

XVII. Opportunity to Provide Comments on U.S. Food and Drug Administration Draft Guidance Documents

The FDA recently released five guidance documents on various aspects of sterile compounding by pharmacies and the production of medication by outsourcing facilities.

Comments were submitted under three categories, and provided under President Weisser's signature.

a. Draft Guidance: For Entities Considering Whether to Register As Outsourcing Facilities under Section 503B of the Federal Food, Drug, and Cosmetic Act

Attachment 1

This guidance states that entities registered with the FDA as outsourcing facilities will be regulated as outsourcing facilities according to current good manufacturing practice requirements (CGMP) for all products they produce or compound. (Federal law allows outsourcing facilities to be sterile compounding pharmacies as well.) There are approximately 50 FDA registered outsourcing facilities, including one in Switzerland.

The outsourcing guidance states that if a facility does not intend to compound all drugs under CGMPs, then the facility should not be registered as an outsourcing facility. Additionally, the facility:

- Must be engaged in the production of compounding sterile human drugs.
- Does Not repackage drugs (except as discussed in other guidance documents)
- Does Not produce biologic drugs
- Does Not produce animal drugs

The board's comments on this guidance are provided in Attachment 1, and a copy of the draft guidance document follows the board's comments.

b. Draft Guidance for Industry: Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food Drug and Cosmetic Act

Attachment 2

This guidance provides that outsourcing facilities are required to report adverse drug events to the FDA within 15 days. Specifically, all serious, unexpected adverse drug experiences associated with the use of their compounded prescription drug products

must be reported and the FDA “strongly recommends” that outsourcing facilities report all serious adverse drug experiences generally.

The guidance lists four elements for the investigation to include: the patient, the reporter, the suspect drug, the serious adverse event. It then describes the specific details about each element to include in the report.

Regarding the board’s outsourcing facility legislative proposal: the 15 day reporting report for adverse events is longer than the 12 hour requirement in existing California law for compounding pharmacies to report to the board any drug recalled. Currently the board is negotiating this amendment in light of the FDA’s recommended guidance standard.

The board’s comments on this guidance is provided in Attachment 2, and a copy of the draft guidance document follows the board’s comments.

c. Draft Memorandum of Understanding Between a State and the U.S. Food and Drug Administration Addressing Certain Distributions of Compounded Human Drug Products

Attachment 3

From page 1 of the document:

“This Memorandum of Understanding (MOU) establishes an agreement between the State of [insert State] and the U.S. Food and Drug Administration (FDA) regarding the distribution of inordinate amounts of compounded human drug products interstate and the appropriate investigation by the State of [insert State] of complaints relating to compounded human drug products distributed outside the state. This is the MOU provided for by section 503A(b)(3)(B)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C 353a), and does not apply to drugs that are compounded by registered outsourcing facilities.”

The MOU exempts the compounded products of pharmacies under specific circumstances, including providing the state has entered into the MOU, from:

- Complying with CGMPs
- Labeling with adequate directions for use
- Possessing FDA prior approval of the drug product

If the state has entered into the MOU, then the MOU:

- Requires the home state to investigate issues arising from the interstate distribution of compounded drugs by a pharmacy and to identify the root cause of the problem, and take response to the action
- Requires the state to review compounding records during the inspections of compounding pharmacies to ensure the compounding pharmacy has not

distributed an inordinate amount of compounded drug product interstate.

- Defines an inordinate amount as not more than 30 percent of the total number of compounded and non-compounded drug products distributed or dispensed (both in-state and interstate).

The board's comments are provided in Attachment 3, and a copy of the draft guidance document follows the board's comments.

At some point in the future, once finalized, the board will need to determine whether it wishes to enter into such an agreement with the FDA.

d. Guidance for Industry: Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities

Attachment 4

The board has not yet submitted comments on this guidance document, but staff intend to provide comments on the guidance document before the July Board Meeting. **Attachment 4** contains the guidance document.

From Page 3 of this guidance:

“When a drug product is prepackaged, its characteristics may change in ways that have not been evaluated during the FDA approval process and that could affect the safety and efficacy of the drug product. Improper repackaging of drug products can cause serious adverse events. Of particular concern is repackaging of sterile drug products which are susceptible to contamination and degradation. For example, failure to properly manipulate sterile drug products under appropriate aseptic conditions could introduce contaminants that could cause serious patient injury or death. Repackaging practices that conflict with approved product labeling could result in drug product degradation and adverse events associated with impurities in the product or lack of efficacy because the active ingredient has deteriorated.”

Drugs that are repackaged are not regulated by the FDA under provisions dealing with pharmacy or outsourcing facilities. The guidance states that the FDA does not intend to take action for certain violations of federal requirements for entities that repackage drugs, provided:

1. The facility is licensed by a state as a pharmacy or holds an outsourcing facility license
2. If the repackaging occurs in a pharmacy or federal institution only: 1. after receipt of a patient-specific prescription or written chart order, or 2. Repackaged in advance of receipt of a patient-specific order based on prior demand for a previous, consecutive 14-day period AND history for prior 14-day periods.

3. The repackaging is done by or under the supervision of a licensed pharmacist
4. For single dose vials, the repackaging does not conflict with drug product labeling
5. For single dose vials repackaged into multiple units, the product is repackaged in a way that does not conflict with drug product labeling
6. The repackaged drug product conforms to specific beyond use dating (BUD)
7. Provides different requirements for BUD for an outsourcing facility, and requires CGPMs for the repackaging processes. Additionally the guidance provides labeling requirements for the repackaged product.
8. The repackaged product is not sold or transferred by an entity other than the one that repackaged the product.
9. The repackaged drug product is distributed only in states in which the facility repackaging the product meets all applicable state requirements.
10. Addresses guidance for repacking drugs on the FDA's drug shortage list.

Attachment 1



California State Board of Pharmacy

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

May 15, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: COMMENTS OF THE CALIFORNIA STATE BOARD OF PHARMACY

Docket No. FDA-2014-D-1399-0001

Guidance for Entities Considering Whether to Register as Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry

To Whom It May Concern:

I write on behalf of the California State Board of Pharmacy (Board). We are pleased to have this opportunity to submit comments on Docket No. FDA-2014-D-1399-0001: "Guidance for Entities Considering Whether to Register as Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry; Availability." We will be brief. We support the concept of a separate license category for facilities engaged in large-scale, non-patient specific compounding, particularly sterile compounding. And we appreciate this effort to explicate and clarify Section 503B. We do have some concerns.

Our first concern is that the Draft Guidance does not sufficiently address the topic of appropriate or required staffing and supervision in an outsourcing facility. It repeats only the statutory prerequisite to the exceptions created by Section 503B: that compounding of human drugs in an outsourcing facility be performed by or under the direct supervision of a licensed pharmacist. This leaves unanswered numerous questions regarding staffing and supervision, including who else may be involved in compounding (licensed or unlicensed personnel), what number or ratio of compounding staff may be supervised by a licensed pharmacist, who may be present in an outsourcing facility, and/or who may manage or supervise the facility.

Our second concern is that the Draft Guidance contemplates and permits the co-location of a Section 503B outsourcing facility and a state-licensed pharmacy (eligible for Section 503A exemptions) in the same premises. We believe this is potentially problematic.

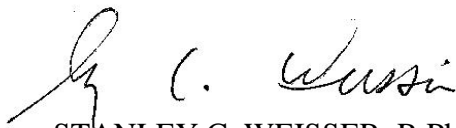
We understand and appreciate that *all* compounds prepared in such a facility would have to meet Section 503B CGMP standards. We also recognize that this (a) may reduce or eliminate the number of those interested in locating a compounding pharmacy in the same premises as an outsourcing facility, because of this requirement, and/or (b) may result in those pharmacies that do so co-locate meeting higher manufacturing standards as they conform to CGMPs.

However, we are concerned about co-mingling of personnel, records, drug components, and finished preparations, across license categories, that this co-licensure allows. Ambiguity, uncertainty, and confusion could result in several different ways. For instance, there may be confusion about whether inspection of a given facility is primarily the responsibility of the state licensing authority or the FDA. Likewise, there will be some ambiguity about whether staffing requirements or limits applicable to licensed pharmacies will apply. There may also be different retention periods for records, and/or different record-keeping requirements. There are also state-law patient consultation requirements for pharmacies, and we have concerns about whether these essential services would be diminished or entirely lost in a co-licensed facility. Additionally, if veterinary products are compounded by the pharmacy, how will violations of CGMPs be treated since veterinary drugs are excluded from compounding by outsourcing facilities? Finally, if a single sterile patient-specific product is compounded by the outsourcing facility pursuant to a prescription, will the outsourcing facility fully clean the premises (and otherwise comply with CGMP requirements) in the same manner as they would following larger production runs? Will a co-licensed facility be allowed to segregate its facility into different production areas?

Ultimately, we are concerned that a facility owner might claim to be acting under the other license when dealing with one authority (e.g., its outsourcing facility when inspected by the state), while claim the opposite when dealing with the other (e.g., its pharmacy license when its facility is subject to inspection by the FDA). Allowing a licensee to “switch hats” in this manner seems likely to lead to enforcement difficulties, jurisdictional disputes, and confusion. These are only some of the problems that we expect may develop from permitting co-licensure. For this reason, legislation currently pending in California for state licensure of outsourcing facilities does not permit an outsourcing facility to also be licensed in California as a pharmacy.

Thank you for your attention to these matters, and for your willingness to hear our input. We look forward to continuing to work together to secure the nation’s drug supply. Please feel free to contact the Board at any time if we can be of assistance. The best route for contact is via Executive Officer Virginia Herold, at (916) 574-7911, or Virginia.Herold@dca.ca.gov.

