
Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act Guidance for Industry

DRAFT GUIDANCE

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

**March 2018
Compounding and Related Documents**

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1 **Evaluation of Bulk Drug Substances Nominated for Use in**
2 **Compounding Under Section 503B of the Federal Food, Drug, and**
3 **Cosmetic Act**
4 **Guidance for Industry¹**
5

6
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
11 for this guidance as listed on the title page.
12

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16 **I. INTRODUCTION AND SCOPE**
17

18 This guidance sets forth FDA’s policy for evaluating bulk drug substances nominated for use in
19 compounding by outsourcing facilities registered under section 503B of the Federal Food, Drug,
20 and Cosmetic Act (FD&C Act) (21 U.S.C. 353b).² Section 503B of the FD&C Act directs FDA
21 to develop a list of bulk drug substances for which there is a clinical need (the 503B Bulks List).
22 Drug products compounded using bulk drug substances on the 503B Bulks List qualify for
23 certain exemptions from the FD&C Act provided the other conditions in section 503B are met.
24 This guidance addresses FDA policies for developing the 503B Bulks List, including the
25 Agency’s interpretation of the phrase *bulk drug substances for which there is a clinical need*, as
26 it is used in section 503B. This guidance also addresses the factors and processes by which the
27 Agency intends to evaluate and list bulk drug substances.³
28

29 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
30 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only

¹ 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.

² This guidance addresses FDA’s evaluation of bulk drug substances nominated by members of the public for use in compounding under section 503B. FDA may also evaluate bulk drug substances for other reasons, including on its own initiative, and in that case expects that its analysis would take into account the factors described in this guidance.

³ FDA previously solicited nominations of bulk drug substances to be considered for the 503B Bulks List and issued the guidance for industry *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* regarding certain interim regulatory policies for outsourcing facilities that compound drug products using bulk drug substances while the 503B Bulks List is being developed. That interim policy remains in effect while FDA evaluates substances for the 503B Bulks List. We update guidances periodically. To make sure you have the most recent version of a guidance, be sure to check the Agency’s guidance website at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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31 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
32 the word *should* in Agency guidances means that something is suggested or recommended, but
33 not required.
34

35

36 **II. BACKGROUND**

37

38 **A. Section 503B of the FD&C Act**

39

40 Section 503B of the FD&C Act describes the conditions that must be satisfied for human drug
41 products compounded by an outsourcing facility to be exempt from the following three sections
42 of the FD&C Act: section 505 (21 U.S.C. 355) (concerning the approval of drugs under new
43 drug applications or abbreviated new drug applications); section 502(f)(1) (21 U.S.C. 352(f)(1))
44 (concerning the labeling of drugs with adequate directions for use); and section 582 (21 U.S.C.
45 360eee-1) (concerning drug supply chain security requirements).⁴
46

47

48 Drug products compounded under the conditions in section 503B are not exempt from current
49 good manufacturing practice (CGMP) requirements in section 501(a)(2)(B) of the FD&C Act.⁵
50 Outsourcing facilities are also subject to FDA inspections according to a risk-based schedule,
51 specific adverse event reporting requirements, and other conditions that help to mitigate the risks
52 of the drug products they compound.⁶ Outsourcing facilities may or may not obtain prescriptions
53 for identified individual patients and can, therefore, distribute compounded drugs to healthcare
54 practitioners for “office stock,” to hold in their offices in advance of patient need.⁷

55

56 One of the conditions that must be met for a drug product compounded by an outsourcing facility
57 to qualify for exemptions under section 503B is that the outsourcing facility may not compound
58 a drug using a bulk drug substance unless (a) the bulk drug substance appears on a list
59 established by the Secretary identifying bulk drug substances for which there is a clinical need,
60 or (b) the drug compounded from such bulk drug substances appears on the drug shortage list in
61 effect under section 506E of the FD&C Act at the time of compounding, distribution, and
62 dispensing.⁸

63

64 For purposes of section 503B, *bulk drug substance* is defined to mean “the same as an active
pharmaceutical ingredient as defined in 21 CFR 207.1(b).”⁹ *Active pharmaceutical ingredient* is

⁴ Section 503B(a) of the FD&C Act.

