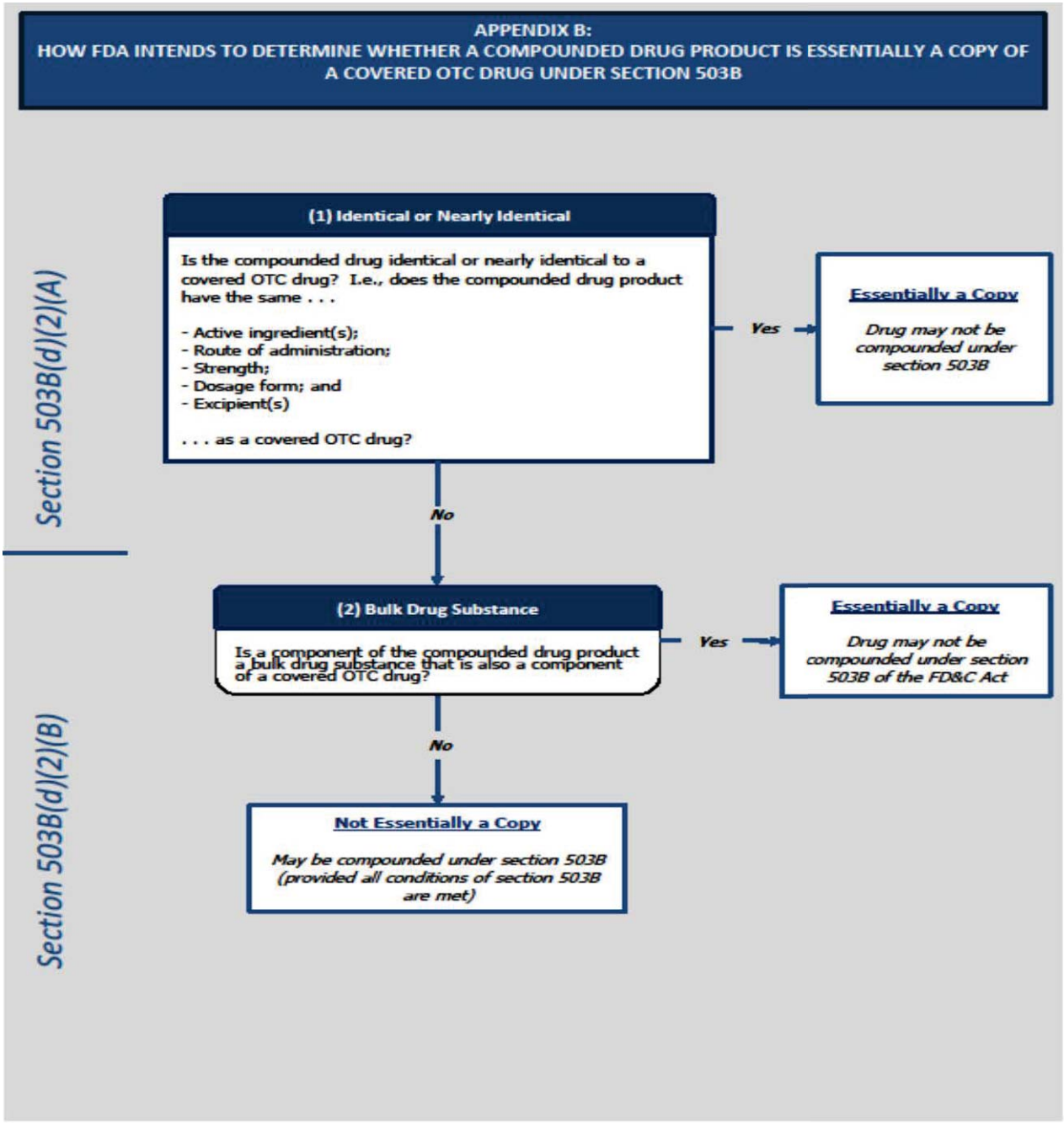
APPENDIX B:
HOW FDA INTENDS TO DETERMINE WHETHER A COMPOUNDED DRUG PRODUCT IS ESSENTIALLY A COPY OF A COVERED OTC DRUG UNDER SECTION 503B
Section 503B(d)(2)(A)
(1) Identical or Nearly Identical
Is the compounded drug identical or nearly identical to a covered OTC drug? I.e., does the compounded drug 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)

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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

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Sara Rothman (CDER) at 301-796-3110.

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

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

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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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Guidance for Industry[1]

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

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.