Sincerely,



STANLEY C. WEISSER, R.Ph.
President, California State Board of Pharmacy

For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B 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)**

**February 2015
Procedural**

For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

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

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Email: 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)**

**February 2015
Procedural**

Contains Nonbinding Recommendations

Draft — Not for Implementation

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3 **Cosmetic Act**
4 **Guidance¹**
5

6
7 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's or the
8 Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and
9 does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies
10 the requirements of the applicable statutes and regulations. If you want to discuss an alternative
11 approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the
12 appropriate FDA staff, call the appropriate number listed on the title page of this guidance.
13

14
15 **I. INTRODUCTION**
16

17 This guidance is intended for entities considering whether to register with the Food and Drug
18 Administration (FDA or Agency) as an outsourcing facility under section 503B of the Federal
19 Food, Drug, and Cosmetic Act (FD&C Act).²
20

21 FDA has received questions about whether entities engaged in various types of activities (e.g., a
22 facility that is compounding only non-sterile drugs or only repackaging biological products)
23 should register as an outsourcing facility. Because entities that register as outsourcing facilities
24 in fiscal year (FY) 2015 (beginning October 1, 2014) must pay a registration fee and FDA has
25 determined that fees paid pursuant to sections 503B and 744K of the FD&C Act will not be
26 refunded, FDA is issuing this guidance to answer some of these questions and to provide
27 potential registrants additional information about the regulatory impact of registering as an
28 outsourcing facility.
29

30 Separate FDA guidance documents contain details on the process for registering as an
31 outsourcing facility³ and explain how outsourcing facilities should report the products they
32 compound to FDA.⁴

¹ This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER), the Center for Veterinary Medicine (CVM), and the Office of Regulatory Affairs (ORA) at the Food and Drug Administration.

² A new section 503B was added to the FD&C Act by the Drug Quality and Security Act (DQSA). See Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).

³ See draft guidance for industry *Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

All FDA guidances are available on the FDA guidance Webpage at
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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33
34 FDA’s guidance documents, including this guidance, do not establish legally enforceable
35 responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should
36 be viewed only as recommendations, unless specific regulatory or statutory requirements are
37 cited. The use of the word *should* in Agency guidances means that something is suggested or
38 recommended, but not required.

39 40 **II. BACKGROUND**

41
42 The Drug Quality and Security Act, signed into law on November 27, 2013, creates a new
43 section 503B of the FD&C Act. Section 503B(d)(4) defines an outsourcing facility as

44
45 a facility at one geographic location or address that— (i) is engaged in the
46 compounding of sterile drugs; (ii) has elected to register as an outsourcing
47 facility; and (iii) complies with all of the requirements of this section.

48 Section 503B(d)(4) further states that an outsourcing facility is not required to be a licensed
49 pharmacy and may or may not obtain prescriptions for identified individual patients.⁵ Section
50 503B(d)(5) defines *sterile drug* as a “drug that is intended for parenteral administration, an
51 ophthalmic or oral inhalation drug in aqueous format, or a drug that is required to be sterile under
52 Federal or State law.”

53 A human drug product compounded by or under the direct supervision of a licensed pharmacist
54 in a registered outsourcing facility can *qualify for exemptions* from the drug approval
55 requirements in section 505 of the FD&C Act (21 U.S.C. 355), the requirement to be labeled
56 with adequate directions for use in section 502(f)(1) of the FD&C Act (21 U.S.C. 352(f)(1)), and
57 the track and trace requirements in section 582 of the FD&C Act (21 U.S.C. 360eee-1).
58 However to qualify, each of the following conditions must be met.

- 59 1. The outsourcing facility must be in compliance with the registration and reporting
60 requirements of section 503B(b). This includes submitting twice yearly reports regarding
61 the drugs compounded by the outsourcing facility and submitting adverse event reports in
62 accordance with section 503B(b)(5).^{6,7}

⁴ See draft guidance for industry *Interim Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

⁵ Although an outsourcing facility may send prescription drugs to healthcare facilities without obtaining prescriptions for identified individual patients, drugs produced by outsourcing facilities remain subject to the requirements in section 503(b) of the FD&C Act. Therefore, an outsourcing facility cannot dispense a prescription drug to a patient without a prescription.

⁶ See section 301(ccc)(3) of the FD&C Act, which makes it a prohibited act for an entity that is registered in accordance with section 503B(b) to fail to report drugs or adverse events as required.

⁷ See sections 503B(a)(1) and (b).

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- 63 2. If the outsourcing facility compounds drugs using one or more bulk drug substances, the
64 bulk drug substances must meet certain requirements.⁸
- 65 3. If the outsourcing facility compounds using ingredients other than bulk drug substances,
66 those ingredients must meet certain requirements.⁹
- 67 4. The outsourcing facility must not compound drugs that appear on a list published by FDA
68 of drugs that have been withdrawn or removed from the market because the drugs or
69 components of such drugs have been found to be unsafe or not effective.^{10,11}
- 70 5. The outsourcing facility must not compound drugs that are essentially a copy of one or
71 more approved drugs.¹²
- 72 6. The outsourcing facility must not compound drugs that appear on a list published by FDA
73 of drugs that present demonstrable difficulties for compounding.¹³
- 74 7. If the outsourcing facility compounds from a drug that is the subject of a risk evaluation
75 and mitigation strategy (REMS) approved with elements to assure safe use pursuant to
76 section 505-1, or from a bulk drug substance that is a component of such drug, the
77 outsourcing facility must demonstrate to FDA before beginning to compound that it will
78 use controls comparable to the controls applicable under the REMS.¹⁴
- 79 8. The outsourcing facility's compounded drugs will not be sold or transferred by an entity
80 other than that outsourcing facility.¹⁵
- 81 9. The outsourcing facility has paid all applicable establishment and reinspection fees owed
82 under section 744(k).^{16,17}
- 83 10. The outsourcing facility must include on the labels and labeling of its compounded drug
84 products the information required under section 503B(a)(10).¹⁸

⁸ See section 503B(a)(2).

⁹ See section 503B(a)(3).

¹⁰ See section 503B(a)(4).

¹¹ The list 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 (the withdrawn-or-removed list) can be found at 21 CFR 216.24. On July 2, 2014, FDA published a proposed rule that would update that list (Additions and Modifications to the List of Drug Products That Have Been Withdrawn or Removed from the Market for Reasons of Safety or Effectiveness, 79 FR 37,687). In the preamble to the proposed rule, FDA explained that FDA is proposing to revise and update the withdrawn-or-removed list at 21 CFR 216.24 for purposes of both sections 503A and 503B. Until the final rule revising and updating the withdrawn-or-removed list is published, drugs included on the existing list at 21 CFR 216.24 may not be compounded under section 503B.

¹² See section 503B(a)(5).

¹³ See section 503B(a)(6).

¹⁴ See section 503B(a)(7).

¹⁵ See section 503B(a)(8).

¹⁶ See section 503B(a)(9).

¹⁷ See also sections 744J and 744K of the FD&C Act, and guidance for industry Fees for Human Drug Compounding Outsourcing Facilities Under Sections 503B and 744K of the FD&C Act.

¹⁸ See section 503B(a)(10).

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85 11. The outsourcing facility must compound all drugs in accordance with section 503B.¹⁹

86
87 Because drugs compounded by outsourcing facilities are not exempt from section 501(a)(2)(B)
88 of the FD&C Act, outsourcing facilities are subject to current good manufacturing practice
89 (CGMP) requirements, among other requirements under the FD&C Act.^{20,21} In addition,
90 outsourcing facilities will be inspected by FDA on a risk-based schedule.²²

91 III. GUIDANCE

92 If you register a facility as an outsourcing facility, you are indicating your intent for the facility's
93 compounded drugs to be regulated under section 503B of the FD&C Act. Under section
94 503B(a)(11), a compounded drug can only qualify for the exemptions from sections 502(f)(1),
95 505, and 582 of the FD&C Act if *all* of the facility's compounded drugs are compounded in
96 accordance with section 503B. As stated above, drugs compounded in accordance with section
97 503B are not exempt from CGMP requirements, and outsourcing facilities will be inspected by
98 FDA on a risk-based schedule.

99
100 If you do not intend to compound *all* drugs at your facility in accordance with section 503B and
101 comply with CGMP requirements, you should not register as an outsourcing facility under
102 section 503B.²³ In addition, entities considering registering as outsourcing facilities should
103 consider the following:

- 104
- 105 • To meet the definition of an *outsourcing facility*, the facility must be engaged in the
106 compounding²⁴ of sterile human drugs.²⁵
 - 107 • The definition of *compounding* in section 503B(d)(1) does not include repackaging.
 - 108 • For purposes of section 503B, a drug, including a sterile drug, does not include a
109 biological product subject to licensure under section 351 of the Public Health Service Act
110 (PHS Act), or an animal drug subject to approval under section 512 of the FD&C Act.²⁶
- 111

¹⁹ See section 503B(a)(11).

²⁰ FDA has issued a draft guidance for industry *Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*. Once finalized, that guidance will represent the Agency's thinking on this topic.

²¹ See section 503B(a).

²² See section 503B(b)(4).

²³ If an entity is not registered as an outsourcing facility under section 503B, its drugs could qualify for the exemptions from sections 505, 502(f)(1), and 501(a)(2)(B) of the FD&C Act, if they meet all of the conditions of section 503A. Otherwise, the drugs would be subject to all of the requirements in the FD&C Act applicable to drugs made by conventional manufacturers.

²⁴ Section 503B(d)(1) defines the term *compounding*, for purposes of that section, to include the combining, admixing, mixing, diluting, pooling, reconstituting, or otherwise altering of a drug or bulk drug substance to create a drug.

²⁵ See section 503B(d)(4).

²⁶ In addition, for purposes of section 503A of the FD&C Act, the term *drug* does not include a biological product subject to licensure under section 351 of the PHS Act.

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112 Therefore, you should ***not*** register a facility as an outsourcing facility if the ***only*** activities
113 conducted at the facility are repackaging, compounding non-sterile or animal drugs, or mixing,
114 diluting, or repackaging biological products subject to licensure under section 351 of the PHS
115 Act because ***none of the products produced at the facility would qualify for the exemptions***
116 ***provided in section 503B.***

117
118 In addition, by registering as an outsourcing facility, an entity is electing to have its compounded
119 drugs regulated under section 503B of the FD&C Act, not section 503A. Drugs compounded at
120 an outsourcing facility are not eligible for the exemptions provided in section 503A, even if the
121 conditions in that section are met with respect to the particular drug.

122
123 FDA is issuing separate draft guidances on (1) mixing, diluting, and repackaging biological
124 products outside the scope of an approved biologics license application and (2) repackaging
125 certain human drug products by pharmacies and outsourcing facilities. These guidance
126 documents will describe FDA's compliance policies with respect to biological products that are
127 mixed, diluted, or repackaged outside the scope of an approved biologics license application
128 (BLA) and repackaged human drugs.

129
130 If a facility compounds sterile human drugs and otherwise meets the definition of an outsourcing
131 facility, any non-sterile human drugs compounded by the facility would also be eligible for the
132 exemptions from sections 505, 502(f)(1), and 582 if the drugs are compounded in accordance
133 with the provisions of section 503B. However, if a facility that meets the definition of an
134 outsourcing facility repackages certain human drugs, or mixes, dilutes, or repackages biological
135 products outside the scope of an approved BLA, FDA does not intend to take action against
136 those products for violations of certain provisions of the FD&C Act or the PHS Act, if
137 applicable, provided those products satisfy the conditions described in the two guidances on
138 biological products and repackaging, referenced above.