⁵ Compare Section 503A(a) of the FD&C Act (exempting drugs compounded in accordance with that section) to Section 503B(a) of the Act (not providing the exemption from CGMP requirements).

⁶ Section 503B(b)(4), 503B(b)(5), *passim*.

⁷ Section 503B(d)(4)(C).

⁸ Section 503B(a)(2)(A) of the FD&C Act.

⁹ 21 CFR 207.3.

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65 defined as “any substance that is intended for incorporation into a finished drug product and is
66 intended to furnish pharmacological activity or other direct effect in the diagnosis, cure,
67 mitigation, treatment, or prevention of disease, or to affect the structure or any function of the
68 body,” but the term “does not include intermediates used in the synthesis of the substance.”^{10,11}

69
70 Bulk drug substances used in compounding under section 503B must also meet certain other
71 statutory requirements, including the following: (1) if an applicable monograph exists under the
72 United States Pharmacopeia, National Formulary, or another compendium or pharmacopeia
73 recognized by the Secretary under section 503B, the bulk drug substance must comply with the
74 monograph; (2) the bulk drug substance must be manufactured by an establishment that is
75 registered under section 510 of the FD&C Act; and (3) the bulk drug substance must be
76 accompanied by a valid certificate of analysis.¹²

77

B. Compounding, Generally

78

79
80 Compounded drugs can serve an important role for patients whose clinical needs cannot be met
81 by an FDA-approved drug product, such as patients who have an allergy and need a medication
82 to be made without a certain dye or hospital inpatients who need infusions of a drug combined
83 with a particular diluent. However, they also pose a higher risk to patients than FDA-approved
84 drugs. In 2012, contaminated injectable drug products that a state-licensed compounding
85 pharmacy shipped to patients and health care practitioners across the country caused a fungal
86 meningitis outbreak that resulted in more than 60 deaths and 750 cases of infection.¹³ This was
87 the most serious of a long history of outbreaks and other serious adverse events, including
88 overdoses, associated with contaminated, superpotent, or otherwise poor quality compounded
89 drugs.

90

91 In response to this outbreak, Congress enacted the Drug Quality and Security Act (DQSA),
92 which, among other things, added new section 503B to the FD&C Act and created the new
93 category of compounders known as outsourcing facilities.¹⁴ Drug products compounded by

¹⁰ Section 503B(a)(2) and 21 CFR 207.1.

¹¹ Inactive ingredients are not subject to section 503B(a)(2) of the FD&C Act and will not be included in the 503B Bulks List because they are not included within the definition of a bulk drug substance. Pursuant to section 503B(a)(3), inactive ingredients used in compounding must comply with the standards of an applicable United States Pharmacopeia or National Formulary monograph, if a monograph exists.

¹² Section 503B(a)(2) of the FD&C Act. A compounded drug product only qualifies for the exemptions in section 503B if it is compounded by an outsourcing facility that compounds all its drugs, both sterile and nonsterile, in accordance with all of the conditions of section 503B. Sections 503B(a)(11), (d)(4)(A)(iii). A complete list of the statutory conditions that must be met for a drug product to qualify for the exemptions in section 503B appears in the guidance *For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

¹³ See <http://www.cdc.gov/HAI/outbreaks/meningitis.html>.

¹⁴ See Pub.L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013). Other compounders, which are not the subject of this guidance, are regulated under section 503A of the FD&C Act. These include licensed pharmacists in State-licensed pharmacies or Federal facilities, and licensed physicians, who have not registered an outsourcing facility

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94 outsourcing facilities in accordance with the conditions of section 503B are exempt from FDA
95 drug approval requirements and the requirement that they be labeled with adequate directions for
96 use.¹⁵ Because compounded drug products are not FDA-approved, they have not undergone
97 FDA premarket review for safety, effectiveness, and quality. Although outsourcing facilities
98 must comply with CGMP requirements and are inspected by FDA according to a risk-based
99 schedule, their drug products lack a premarket inspection and finding of manufacturing quality
100 that is part of the drug approval process. Because compounded drug products are subject to a
101 lower regulatory standard than FDA-approved drugs, they should only be used by patients whose
102 medical needs cannot be met by an FDA-approved drug.