Attachment 2



California State Board of Pharmacy

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

May 15, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: COMMENTS OF THE CALIFORNIA STATE BOARD OF PHARMACY

Docket No. FDA-2014-D-2138

Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry

To Whom It May Concern:

I write on behalf of the California State Board of Pharmacy (Board). We are pleased to have this opportunity to submit comments on Docket No. FDA-2014-D-1399-0001: “Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry; Availability.” We will be brief. We support the concept of requiring and specifying adverse event reporting by outsourcing facilities, but we are concerned that the requirements and timelines specified do not sufficiently protect the public.

As we have learned again from tragic events over the last few years, contaminants and other problems with compounded drugs, particularly sterile preparations, have the potential to be significant threats to the health of individuals and the public. It is imperative that we get notice of these potential problems and initiate recalls as quickly as possible. This is especially urgent with regard to outsourcing facilities, which could be shipping large quantities of drugs that are not being tracked by patient, and where a single contaminated lot or contaminants in the facility could be spread nationwide in a matter of hours or days. The urgency of a quick response is at least as great as it would be for finished drugs, and given the direct injection or administration of many of the drugs produced by outsourcing facilities, the consequences could be far worse.

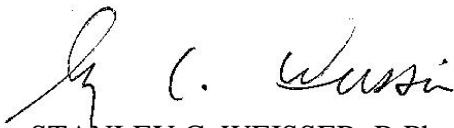
Under these circumstances, the *15 calendar days* that can elapse before an outsourcing facility is required to report a serious and unexpected adverse drug experience is far too long, as is the allowance for an additional 15 days to do investigation and follow-up reporting. During this 30-day period, an untold number of illnesses, injuries, or deaths might result. Moreover, allowing this kind of delay in reporting will likely also delay initiation of recall procedures.

This time period for reporting should be significantly cut down, to no more than 48 or 72 hours, with an equally prompt follow-up and investigation period, and an immediate decision on a recall. The first concern should be adequate protection of patients or potential patients.

Moreover, we believe that if the FDA “strongly recommends” that outsourcing facilities report all serious adverse drug events and experiences if associated with an outsourcing facility’s compounded prescription drug products (i.e., regardless of expectation), the FDA should require such reporting. We agree with the FDA’s concluding remarks that such reporting of all serious adverse events would provide important information required for public health. We also suggest that the FDA immediately share all adverse events reported with the home state regulator, so this state agency is also aware of potential problems at one of its licensee’s facilities.

Thank you for your attention to these matters, and for your willingness to hear our input. We look forward to continuing to work together to secure the nation’s drug supply. Please feel free to contact the Board at any time if we can be of assistance. The best route for contact is via Executive Officer Virginia Herold, at (916) 574-7911, or Virginia.Herold@dca.ca.gov.

Sincerely,

A handwritten signature in black ink, appearing to read "S. C. Weisser". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

STANLEY C. WEISSER, R.Ph.
President, California State Board of Pharmacy

Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document contact H. Joy Sharp at 301-796-3647 or Joy.Sharp@fda.hhs.gov.

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

**February 2015
Drug Safety**

Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

Additional copies are available from:

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**U.S. Department of Health and Human Services
Food and Drug Administration
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1 **Adverse Event Reporting for Outsourcing Facilities**
2 **Under Section 503B of the Federal Food, Drug, and Cosmetic Act**
3 **Guidance for Industry¹**
4
5
6

7
8 This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s or the
9 Agency’s) current thinking on this topic. It does not create or confer any rights for or on any person and
10 does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies
11 the requirements of the applicable statutes and regulations. If you want to discuss an alternative
12 approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the
13 appropriate FDA staff, call the appropriate number listed on the title page of this guidance.
14

15
16
17
18 **I. INTRODUCTION**
19

20 This guidance is intended for firms that have registered with the Food and Drug Administration
21 (FDA) under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) as human
22 drug compounding outsourcing facilities (outsourcing facilities). Under section 503B(b)(5) of
23 the FD&C Act, an outsourcing facility must submit adverse event reports to FDA “in accordance
24 with the content and format requirements established through guidance or regulation under
25 section 310.305 of title 21, Code of Federal Regulations (or any successor regulations).”² This
26 guidance explains FDA’s current thinking on adverse event reporting for outsourcing facilities.
27

28 FDA’s guidance documents, including this guidance, do not establish legally enforceable
29 responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should
30 be viewed only as recommendations, unless specific regulatory or statutory requirements are
31 cited. The use of the word *should* in Agency guidances means that something is suggested or
32 recommended, but not required.
33

34 **II. BACKGROUND**
35

36 **A. Statutory and Regulatory Framework**
37

¹ This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research (CDER) in cooperation with the Office of Regulatory Affairs (ORA) at the Food and Drug Administration.

² 21 U.S.C. 353b(b)(5).

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38 On November 27, 2013, the Drug Quality and Security Act (DQSA) was signed into law. Title I
39 of the DQSA contains important provisions related to the oversight of human drug
40 compounding.³ The DQSA added section 503B to the FD&C Act. Under section 503B(b), a
41 compounder can register as an *outsourcing facility* with FDA.⁴ Under section 503B(b)(5), an
42 outsourcing facility must submit adverse event reports to FDA “in accordance with the content
43 and format requirements established through guidance or regulation under section 310.305 of
44 title 21, Code of Federal Regulations (or any successor regulations).”⁵

45
46 Section 310.305 requires, among other things, that manufacturers, packers, and distributors of
47 marketed prescription drug products that are not the subject of an approved new drug application
48 or an abbreviated new drug application establish and maintain records and make reports to FDA
49 of all serious, unexpected adverse drug experiences⁶ associated with the use of their prescription
50 drug products. For purposes of reporting adverse drug experiences, the term *prescription drug*
51 *products* includes any compounded drug product subject to the prescription requirements in
52 section 503(b)(1) of the FD&C Act. The adverse event reporting requirements apply to
53 prescription drug products regardless of whether the outsourcing facility distributes them
54 pursuant to prescriptions.⁷

55
56 In addition, on June 10, 2014, FDA issued a final rule requiring, among other things, that
57 postmarketing safety reports required under 21 CFR 310.305, 314.80, 314.98, and 600.80 be
58 submitted to FDA in an electronic format the Agency can process, review, and archive. The final
59 rule also adds 21 CFR 329.100 to address electronic submission of safety reports required by
60 section 760 of the FD&C Act regarding serious adverse event reporting for nonprescription
61 drugs.⁸ These requirements are effective as of June 10, 2015.⁹

62
63 Under section 503B, outsourcing facilities are required to submit adverse event reports to FDA,
64 in accordance with content and format requirements established through guidance or regulation
65 under 21 CFR 310.305 (or any successor regulations).

³ See text of Compounding Quality Act at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm376732.htm>.

⁴ 21 U.S.C. 353b(b).

⁵ *Id.* at 353b(b)(5).

⁶ This guidance uses the terms *adverse drug experience* and *adverse event* interchangeably.

⁷ Section 503B(d)(4)(C) of the FD&C Act provides that outsourcing facilities may or may not obtain prescriptions for identified individual patients. Although outsourcing facilities may send prescription drugs to healthcare facilities without obtaining prescriptions for identified individual patients, drugs produced by outsourcing facilities remain subject to the requirements in section 503(b) of the FD&C Act. Therefore, an outsourcing facility cannot dispense a prescription drug to a patient without a prescription.

⁸ 21 U.S.C. 379aa.

⁹ See 79 FR 33072. FDA intends to issue guidance reflecting the requirements of the final rule before they become effective.

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66
67 Failure to report adverse events by an entity that is registered in accordance with section 503B(b)
68 is a prohibited act under section 301(ccc)(3) of the FD&C Act.¹⁰ Violations relating to this
69 provision are subject to regulatory and enforcement action.

70
71 **B. Section 310.305**

72
73 Section 310.305(b) defines a *serious adverse drug experience* to mean:

74
75 Any adverse drug experience occurring at any dose that results in any of the
76 following outcomes:

- 77
- 78 • Death,
 - 79 • A life-threatening adverse drug experience,
 - 80 • Inpatient hospitalization or prolongation of existing hospitalization,
 - 81 • A persistent or significant disability/incapacity, or
 - 82 • A congenital anomaly/birth defect

83 Important medical events that may not result in death, be life-threatening, or
84 require hospitalization may be considered a serious adverse drug experience
85 when, based upon appropriate medical judgment, they may jeopardize the
86 patient or subject and may require medical or surgical intervention to prevent
87 one of the outcomes listed in this definition. Examples of such medical
88 events include

- 89
- 90 • allergic bronchospasm requiring intensive treatment in an emergency
91 room or at home,
 - 92 • blood dyscrasias or convulsions that do not result in inpatient
93 hospitalization, or
 - 94 • the development of drug dependency or drug abuse.

95 Section 310.305(b) defines an *unexpected adverse drug experience* as any adverse drug
96 experience that is not listed in the current labeling for the drug product. This includes events that
97 may be symptomatically and pathophysiologically related to an event listed in the labeling, but
98 differ from the event because of greater severity or specificity. The term *unexpected*, as used in
99 this definition, refers to an adverse drug experience that has not been previously observed (i.e.,
100 included in the labeling), rather than from the perspective of such experience not being
101 anticipated from the pharmacological properties of the pharmaceutical product.

102
103 The regulations require reporting of each adverse drug experience received or otherwise obtained
104 that is both serious and unexpected as soon as possible, but in no case later than 15 calendar days
105 of initial receipt of the information along with a copy of the drug product's current labeling.¹¹ In
106 addition, all serious, unexpected adverse drug experiences that are the subject of these reports

¹⁰ 21 U.S.C. 331(ccc)(3).

¹¹ See 21 CFR 310.305(c)(1)(i).

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107 shall be promptly investigated and a follow-up report must be submitted within 15 calendar days
108 of receipt of new information or as requested by FDA.¹²

109
110 FDA’s regulations also state that information on the names and addresses of individual patients
111 should **not** be included.¹³ A unique code number should therefore be assigned instead for each
112 individual patient and placed in section A1 of Form FDA 3500A (Patient Identifier).

113
114 The regulations require that firms maintain certain records relating to adverse drug experiences
115 required to be reported under section 310.305 for 10 years and provide FDA access to them.¹⁴

116 The regulations also provide a disclaimer that the report or information submitted (and any
117 release by FDA of that report or information) does not necessarily reflect a conclusion that the
118 report or information constitutes an admission that the drug caused or contributed to an adverse
119 effect.¹⁵

120

121 **III. Adverse Event Reporting by Outsourcing Facilities**

122

123 **A. What to Report**

124

125 Outsourcing facilities must report all serious, unexpected adverse drug experiences associated
126 with the use of their compounded prescription drug products.

127

128 In addition, FDA strongly recommends that outsourcing facilities report ***all*** serious adverse drug
129 experiences associated with their compounded prescription drug products. We believe reporting
130 ***all*** serious adverse events would provide important information about potential product quality
131 issues or public health risks associated with drug products compounded by outsourcing facilities.

132

133 **B. Threshold for Reporting**

134

135 As noted above, outsourcing facilities must submit to FDA reports of all serious, unexpected
136 adverse events associated with their compounded prescription drugs.¹⁶

137

138 When considering any adverse drug experience for submission to FDA in a report, after
139 receiving information about the adverse drug experience, an outsourcing facility should actively
140 investigate the following four data elements, which are described in greater detail later in this
141 section:

142

- 143 1. An identifiable patient

¹² See 21 CFR 310.305(c)(2).

¹³ See 21 CFR 310.305(e).

¹⁴ See 21 CFR 310.305(f).

¹⁵ See 21 CFR 310.305(g).

¹⁶ See 21 CFR 310.305(c).

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- 144 2. An identifiable reporter
145 3. A suspect drug
146 4. A serious adverse event
147

148 Although an outsourcing facility should actively seek to obtain each of these four data elements,
149 the facility must submit the report as a *15-day “Alert report”* to FDA as soon as possible, but no
150 later than 15 calendar days after first receiving information about the adverse event.¹⁷ **Reports**
151 **should be submitted as long as the outsourcing facility has information on at least the**
152 **suspect drug and the adverse event.**
153

154 The outsourcing facility must also promptly investigate adverse events that are the subject of a
155 15-day “Alert report”.¹⁸ If the outsourcing facility was not able to include all four of the data
156 elements in its initial report, it should exercise due diligence to obtain information about any of
157 the remaining elements. Additionally, the outsourcing facility should report new information it
158 obtains regarding data elements listed in its initial report when the information could assist FDA
159 in investigating an adverse event. If additional information is not obtainable, the outsourcing
160 facility should maintain records of the steps that were taken to attempt to seek the additional
161 information.¹⁹
162

163 An outsourcing facility must submit a follow-up report within 15 calendar days of receipt of new
164 information about the adverse event, or as requested by FDA.²⁰
165

166 1. *Identifiable Patient*
167

168 To have an identifiable patient, there should be enough information to indicate the existence of a
169 specific patient. One or more of the following would qualify a patient as identifiable:
170

- 171 • Age or age category (e.g., adolescent, adult, elderly)
- 172 • Gender
- 173 • Initials
- 174 • Date of birth
- 175 • Name
- 176 • Patient identification number
177

178 A report stating that “an elderly woman had anaphylaxis” or “a young man experienced
179 anaphylaxis” would be sufficient. If a report refers to groups of unknown size, such as “some”
180 or “a few” college students had anaphylaxis, the outsourcing facility should follow up to find out

¹⁷ See 21 CFR 310.305(c)(1)(i).

¹⁸ See 21 CFR 310.305(c)(2).

¹⁹ Id.

²⁰ Id.

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181 how many students were involved and submit a separate report to FDA for each student, because
182 each is considered to be an identifiable patient. The outsourcing facility should distinguish each
183 identifiable patient so that it is clear that each report is not a duplicate report of a single adverse
184 event.

185

186 Patients should not be identified by name or address when reporting to FDA. Instead, the
187 outsourcing facility should assign a unique code number for each patient.²¹

188

189 2. *Identifiable Reporter*

190

191 A reporter is a person who initially notifies the outsourcing facility about an adverse event. An
192 initial reporter can be a patient, consumer, family member, doctor, pharmacist, other health care
193 professional, or other individual. The outsourcing facility should obtain, if possible, sufficient
194 information to indicate that the reporter is an identifiable person who purports to have knowledge
195 about the patient, adverse event, and drug involved. One or more of the following would qualify
196 a reporter as identifiable:

197

- 198 • A personal identifier (e.g., name)
- 199 • A professional identifier (e.g., doctor, nurse, pharmacist)
- 200 • Contact information (e.g., e-mail address, phone number)

201

202 When possible, the outsourcing facility should attempt to obtain the initial reporter's contact
203 information so that the outsourcing facility and/or FDA can conduct follow-up investigations. If
204 an identifiable reporter provides contact information, but requests that the outsourcing facility
205 not forward this information to FDA, the outsourcing facility can submit a report to FDA without
206 specifically identifying the reporter by filling out the *initial reporter identity fields* on Form FDA
207 3500A with a statement such as "Requested Anonymity."

208

209 If an adverse event is reported anonymously to an outsourcing facility, the outsourcing facility
210 should note when submitting the report to FDA that the initial reporter is anonymous (section E1
211 of the Form FDA 3500A).

212

213 3. *Suspect Drug*

214

215 A *suspect drug product* is one that the initial reporter suspected was associated with the adverse
216 event.

217

218 For reporting purposes, an adverse event report should describe the known product attributes
219 (e.g., active ingredient(s), dosage form, strength, color, lot number). If an adverse event involves
220 multiple suspect drug products that are compounded by the same outsourcing facility, the
221 outsourcing facility should submit only one report that notes the drug product considered most

²¹ See 21 CFR 310.305(e).

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222 suspect by the reporter. If the reporter views each drug product as equally suspect, the
223 outsourcing facility should submit only one report that lists all of the drug products as suspect.
224 In all cases, including those where not all of the drug products were made by the outsourcing
225 facility, the report would include information on all suspect drug products.

226

227 4. *Serious Adverse Event*

228

229 As described above, outsourcing facilities must report an unexpected adverse event to FDA
230 that results in one or more of the following patient outcomes:

231

- 232 • Death,
- 233 • A life-threatening adverse drug experience,
- 234 • Inpatient hospitalization or prolongation of existing hospitalization,
- 235 • A persistent or significant disability or incapacity, or
- 236 • A congenital anomaly or birth defect.²²

237

238 Inpatient hospitalization includes initial admission to the hospital on an inpatient basis (even if
239 released the same day).

240

241 Important medical events that may not result in death, be life-threatening, or require
242 hospitalization may be considered a serious adverse drug experience if, when based upon
243 appropriate medical judgment, they may jeopardize the patient or subject and may require
244 medical or surgical intervention to prevent one of the outcomes listed above.

245

246 The outsourcing facility must report the adverse event to FDA if it is serious and unexpected.
247 For reporting purposes, an adverse event should be described in terms of signs (including
248 abnormal laboratory findings, if appropriate), symptoms, or disease diagnosis (including any
249 colloquial descriptions obtained), if available.

250

251 As part of the adverse event report, we encourage, as appropriate, attachment of the following:
252 (1) hospital discharge summaries, (2) autopsy reports/death certificates, (3) relevant laboratory
253 data, and (4) other critical clinical data. In the case of a death, outsourcing facilities should
254 also provide any available information on the event(s) that led to the death.

255

256 **C. How to Report Adverse Events**

257

258 Outsourcing facilities must report adverse events using Form FDA 3500A or an alternate method
259 in accordance with 21 CFR 310.305(d) and should submit the report to FDA as described here.
260 FDA is currently modifying its process to specifically identify reports from outsourcing facilities
261 and drug products compounded by outsourcing facilities. Until those actions are completed,
262 FDA will not be able to effectively accept adverse event reports from outsourcing facilities

²² See 21 CFR 310.305(b).

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263 through the electronic system, but FDA will issue additional guidance when the electronic
264 interface is ready to accept these reports.

265

266 1. *Obtaining Form FDA 3500A*

267

268 Outsourcing facilities can access paper copies of Form FDA 3500A as follows:

269

- 270 • Download and print the Form FDA 3500A and instructions from the Internet at
271 <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf>
272
- 273 • Request a paper copy of Form FDA 3500A and instructions from CDER’s Division of
274 Drug Information:

275

276 By e-mail: druginfo@fda.hhs.gov

277

278 By phone: 1-800-FDA-1088
279 1-888-INFO-FDA
280 1-888-463-6332 or (301) 796-3400

281

282 By mail: Division of Drug Information
283 10903 New Hampshire Avenue
284 WO51-2201
285 Silver Spring, MD 20993-0002

286

287 2. *How to Submit Adverse Event Reports*

288

289 Until FDA modifies its adverse event collection database to more effectively accommodate
290 direct electronic submissions from outsourcing facilities, adverse event reports and follow-up
291 reports for compounded drug products should be provided in hard copy.²³ In accordance with
292 section 310.305(c), outsourcing facilities must submit a copy of Form FDA 3500A to:

293

294 Central Document Room
295 Center for Drug Evaluation and Research
296 Food and Drug Administration
297 5901-B Ammendale Rd.
298 Beltsville, MD 20705-1266

299

300 3. *What Should Be Included*

301

²³ FDA is currently modifying its database to include fields specifically identifying reports from outsourcing facilities and drug products compounded by outsourcing facilities. As noted above, on June 10, 2014, FDA issued a final rule requiring that, among other things, postmarketing safety reports under 21 CFR 310.305 be submitted to FDA in electronic format (79 FR 33072). This rule is effective as of June 10, 2015.

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302 Outsourcing facilities must indicate whether the report is a 15-day Alert report or a 15-day Alert
303 report-follow-up²⁴ and should include the following header on the first page of a cover letter
304 accompanying each Form FDA 3500A:

305

306 *Adverse event report submitted by human drug compounding outsourcing facility (503B)*

307

308 If the compounded drug product contains multiple components (e.g., excipients, drug substances,
309 finished dosage forms), the outsourcing facility should list each component and its manufacturer,
310 if known, in section C10 of Form FDA 3500A. The outsourcing facility should also list in
311 section C10, in addition to the components of the compounded drug and each component's
312 manufacturer, any other medical product(s) the patient was taking at the time he or she
313 experienced the adverse event and the manufacturer of that product(s) (i.e., any concomitant
314 medical products).

315

316 As part of each adverse event report, outsourcing facilities must submit a copy of the current
317 labeling for the compounded drug product that is the subject of the report.²⁵

318

319 When submitting a follow-up report under 21 CFR 310.305(c)(2), the report should be assigned
320 the same manufacturer report number that appears in section G9 of the initially submitted Form
321 FDA 3500A.