C. Compounding Drugs From Bulk Drug Substances

106 Outsourcing facilities sometimes compound drug products using bulk drug substances to meet
107 the medical needs of patients that cannot be met by an approved drug product or by a drug
108 product compounded from an FDA-approved drug product. A patient may need a drug product
109 compounded using the bulk drug substance because the FDA-approved drug that includes the
110 bulk drug substance as a component also includes inactive ingredients or additional active
111 ingredients that are inappropriate for the patient population. For example, certain inactive
112 ingredients that may be appropriate for the route of administration of the FDA-approved drug
113 product may not be appropriate for another route of administration. Similarly, an outsourcing
114 facility might compound a drug product from a bulk drug substance when patients have an
115 allergy to an inactive ingredient in the approved drug product containing that bulk drug
116 substance. In situations such as these, compounding from bulk drug substances could meet an
117 important patient medical need.

118
119 In other situations, however, compounding using the FDA-approved drug product instead of a
120 bulk drug substance would meet patients' medical needs and present less risk. For example,
121 outsourcing facilities often dilute FDA-approved drug products to produce intravenous bags for
122 hospitals. Similarly, when pediatric or elderly patients are unable to swallow an FDA-approved
123 tablet, outsourcing facilities can sometimes manipulate (e.g., crush) the tablet to produce a liquid.
124 In general, compounding using bulk drug substances presents a greater risk than compounding
125 using FDA-approved drug products.

126
127 The source, safety, and quality of the starting material are better known and established when an
128 FDA-approved drug product is used instead of bulk drug substance for compounding. FDA-
129 approved drug products are subject to premarket review for safety, effectiveness, and quality,
130 and are manufactured by a facility that is subject to premarket assessment, including site
131 inspection. After the premarket assessment, FDA conducts routine, risk-based inspections to
132 verify that the manufacturer has systems in place to assure proper design, monitoring, and
133 control of manufacturing processes and facilities. In addition, during pre-market review of FDA-

with FDA. Drug products compounded by section 503A compounders are exempt from sections 505 (new drug approval requirements), 502(f)(1) (labeling with adequate directions for use), and 501(a)(2)(B) (CGMP requirements) if the conditions of section 503A are met, including that compounding is based on the receipt of valid prescriptions for identified individual patients (section 503A(a)). In general, section 503A compounders do not register with and are not routinely inspected by FDA, and they are primarily overseen by the states.

¹⁵ Section 503B(a).

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134 approved drug products, the quality standards and controls with respect to ingredients, and the
135 specific processes and facilities used to produce the bulk drug substance and drug products, are
136 similarly assessed. This includes a review of evidence to evaluate the safety of the bulk drug
137 substance and any inactive ingredients used in the product. For example, FDA evaluates whether
138 the sponsor's proposed specifications for purity, potency, and other attributes of the bulk drug
139 substance are appropriate for its use in the drug product, and whether studies demonstrate that
140 the levels of impurities are not unsafe and the bulk drug substance will be stable through the
141 product's expiration date. In contrast, the quality standards, specifications, and controls for bulk
142 drug substances used in compounding have not been assessed by FDA, and such bulk drug
143 substances may be manufactured by a facility that is not subject to FDA premarket assessment,
144 including premarket site inspection to verify manufacturing operations are in control.
145

146 Compounding from bulk drug substances also involves more complex and numerous inter-
147 related manipulations by the compounder than compounding drugs from FDA-approved drug
148 products, and involves the compounder addressing risks related to ingredient quality. For
149 example, to compound a sterile drug product from a non-sterile bulk drug substance, the
150 outsourcing facility first acquires ingredients that were made under conditions that result in low
151 and known bioburden levels, including limits on endotoxins. It handles the materials to avoid
152 contamination by harmful microorganisms or compounds and then performs a sterilization
153 process, such as sterile filtration followed by aseptic filling. The outsourcing facility then either
154 maintains the sterility of the material through subsequent manipulations or performs terminal
155 sterilization. If an outsourcing facility performs any of the sterilization steps improperly, such as
156 by failing to control air quality or maintain aseptic conditions, the drug may fail to achieve
157 sterility or be further contaminated. If a terminal sterilization step is performed improperly, the
158 drug could fail to achieve sterility, or the conditions of the sterilization process could cause the
159 drug to degrade, resulting in a lower strength (sub-potent) and an increase in impurities. In
160 contrast, compounding a sterile drug product using an FDA-approved sterile drug product does
161 not entail sterilizing a non-sterile substance. Rather, the outsourcing facility would ensure that
162 the sterile drug product being compounded retains its sterility.
163