322

D. Inspection of Adverse Event Reporting

323

324 Under section 503B(b)(4) of the FD&C Act, outsourcing facilities are subject to inspection
325 pursuant to section 704 of the FD&C Act and are not eligible for the exemption under section
326 704(a)(2)(A) of the FD&C Act.

327

328 As part of its inspections of outsourcing facilities, FDA may review adverse event information
329 received by the outsourcing facility.²⁶ FDA may also review whether the outsourcing facility has
330 developed and implemented written processes for the surveillance, receipt, evaluation, and
331

²⁴ 21 CFR 310.305(c)(4).

²⁵ See section 21 CFR 310.305(c)(1)(i).

²⁶ See section 21 CFR 310.305(f)(3).

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332 reporting of adverse events for the drug products it compounds as described in 21 CFR
333 310.305(a) and 211.198.²⁷

334

335 **E. Recordkeeping**

336

337 Under section 310.305, all entities subject to the regulation must maintain for 10 years the
338 records of all adverse events required to be reported under this section, including raw data and
339 any correspondence relating to the adverse event, and allow FDA access to review, copy, and
340 verify these records, in accordance with 21 CFR 310.305(f). In addition, the outsourcing facility
341 should maintain records of its efforts to obtain the four data elements discussed in section III.B.
342 for each individual case report.

²⁷ Outsourcing facilities are subject to current good manufacturing practice (CGMP) requirements. Pending the development of further regulations, FDA expects outsourcing facilities, among other things, to comply with the CGMP requirements in 21 CFR 211.198, which is a companion to 21 CFR 310.305. This section requires that “[w]ritten procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed,” and further requires that these procedures must include “provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience which is required to be reported to the Food and Drug Administration in accordance with [section] 310.305 ... of this chapter.” See FDA’s guidance for industry, *Current Good Manufacturing Practice—Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM403496.pdf>.

Attachment 3



California State Board of Pharmacy

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

May 15, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: COMMENTS OF THE CALIFORNIA STATE BOARD OF PHARMACY
Docket No. FDA-2014-N-1459
*Draft MOU Addressing Certain Distributions of Compounded Human Drug Products
Between the State of [Insert State] and the U.S. Food and Drug Administration*

To Whom It May Concern:

I write on behalf of the California State Board of Pharmacy (Board). We are pleased to have this opportunity to submit comments on Docket No. FDA-2014-N-1459-0001: "Draft Memorandum of Understanding Addressing Certain Distributions of Compounded Human Drug Products Between the State of [Insert State] and the U.S. Food and Drug Administration." We will be brief. We understand the origin of the Draft MOU in the statutory language of Section 503A, as well as the intent to promote uniformity across the different states. However, we are concerned about some of the language and the provisions in the Draft MOU.

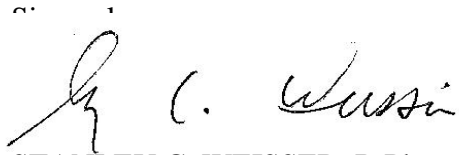
For instance, as an initial matter, the Draft MOU contemplates that physicians will be engaged in compounding. Under California law, however, only a licensed pharmacist has the authority to do or supervise compounding, and only in a licensed pharmacy. We would ask for a modification specific to California that would recognize this state-law limitation.

We are also concerned about the one-sided nature of the Draft MOU, which specifies the investigatory, enforcement, reporting, and record-keeping requirements applicable to the states, but contains no equivalent provisions calling for reciprocal obligations for the FDA. If we are going to specify the enforcement and investigatory responsibilities of the states, why not also spell out the equivalent responsibilities of the FDA or other federal agencies? Likewise, the Draft MOU places limitations on the conditions for FDA sharing of information, and/or on the information that may be shared, but places no such limits on the submissions *required* of states. The "Period of Agreement" clause(s) are similarly non-mutual, in that VI.b. permits FDA to terminate based on non-compliance by a state, but does not give the state an equivalent right. (As a drafting matter, it is also unclear whether the termination provision in VI.b. would in any event be subsumed by the termination provision in VI.a., which appears to give either party the right to termination with 30 days' notice, without requiring any cause for termination.)

Additionally, because the MOU deals only with human drugs, it is not clear how the MOU will affect pharmacy/503A compounding of veterinary drugs or human drugs that will be administered to animals. Will such products be included in either the numerator or denominator?

Finally, we question the establishment and application of the 5% and 30% thresholds for interstate shipment of compounded medications under Section 503A (without a signed MOU and with a signed MOU), not because we object to these percentages, *per se*, but because there is no explanation of how or why these percentages were chosen, nor is it clear how these percentages would be enforced. We are given no explanation for why 5% or 30% is an ideal percentage (or a percentage above which the risk outweighs the reward of permitting this practice). Nor does the MOU clearly specify how the numerator and denominator for calculating these percentages will be populated. And although the Draft MOU specifies that states will be required to report to the FDA on pharmacies that are exceeding the 30% figure, the Draft MOU does not specify whether enforcement of that limitation will be an FDA responsibility, a state responsibility, or shared. Nor does the Draft MOU identify any enforcement mechanism for the 5% threshold where the state has not signed the Draft MOU. That may need to be the subject of a different rulemaking.

Thank you for your attention to these matters, and for your willingness to hear our input. We look forward to continuing to work together to secure the nation's drug supply. Please feel free to contact the Board at any time if we can be of assistance. The best route for contact is via Executive Officer Virginia Herold, at (916) 574-7911, or Virginia.Herold@dca.ca.gov.



STANLEY C. WEISSER, R.Ph.
President, California State Board of Pharmacy

DRAFT MEMORANDUM OF UNDERSTANDING ADDRESSING CERTAIN
DISTRIBUTIONS OF COMPOUNDED HUMAN DRUG PRODUCTS
BETWEEN THE STATE OF [insert STATE] AND
THE U.S. FOOD AND DRUG ADMINISTRATION

I. PURPOSE

This Memorandum of Understanding (MOU) establishes an agreement between the State of [insert State] and the U.S. Food and Drug Administration (FDA) regarding the distribution of inordinate amounts of compounded human drug products interstate and the appropriate investigation by the State of [insert State] of complaints relating to compounded human drug products distributed outside such State. This is the MOU provided for by section 503A(b)(3)(B)(i) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 353a), and does not apply to drugs that are compounded by registered outsourcing facilities.

II. BACKGROUND

- a. Section 503A of the FD&C Act describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist or licensed physician to be exempt from three sections of the FD&C Act requiring:
 1. Compliance with current good manufacturing practice (CGMP) (section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B));
 2. Labeling with adequate directions for use (section 502(f)(1) (21 U.S.C. 352(f)(1)); and
 3. FDA approval prior to marketing (section 505 (21 U.S.C. 355)).
- b. To qualify for these exemptions, among other things, a compounded human drug product must meet the condition in section 503A(b)(3)(B) of the FD&C Act, under which the drug product is compounded in a State that:
 1. Has entered into an MOU with FDA that addresses the distribution of inordinate amounts¹ of compounded human drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded human drug products distributed outside such State (section 503A(b)(3)(B)(i)); or

¹The definition of *inordinate amounts* in this MOU is separate and distinct from and should not be used in relation to the term *inordinate amounts* as it is used in section 503A(b)(1)(D) of the FD&C Act (pertaining to compounding a drug product that is essentially a copy of a commercially available drug product).

2. Has not entered into an MOU with FDA and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded human drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician (section 503A(b)(3)(B)(ii)).
- c. Section 503A(b)(3) of the FD&C Act directs FDA to develop a standard MOU for use by the States in complying with section 503A(b)(3)(B)(i). The content of this MOU conforms with the standard MOU developed by FDA for this purpose.

III. SUBSTANCE OF AGREEMENT

- a. Investigation of Complaints Relating to Compounded Human Drug Products Distributed Outside the State
 1. Appropriate agencies of the State of [insert State] will investigate complaints received relating to human drug products compounded by a pharmacist, pharmacy, or physician located in the State of [insert State] and distributed outside the State. Primary responsibility for investigating complaints involving human drug products compounded by a pharmacy or pharmacist will generally lie with the [insert State Board of Pharmacy or other appropriate State agency] and similar responsibility for human drug products compounded by a physician will generally lie with the [insert State Medical Licensing Board or other appropriate State agency], except where State laws otherwise require. The [insert State Board of Pharmacy or other appropriate State agency] and [insert State Medical Licensing Board or other appropriate State agency] will cooperate in investigating any complaints involving overlapping jurisdiction.
 2. Complaints relating to compounded human drug products distributed outside the State that will be investigated include reports received by the State concerning adverse drug experiences, or product quality issues that if left uncorrected could lead to potential public health risks or safety concerns. See Appendix A for definitions of *adverse drug experiences* and *product quality issues*.
 3. Any investigations performed by the State of [insert State] under this MOU will include, but are not limited to (1) determination of whether there is a potential public health risk or safety concern associated with the compounded human drug product; and (2) confirmation that any risk or safety concern associated with the product is adequately contained (i.e., there is no ongoing risk to the public).

4. Based on findings from an investigation of a complaint about compounded human drug products distributed outside the State, if the complaint is found to be valid, the State of [insert State], in accordance with State law, will take appropriate action to ensure that the relevant compounding pharmacist, pharmacy, or physician determines the root cause of the problem that is the subject of the complaint and undertakes sufficient corrective action to eliminate any identified public health risk relating to the complaint, including the risk that future similar complaints may occur.
 5. The State of [insert State] will notify FDA by sending an e-mail to StateMOU@fda.hhs.gov (see section III.c.1 of this MOU) within 72 hours of receiving any complaint relating to a compounded human drug product distributed outside the State involving a public health risk or immediate safety concern, such as a report of a serious adverse drug experience or serious product quality issue. The notification will include the State's initial assessment of the validity of the complaint relating to a compounded human drug product distributed outside the State, as well as a description of any actions the State has taken or plans to take to address such complaints. See Appendix A for definitions of *serious adverse drug experience* and *serious product quality issue*.
 6. The State of [insert State] will maintain records of the complaint, the investigation of the complaint, and any response to or action taken as a result of the complaint, beginning when the State receives notice of the complaint. The State will maintain these records for at least 3 years. The 3-year period begins on the date of final action on a complaint, or the date of a decision that the complaint requires no action.
- b. Distribution of Inordinate Amounts of Compounded Human Drug Products Interstate
1. The State of [insert State] will review compounding records during inspections of compounding pharmacies to identify whether the compounding pharmacy, or the compounding pharmacist or physician, is distributing inordinate amounts of compounded human drug products interstate. See Appendix A for the definition of *distribution*.
 2. The State of [insert State] will notify FDA by sending an e-mail to StateMOU@fda.hhs.gov (see section III.c.1 of this MOU) within 7 days of identifying a pharmacist, pharmacy, or physician within its jurisdiction that has distributed inordinate amounts of compounded human drug products interstate.
 3. The State of [insert State] will take action regarding any pharmacy, pharmacist, or physician that distributes inordinate amounts of

compounded human drug products interstate. State action may include a warning letter, enforcement action, suspension or revocation of a license, or other action consistent with State law. FDA may also take action regarding any pharmacy, pharmacist, or physician that distributes inordinate amounts of compounded human drug products interstate.

4. For purposes of this MOU, a pharmacist, pharmacy, or physician has distributed an inordinate amount of compounded human drug products interstate if the number of units of compounded human drug products distributed interstate during any calendar month is equal to or greater than 30 percent of the number of units of compounded and non-compounded drug products distributed or dispensed both intrastate and interstate by such pharmacist, pharmacy, or physician during that month. Exception: For purposes of this MOU, FDA does not intend to include, in the consideration of inordinate amounts, prescriptions dispensed to a patient (or patient's agent), if the patient (or patient's agent) to whom the drug is dispensed carries the drug across State lines after it has been dispensed to the patient (or patient's agent) at the facility in which the drug was compounded.

c. Submission and Disclosure of Information

1. When submitting information to StateMOU@fda.hhs.gov regarding complaints relating to compounded drug products distributed outside the State or distribution of inordinate amounts of drugs interstate, the following minimum information will be included:
 - Name and contact information of the complainant, in the case of a complaint;
 - Name and address of the pharmacist/pharmacy/physician that is the subject of the complaint or distribution in inordinate amounts;
 - Description of the complaint, or description of the evidence indicating that the pharmacist/pharmacy/physician has distributed inordinate amounts of compounded human drug products interstate, including a description of any compounded drug product that is the subject of the complaint or distribution;
 - State's initial assessment of the validity of the complaint relating to a compounded human drug product distributed outside the State; and

- Description and date of any actions the State has taken to address the complaint or the distribution of inordinate amounts of compounded human drug products interstate.
2. The parties to this MOU will share information consistent with applicable statutes and regulations. The parties recognize that a separate agreement under 21 CFR 20.88 or commissioning of officials under 21 CFR 20.84 may be necessary before FDA can share information that is protected from public disclosure. Such an agreement, or commissioning terms, will govern FDA's sharing of the following types of information:
- confidential commercial information, such as the information that would be protected from public disclosure under Exemption 4 of the Freedom of Information Act (FOIA) (5 U.S.C. 552(b)(4));
 - personal privacy information, such as information that would be protected from public disclosure under Exemption 6 or 7(C) of the FOIA (5 U.S.C. 552(b)(6) and(7)(C)); or
 - information that is otherwise protected from public disclosure by Federal statutes and their implementing regulations (e.g., Trade Secrets Act (18 U.S.C. 1905)), the Privacy Act (5 U.S.C. 552a), other Freedom of Information Act exemptions not mentioned above (5 U.S.C. 552(b)), the FD&C Act (21 U.S.C. 301 et seq.), the Health Insurance Portability and Accountability Act (Public Law 104-191), and FDA's regulations in parts 20 and 21 (21 CFR parts 20 and 21)).

FDA agrees that information provided to FDA by the State of [insert State] will only be disclosed consistent with applicable federal law and regulations governing the disclosure of such information, including, but not limited to, the FOIA (5 U.S.C. 552(b)), the FD&C Act (21 U.S.C. 301 et seq.), 21 U.S.C. 331(j), 21 U.S.C. 360j(c), the Trade Secrets Act (18 U.S.C. 1905), FDA's regulations in 21 CFR parts 20 and 21, and other pertinent laws and regulations.

IV. ENFORCEMENT AUTHORITIES AND LEGAL STATUS OF AGREEMENT

The parties to this MOU recognize that FDA and the State of [insert State] retain the statutory and regulatory authorities provided by the FD&C Act, other Federal statutes and attendant regulations, and State statutes and regulations. The parties also recognize that this agreement does not restrict FDA or any other Federal agency from taking enforcement action, when appropriate, to ensure compliance with Federal statutes, including the FD&C Act and attendant regulations, or

prevent the State of [insert State] from taking enforcement action, as appropriate, to ensure compliance with applicable State statutes and regulations. This MOU does not create or confer any rights for or on any person. By signing this MOU, the State of [insert State] affirms that it now possesses and will maintain, at the discretion of the State legislature, the legal authority (under State statutes and/or regulations) and the resources necessary to effectively carry out all aspects of this MOU. If State law changes such that the State no longer has the legal authority or resources necessary to effectively carry out all aspects of this MOU, the State will notify FDA.

V. NAME AND ADDRESS OF PARTICIPATING AGENCIES

U.S. Food and Drug Administration
Center of Drug Evaluation and Research
Office of Compliance
Office of Unapproved Drugs and Labeling Compliance
10903 New Hampshire Avenue
Bldg. 51, Suite 5100
Silver Spring, MD 20993-0002
Telephone: (301) 796-3110
E-mail: StateMOU@fda.hhs.gov

[State]
TBD

Upon signing the MOU, each party must designate one or more liaisons to act as points of contact. Each party may designate new liaisons at any time by notifying the other party's liaison(s) in writing. If, at any time, an individual designated as a liaison under this agreement becomes unavailable to fulfill those functions, the parties will name a new liaison within 2 weeks and notify the other party's liaison(s).

VI. PERIOD OF AGREEMENT

- a. When accepted by both parties, this MOU will be effective from the date of the last signature and will continue until terminated by either party. It may be terminated in writing by either party, upon a 30-day notice of termination. Notice of termination will be sent to the address listed in section V of this MOU.
- b. If the State does not adhere to the provisions of this MOU, including conducting an investigation of complaints related to compounded human drug products distributed outside the State, the MOU may be terminated upon 30-days' notice of termination.

In case of termination, FDA will post a notice of the termination on its Web site and the State will notify all pharmacists, pharmacies, and physicians within the

State of the termination and advise them that as of 30 days from the date of the posting of the termination notice, compounded human drug products may be distributed (or caused to be distributed) out of the State only in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by the licensed pharmacist, licensed pharmacy, or licensed physician (section 503A(b)(3)(B)(ii) of the FD&C Act).

VII. APPROVALS

APPROVED AND ACCEPTED FOR THE U.S. FOOD AND DRUG ADMINISTRATION	APPROVED AND ACCEPTED FOR THE STATE OF [insert State]
By (Type Name)	By (Type Name)
Title	Title
Date	Date

Appendix A. Definition of Terms Used in the MOU

- **Adverse Drug Experience:** Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: an adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose, whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action (21 CFR 310.305(b)).
- **Distribution:** *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.

Note: To qualify for the exemptions under section 503A, a compounding must obtain a prescription for an individually identified patient (section 503A(a) of the FD&C Act). This MOU will not alter this condition.

- **Product Quality Issue:** Information concerning (1) any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or (2) any bacteriological contamination; any significant chemical, physical, or other change or deterioration in the distributed drug product; or any failure of one or more distributed batches of the drug product to meet the applicable specifications (21 CFR 314.81(b)(1)). Contamination in general, including but not limited to mold, fungal, bacterial, or particulate contamination, is a product quality issue.
- **Serious Adverse Drug Experience:** Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 310.305(b)).
- **Serious Product Quality Issue:** Any product quality issue that may have the potential to cause a serious adverse drug experience (e.g., possible contamination, superpotent product).

Attachment 4

Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing 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 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 Gail Bormel, CDER Office of Unapproved Drugs and Labeling Compliance (OUDLC), 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**

**February 2015
Compliance**

Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing 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
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: 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/OU DLC

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1 **Repackaging of Certain Human Drug Products by Pharmacies and**
2 **Outsourcing Facilities¹**
3 **Guidance for Industry²**
4

5
6 This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current
7 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
8 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of
9 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
10 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
11 the appropriate number listed on the title page of this guidance.
12

13
14
15 **I. INTRODUCTION AND SCOPE**
16

17 This guidance sets forth the Food and Drug Administration’s (“FDA” or “the Agency”) policy
18 regarding repackaging by state-licensed pharmacies, Federal facilities, and facilities that register
19 with FDA as outsourcing facilities under section 503B of the Federal Food, Drug, and Cosmetic
20 Act (FD&C Act or the Act). This guidance describes the conditions under which FDA does not
21 intend to take action for violations of sections 505, 502(f)(1), and where specified, section
22 501(a)(2)(B) of the Act, when a state-licensed pharmacy, a Federal facility, or an outsourcing
23 facility repackages human prescription drug products.
24

25 This guidance **does not address** the following:

- 26 • Biological products that are subject to licensure under section 351 of the Public Health
27 Service (PHS) Act. The repackaging of biological products subject to licensure under
28 section 351 is addressed in a separate draft guidance document.³

¹ “Outsourcing facility” refers to a facility that meets the definition of an outsourcing facility under section 503B(d)(4) of the Federal Food, Drug, and Cosmetic Act.

² This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research (CDER) and in consultation with the Office of Regulatory Affairs at the Food and Drug Administration.

³ FDA has issued a draft guidance, titled *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved Biologics License Application*. Once finalized, that guidance will represent FDA’s thinking on this topic.

All FDA guidances are available on the Agency’s guidance website at <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm>. FDA updates guidances regularly. To ensure that you have the most recent version, please check this web page.

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- 29 • Repackaging drug products for use in animals. FDA will consider addressing this issue
30 in a separate guidance document.
- 31 • Repackaging by entities that are not state-licensed pharmacies, Federal facilities, or
32 outsourcing facilities. See additional information in section III.A. of this draft guidance
33 document.
- 34 • Removing a drug product from the original container at the point of care for immediate
35 administration to a single patient after receipt of a patient-specific prescription or order
36 for that patient (e.g., drawing up a syringe to administer directly to the patient). FDA
37 does not consider this to be “repackaging,” for purposes of this guidance document.
- 38 • Upon receipt of an individual patient-specific prescription, a licensed pharmacy removing
39 from one container the quantity of solid oral dosage form drug products necessary to fill
40 the prescription and placing it in a smaller container to dispense directly to its customer.