164 Compounding from bulk drug substances also increases the potential for errors that could result
165 in a sub-potent or super-potent product. Such compounding involves certain operations, such as
166 weighing, handling, or mixing, that depend, in part, on the unique characteristics of different
167 types of bulk drug substances (e.g., powders, liquids) such as powder flow properties,
168 hygroscopicity, and liquid viscosity. Failure to take into account these characteristics can
169 adversely impact weighing, handling, mixing, or other compounding operations. In addition,
170 these operations are generally conducted under circumstances in which cross-contamination is
171 more likely to occur. For example, these operations may involve the use of powders, which are
172 often similar in appearance and challenging to control. This can result in mix-ups (e.g.,
173 accidental use of wrong materials or contaminated equipment), carryover of residues, and
174 airborne transfers of potential contaminants. In contrast, compounding drug products using
175 FDA-approved drug products generally does not present the same degree of risk. For example,
176 when an FDA-approved product is not a powder, compounding with the approved drug will not
177 involve several of the considerations and steps described above and is therefore less likely to
178 lead to errors.
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180 Finally, compounding a drug product from a bulk drug substance that is a component of an FDA-
181 approved drug when there is no clinical need to do so, perhaps because of economic incentives,
182 undermines the drug approval process. For example, use of bulk drug substances to compound a
183 formulation of a needed concentration, route of administration or dosage form rather than simply
184 diluting or otherwise manipulating the approved drug reduces the incentive for sponsors to invest
185 in and seek FDA-approval of such drugs. The drug approval process is critical to ensure patient
186 access to pharmaceuticals whose quality, safety and effectiveness have been established.
187

188 In light of the foregoing concerns about drug quality and the integrity of the drug approval
189 process, section 503B's limitation on the 503B Bulks List to substances for which there is a
190 clinical need serves important public health functions. First, it helps to limit patient exposure to
191 drugs that have not been demonstrated to be safe and effective, and that may be of substandard
192 quality, to those situations in which the drug is necessary for patient treatment. Second, it
193 preserves the incentives for sponsors to invest in the research and testing required to obtain FDA
194 approval, thereby helping to maintain a supply of high-quality, safe, and effective drugs.
195

D. Process for Developing the 503B Bulks List

196
197
198 In the *Federal Register* of December 4, 2013 (78 FR 72838), FDA requested nominations for
199 specific bulk drug substances for the Agency to consider for inclusion on the 503B Bulks List.
200 In response to that request, interested groups and individuals nominated a wide variety of
201 substances. However, many of those nominations were not for substances used in compounding
202 as active pharmaceutical ingredients or did not include sufficient information to allow FDA to
203 evaluate the nominated substance. To improve the efficiency of the process for the development
204 of the list of bulk drug substances, FDA reopened the nomination process in the *Federal Register*
205 of July 2, 2014 (79 FR 37750), and provided more detailed information on what it needs to
206 evaluate nominations for the list. On October 27, 2015 (80 FR 65770), the Agency opened a
207 new docket, FDA- 2015-N-3469, to provide an opportunity for interested persons to submit new
208 nominations of bulk drug substances or to re-nominate substances with sufficient information.
209 This docket is currently open.
210

211 If the information provided by the nominator did not include sufficient supporting information
212 for FDA to evaluate,¹⁶ the nominator should re-nominate the substance with sufficient supporting
213 information if it wishes to ensure that the bulk drug substance will be reviewed for potential
214 inclusion on the 503B Bulks List.
215

216 In June 2016, FDA published the guidance for industry *Interim Policy on Compounding Using*
217 *Bulk Drug Substance Under Section 503B of the Federal Food, Drug, and Cosmetic Act*. This
218 guidance, which was revised in January 2017, sets forth interim regulatory policies for
219 outsourcing facilities compounding using bulk drug substances and provides information about
220 the Agency's procedures for establishing the 503B Bulks List.