41
42 FDA’s guidance documents, including this guidance, do not establish legally enforceable
43 responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should
44 be viewed only as recommendations, unless specific regulatory or statutory requirements are
45 cited. The use of the word *should* in Agency guidances means that something is suggested or
46 recommended, but not required.

47 48 **II. BACKGROUND**

49 50 **A. Repackaging, Generally**

51
52 FDA regards repackaging as the act of taking a finished drug product from the container in
53 which it was distributed by the original manufacturer and placing it into a different container
54 without further manipulation of the drug. Repackaging also includes the act of placing the
55 contents of multiple containers (e.g., vials) of the same finished drug product into one container,
56 as long as the container does not include other ingredients. If a drug is manipulated in any other
57 way, including if the drug is reconstituted, diluted, mixed, or combined with another ingredient,
58 that act is not considered repackaging.

59
60 Repackaging is performed by a range of entities, including facilities that specialize in
61 repackaging drug products, and pharmacies, including pharmacies in hospitals and health
62 systems. FDA is aware that repackaging is done for a variety of reasons including: to meet the
63 needs of specific groups of patients (e.g., pediatric patients or ophthalmic patients who require
64 smaller doses of approved sterile drug products that may not be available commercially); to
65 reduce medication errors associated with drawing up a dose from a vial at the point of patient
66 care; to reduce the availability of drug products of abuse when controlled substances are left over
67 in a vial after a dose is drawn out; to provide a particular sized container to fit into a particular
68 device to administer the drug (such as a particular pain medication pump); for convenience for
69 the practitioner administering an injection to a patient; and in some cases to reduce cost. Some
70 repackagers repack both sterile and non-sterile drug products. For example, tablets and
71 capsules are repackaged from large containers into smaller containers or blister packs, and
72 creams and lotions are sometimes purchased in bulk and repackaged into smaller tubes or
73 containers.

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75 As part of the drug application review and approval process, FDA evaluates the container closure
76 system and the packaging into which the drug will be placed, as well as the conditions under
77 which the drug will be packaged. The container closure system and packaging can affect the
78 quality of the drug product when it is on the market. In particular, during the approval process
79 FDA reviews whether the container closure system and the packaging are appropriate for
80 maintaining the stability of the drug product through its expiration date, as long as the container
81 and package are not breached, and the drug is stored according to the conditions specified in the
82 application. For drug products required to be sterile, FDA also considers whether the container
83 closure system and packaging are adequate to ensure that the drug product will remain sterile
84 until its expiration date, as long as the container closure is not breached and the drug product is
85 stored appropriately.

86
87 When a drug product is repackaged, its characteristics may change in ways that have not been
88 evaluated during the FDA approval process and that could affect the safety and efficacy of the
89 drug product. Improper repackaging of drug products can cause serious adverse events. Of
90 particular concern is repackaging of sterile drug products, which are susceptible to contamination
91 and degradation. For example, failure to properly manipulate sterile drug products under
92 appropriate aseptic conditions could introduce contaminants that could cause serious patient
93 injury or death. Repackaging practices that conflict with approved product labeling could result
94 in drug product degradation and adverse events associated with impurities in the product or lack
95 of efficacy because the active ingredient has deteriorated.

B. Regulatory Framework for Repackaging

96
97
98
99 Repackaged drug products are generally not exempt from any of the provisions of the FD&C Act
100 related to the production of drugs. For example, repackaged drug products are generally subject
101 to the premarket approval, misbranding, and adulteration provisions of the FD&C Act, including
102 section 505 (concerning new drug applications),⁴ section 502(f)(1) (concerning labeling with
103 adequate directions for use), and section 501(a)(2)(B) (concerning current good manufacturing
104 practice (CGMP)).

105
106 Drugs that are repackaged are not subject to sections 503A and 503B of the FD&C Act.⁵
107 Therefore, drug products repackaged by state-licensed pharmacies, Federal facilities, or
108 outsourcing facilities are not eligible for the exemptions provided under those sections. In this

⁴ But see *U.S. v. Kaybel*, 430 F.2d 1346 (3d Cir. 1970) (holding that repackaging of approved Enovid (estrogen) tablets from large bottles into small bottles did not require pre-approval under section 505 of the FD&C Act).

⁵ Section 503A of the FD&C Act exempts compounded drug products from sections 505, 502(f)(1), and 501(a)(2)(B) of the FD&C Act provided certain conditions are met, including that the drug product is compounded pursuant to a prescription for an individually identified patient from a licensed practitioner. The Drug Quality and Security Act added a new section 503B to the FD&C Act. Under section 503B(b), a compounder can register as an outsourcing facility with FDA. Drug products compounded under the direct supervision of a licensed pharmacist in an outsourcing facility can qualify for exemptions from the FDA approval requirements in section 505 of the FD&C Act and the requirement to label drug products with adequate directions for use under section 502(f)(1) of the FD&C Act if the conditions in section 503B are met. Drug products compounded in outsourcing facilities are not exempt from the CGMP requirements of section 501(a)(2)(B).

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109 guidance, FDA describes the conditions under which it does not intend to take action regarding
110 violations of certain requirements of the FD&C Act, in the context of drug repackaging.

111

C. Hospital and Health System⁶ Repackaging of Drugs In Shortage For Use in the Health System (Section 506F of the FD&C Act)

114

115 The Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law in
116 July, 2012, added section 506F to the FD&C Act. This section exempts certain hospitals within
117 a health system from registration requirements in section 510 of the Act provided certain
118 conditions are met, including that the drugs are, or have recently been, listed on FDA’s drug
119 shortage list⁷ and are repackaged for the health system. Section 506F of the FD&C Act defines
120 “repackaging,” for purposes of that section only, as “divid[ing] the volume of a drug into smaller
121 amounts in order to—(A) extend the supply of a drug in response to the placement of the drug on
122 a drug shortage list under section 506E; and (B) facilitate access to the drug by hospitals within
123 the same health system.”

124

125 Section 506F of the FD&C Act has a termination clause that states “This section [506F] shall not
126 apply on or after the date on which the Secretary issues final guidance that clarifies the policy of
127 the Food and Drug Administration regarding hospital pharmacies repackaging and safely
128 transferring repackaged drugs to other hospitals within the same health system during a drug
129 shortage.”⁸ These issues are addressed and clarified by this guidance and the guidance on
130 *Mixing, Diluting, or Repackaging Biological Products Outside the Scope of an Approved*
131 *Biologics License Application*. Therefore, when these guidances become final, section 506F of
132 the FD&C Act will no longer apply.

133

III. POLICY

134

A. General Policy

135

136 As discussed above, repackaged drug products are generally subject to the adulteration,
137 misbranding, and approval provisions of the FD&C Act.⁹ FDA does not intend to take action for
138 violations of sections 505 and 502(f)(1) if a state-licensed pharmacy, a Federal facility, or an
139
140

⁶ For purposes of this guidance, the term “*health system*” refers to a collection of hospitals that are owned and operated by the same entity and that share access to databases with drug order information for their patients.

⁷ See section 506F(b) (providing that the exemption may be available if, among other factors, the drug is repackaged (1) during any period in which the drug is listed on the drug shortage list under section 506E; or (2) during the 60-day period following any period described in paragraph (1)).

⁸ See section 506F(d) of the FD&C Act.

⁹ As described in section II.B., repackaged drug products are generally not exempt from any of the provisions of the FD&C Act related to the production of drugs. Therefore, drug products that do not meet the conditions in this guidance, including drug products repackaged by entities that are not state-licensed pharmacies, Federal facilities, or outsourcing facilities, generally must comply with requirements in the FD&C Act and FDA regulations applicable to drug products including, but not limited to, CGMP and new drug approval requirements.

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141 outsourcing facility repackages drug products in accordance with the conditions described below,
142 and any applicable requirements.¹⁰ In addition, FDA does not intend to take action for violations
143 of section 501(a)(2)(B) of the FD&C Act if the drug product is repackaged by a state-licensed
144 pharmacy or a Federal facility in accordance with the conditions described below, and any
145 applicable requirements.

146

147 The conditions referred to in the preceding paragraph are as follows:

148

149 1. The drug that is being repackaged is a prescription drug product approved under
150 section 505 of the FD&C Act, except as provided in section III.B of this guidance
151 regarding repackaging unapproved drug products that appear on FDA’s drug shortage
152 list under section 506E.

153

154 2. The drug product is repackaged in a state-licensed pharmacy, a Federal facility, or an
155 outsourcing facility.

156

157 3. If the drug product is repackaged in a state-licensed pharmacy or a Federal facility
158 (but not an outsourcing facility), it is repackaged and distributed¹¹ after (a) the receipt
159 of a valid prescription for an identified, individual patient directly from the
160 prescribing practitioner, patient, or patient’s agent; or (b) a written order in a patient’s
161 chart in a health care setting, unless it is repackaged (but not distributed) in advance
162 of receipt of such a prescription or a written order in a patient’s chart in a quantity
163 that does not exceed the amount of drug product that the state-licensed pharmacy or
164 the Federal facility repackaged pursuant to patient-specific prescriptions or written
165 orders in a previous, consecutive 14-day period, and based on a history of receipt of
166 prescriptions or written orders over a consecutive 14-day period for such repackaged
167 drug products.

168

169 4. The drug product is repackaged by or under the direct supervision of a licensed
170 pharmacist.

171

172 5. Except as provided below for a single-dose vial, the drug product is repackaged in a
173 way that does not conflict with approved drug product labeling.¹²

174

175 For a single-dose vial that is repackaged into multiple units, the drug product is
176 repackaged in a way that does not conflict with the approved labeling, except for the

¹⁰ Applicable requirements include, for example, the requirement that manufacturers not adulterate a drug product by preparing, packing, or holding the drug product under insanitary conditions. See section 501(a)(2)(A) of the FD&C Act.

¹¹ Distribution means that the repackaged drug product has left the facility in which it was repackaged.

¹² For example, if the approved labeling contains instructions for handling or storage of the product, the repackaging is done in accordance with those instructions. Otherwise, it would be considered to be in conflict with the approved labeling.

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177 statements designating the product as a single dose or single use product, and related
178 language (e.g., discard remaining contents).¹³

179
180 6. The repackaged drug product is assigned a beyond-use-date (BUD)¹⁴ as described below:

181
182 a. **FDA-approved drug product with a specified in-use time:** If the drug product
183 being repackaged is an FDA-approved drug product that specifies in the labeling a
184 time within which the opened product is to be used (an “in-use” time), the repackaged
185 drug product is assigned a BUD (1) that is established in accordance with the in-use
186 time on the drug product being repackaged; or (2) that is the expiration date on the
187 drug product being repackaged, whichever is shorter.¹⁵

188
189 b. **FDA-approved drug product without an in-use time or unapproved drug**
190 **product:** If the drug product being repackaged is an FDA-approved drug product
191 whose labeling does not specify an in-use time, or if it is an unapproved drug product
192 on the FDA drug shortage list (which does not have an in-use time reviewed by FDA
193 as part of the drug approval process), the repackaged drug product is assigned a BUD
194 (1) that is established in accordance with the time described in (i) or (ii) below, as
195 applicable, or (2) that is the expiration date on the drug product being repackaged,
196 whichever is shorter.¹⁶

197
198 i. **Sterile Drug Products:** The repackaged drug product is assigned a BUD no
199 longer than the following, even if the time until the expiration date on the drug
200 product being repackaged is longer:

201
202 1. **If repackaged in a state-licensed pharmacy or Federal facility,** the
203 repackaged drug product is assigned a BUD that is¹⁷:

¹³ This condition would not be satisfied if a drug product repackaged from a single-dose vial is repackaged in a way that conflicts with other language in the approved labeling (e.g., regarding storage conditions).

¹⁴ Unless otherwise indicated, the BUD timeframes in this condition begin from the time in which the container of the original drug product to be repackaged is punctured or otherwise opened.

¹⁵ For example, if an approved drug product that includes a 3-day in-use time and an expiration date of January 15, 2015 on the label is repackaged on January 1, 2015, the applicable BUD for the repackaged drug product would be January 4, 2015, because the labeled in-use time of 3 days is shorter than the time until the labeled expiration date of the drug product (14 days). If the drug product is repackaged on January 14, 2015, the applicable BUD for the repackaged drug product would be January 15, 2015, because the time until the labeled expiration date of the approved drug product is 1 day, which is shorter than the labeled 3-day in-use time.

¹⁶ In other words, if the FDA-approved drug product does not have an in-use time, or the drug product being repackaged is an unapproved drug product, the times in (i) and (ii) are the default BUDs, unless the expiration date on the drug product being repackaged is shorter, in which case the BUD would be the same as the expiration date.

¹⁷ These BUDs are consistent with the BUDs established by USP Chapter <797> for “medium-risk” compounded sterile preparations. Although USP <797> addresses *compounded* sterile preparations, many of the same principles for conditions and practices to assure sterility and stability of compounded drug products, such as the requirement to maintain a sterile environment, engage in appropriate sterile processing techniques, and put appropriate BUDs on the product, also apply to repackaged sterile drug products to help ensure their quality is not compromised during

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- ≤ 30 hours if stored at USP controlled room temperature;
 - ≤ 9 days if stored in a refrigerator; or
 - ≤ 45 days if stored in a solid frozen state between -25°C and -10°C
2. **If repackaged in an outsourcing facility**, the outsourcing facility conducts a sterility test in accordance with CGMP requirements¹⁸ (e.g., using the sterility test described in USP Chapter <71>) and receives passing results before release, and the repackaged drug product is assigned a BUD that is¹⁹:
- Not more than 14 days beyond completion of the sterility test or 28 days from the time of repackaging, whichever is shorter, if stored at USP controlled room temperature or in a refrigerator; or
 - Not more than 45 days beyond completion of the sterility test or 59 days from the time of repackaging, whichever is shorter, if stored in a solid frozen state between -25°C and -10°C²⁰
- ii. **Non-sterile Drug Products:** The BUD for the repackaged drug product is no longer than the expiration date on the original drug product being repackaged.
7. Except with regard to BUDs, which are addressed in condition 6, above:
- a. If the drug product is repackaged in a state-licensed pharmacy or a Federal facility:
 - i. If it is a non-sterile drug product, it is repackaged in accordance with USP Chapter <795>; or

and after the repackaging operation. The BUDs for medium-risk compounded preparations in USP <797> are appropriate for sterile drug products that do not include an “in-use” time and are repackaged by a state-licensed pharmacy or Federal facility because the two activities present comparable risks.

¹⁸ See 21 CFR part 211.

¹⁹ These longer BUDs reflect that outsourcing facilities must comply with CGMP requirements and are subject to FDA inspections on a risk-based schedule. Conditions maintained to comply with CGMP requirements provide greater assurance of the quality of manufacturing operations and the products that are produced at the facility. FDA has issued a draft guidance entitled, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (“Interim CGMP Guidance”). (See <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM403496.pdf>) The Interim CGMP Guidance, when finalized, will describe FDA’s expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until more specific CGMP regulations for outsourcing facilities are promulgated. The BUDs set forth for sterile drug products repackaged by outsourcing facilities in this condition are consistent with the BUDs listed in the Interim CGMP Guidance that are applicable to sterile drug products compounded at outsourcing facilities.

²⁰ The 28-day and 59-day timeframes provide for the 14 days it takes to receive results from the sterility test conducted under USP Chapter <71>.

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- 229 ii. If it is sterile drug product, it is repackaged in accordance with USP
230 Chapter <797>, e.g., a sterile drug product is repackaged in an area
231 with air quality that meets or exceeds ISO Class 5 standards (see USP
232 Chapter <797>, Table 1).
- 233 b. If the drug product is repackaged in an outsourcing facility, repackaging is
234 conducted in accordance with CGMP requirements.
- 235
- 236 8. The drug product that is being repackaged does not appear on a list of drug products
237 that have been withdrawn or removed from the market because they have been found
238 to be unsafe or ineffective. For purposes of this provision, repackagers should refer
239 to the list of drug products in 21 CFR 216.24, developed for use with sections 503A
240 and 503B.
- 241
- 242 9. The drug product is not sold or transferred by an entity other than the entity that
243 repackaged such drug product. For purposes of this condition, a sale or transfer does
244 not include administration of a repackaged drug product in a health care setting.
- 245
- 246 10. The repackaged drug product is distributed only in states in which the facility
247 repackaging the drug product meets all applicable state requirements.
- 248
- 249 11. If the drug product is repackaged by an outsourcing facility:
- 250
- 251 a. The label on the immediate container (primary packaging, e.g., the syringe) of
252 the repackaged product includes the following:
- 253 i. The statement “This drug product was repackaged by [name of
254 outsourcing facility]”
- 255 ii. The address and phone number of the outsourcing facility that
256 repackaged the drug product
- 257 iii. The established name of the original, approved drug product that
258 was repackaged
- 259 iv. The lot or batch number of the repackaged drug product
- 260 v. The dosage form and strength of the repackaged drug product
- 261 vi. A statement of either the quantity or volume of the repackaged
262 drug product, whichever is appropriate
- 263 vii. The date the drug product was repackaged
- 264 viii. The BUD of the repackaged drug product
- 265 ix. Storage and handling instructions for the repackaged drug
266 product
- 267 x. The National Drug Code (NDC) number of the repackaged drug
268 product, if available²¹
- 269 xi. The statement “Not for resale,” and, if the drug product is
270 distributed by an outsourcing facility other than pursuant to a

²¹ The NDC number of the original approved drug product should not be placed on the repackaged drug product.

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- 271 prescription for an individual identified patient, the statement
272 “Office Use Only”
- 273 xii. If included on the label of the FDA-approved drug product from
274 which the drug product is being repackaged, a list of the active
275 and inactive ingredients, unless such information is included on
276 the label for the container from which the individual units are
277 removed, as described below in 11.b.i.
- 278
- 279 b. The label on the container from which the individual units are removed for
280 administration (secondary packaging, e.g., the bag, box, or other package in
281 which the repackaged products are distributed) includes:
- 282 i. The active and inactive ingredients, if the immediate drug
283 product label is too small to include this information
- 284 ii. Directions for use, including, as appropriate, dosage and
285 administration, and the following information to facilitate
286 adverse event reporting: www.fda.gov/medwatch and 1-800-
287 FDA-1088.
- 288
- 289 c. Each repackaged drug product is also accompanied by a copy of the
290 prescribing information that accompanied the original drug product that was
291 repackaged.
- 292
- 293 d. The drug product is included on a report submitted to FDA each June and
294 December identifying the drug products made by the outsourcing facility
295 during the previous 6-month period, and providing the active ingredient(s);
296 source of the active ingredient(s); NDC number of the source ingredient(s), if
297 available; strength of the active ingredient(s) per unit; the dosage form and
298 route of administration; the package description; the number of individual
299 units produced; and the NDC number of the final product, if assigned.²²
- 300
- 301 e. The outsourcing facility reports serious adverse events to FDA that may be
302 associated with its repackaged drug products.
- 303

B. Repackaging Drugs on FDA’s Drug Shortage List

306 This guidance addresses repackaging of prescription drug products, including drug products on
307 FDA’s drug shortage list, by a state-licensed pharmacy, Federal facility, or outsourcing facility,
308 including within a hospital or health system. This guidance also specifically addresses the
309 repackaging of single-dose vials, a practice that is sometimes used to extend the supply of a drug

²² FDA has issued a draft guidance for industry, *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*, which prescribes how human drug compounding facilities are to submit drug product reports to FDA. Once finalized, that guidance will represent the Agency’s current thinking on that topic. Although that guidance addresses reporting of compounded human drug products, outsourcing facilities should follow the same procedure to electronically report the drug products they repackaged.

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310 product that is on the FDA drug shortage list. In addition, the first condition described in section
311 III.A.1 of this guidance provides that the drug product being repackaged is a prescription drug
312 product approved by FDA under section 505 of the FD&C Act. However, with respect to an
313 unapproved drug product that appears on FDA’s drug shortage list, FDA also does not intend to
314 take action for violations of sections 505, 502(f)(1), and, as specified above, section
315 501(a)(2)(B), provided that the state-licensed pharmacy, the Federal facility, or the outsourcing
316 facility (including within a hospital or health system) meets all of the conditions of this guidance,
317 and the repackaged drug product is distributed during any period in which the drug product is
318 listed on the drug shortage list under section 506E of the FD&C Act or during the 30 days
319 following such period. As stated above, this guidance and the guidance on *Mixing, Diluting, or*
320 *Repackaging Biological Products Outside the Scope of an Approved Biologics License*
321 *Application* clarify the Agency’s policy regarding hospital pharmacies repackaging and safely
322 transferring repackaged drug products to other hospitals within the same health system during a
323 drug shortage. Therefore, when these guidances become final, section 506F of the FD&C Act
324 will no longer apply.