¹⁶ If the substance was not nominated with adequate supporting information, it will appear in Category 3, as described in FDA's guidance, *Interim Policy on Compounding Using Bulk Drug Substance Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

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221
222 As explained in the interim guidance, as FDA evaluates bulk drug substances, it intends to
223 publish a notice for public comment in the *Federal Register* that describes its proposed position
224 on each substance along with the rationale for that position.¹⁷ After considering any comments
225 on FDA’s proposals regarding whether to include nominated substances on the 503B Bulks List,
226 FDA will consider whether input from the Pharmacy Compounding Advisory Committee
227 (PCAC) on the nominations would be helpful to the Agency in making its determination, and if
228 so, it will seek PCAC input.¹⁸ Depending on its review of the docket comments and other
229 relevant information before the Agency, the Agency may finalize its proposed determination
230 without change, or it may finalize a modification to its proposal to reflect new evidence or
231 analysis regarding clinical need. FDA will then publish in the *Federal Register* a list identifying
232 the bulk drug substances for which it has determined there is a clinical need and FDA’s rationale
233 in making that final determination. FDA will also publish in the *Federal Register* a list of those
234 substances it considered but found that there is no clinical need to use in compounding and
235 FDA’s rationale in making this decision.

236
237 FDA intends to maintain a current list of all bulk drug substances it has evaluated on its website,
238 with separate lists for bulk drug substances it has placed on the 503B Bulks List and those it has
239 decided not to place on the list. FDA will only place a bulk drug substance on the 503B Bulks
240 List where it has determined there is a clinical need for outsourcing facilities to compound drug
241 products using the bulk drug substance. If a clinical need to compound drug products using the
242 bulk drug substance has not been demonstrated, based on the information submitted by the
243 nominator and the information considered by the Agency, the Agency will not place a substance
244 on the 503B Bulks List.

245
246 FDA intends to evaluate the substances nominated for the 503B Bulks List on a rolling basis.
247 FDA will evaluate and publish in the *Federal Register* its proposed and final determinations in
248 groups of bulk drug substances until all nominated substances that were sufficiently supported
249 have been evaluated and either placed on the 503B Bulks List or identified as bulk drug
250 substances that were considered but determined not to be appropriate for inclusion on the 503B
251 Bulks List.

252
253 FDA will not consider a substance for inclusion on the 503B Bulks List if the substance is not
254 eligible for the exemptions available under section 503B, such as biological products subject to
255 licensure in a biologics license application under section 351 of the Public Health Service Act or
256 substances that appear on the list of drugs that have been withdrawn or removed from the market
257 because such drug products or components of such drug products have been found to be unsafe
258 or ineffective.

259
260 Below, we discuss the Agency’s interpretation of *clinical need* as used in section 503B(a)(2),
261 factors the Agency intends to use to evaluate bulk drug substances that have been nominated, and
262 certain additional procedures the Agency intends to follow during its review.

263

¹⁷ This procedure is set forth in section 503B(a)(2)(A)(i).

¹⁸ Section 503B does not require FDA to consult the PCAC before developing a 503B Bulks List.

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III. POLICY

In the next section, we discuss how we interpret *bulk drug substances for which there is a clinical need*, and in the following section we provide a more detailed discussion of the analysis we intend to conduct in evaluating bulk drug substances that have been nominated for inclusion on the 503B Bulks List.

A. Bulk Drug Substance for Which There Is a Clinical Need

1. Clinical Need Standard

Section 503B authorizes FDA to publish a list identifying “bulk drug substances for which there is a clinical need.” FDA interprets this to mean that the 503B Bulks List may include a bulk drug substance if:

- (1) there is a clinical need for an outsourcing facility to compound the drug product, and
- (2) the drug product must be compounded using the bulk drug substance.

This interpretation is consistent with the text of section 503B(a)(2)(A), and the purpose of the 503B Bulks List, which is to identify the bulk drug substances that can be used in compounding under the exemptions in section 503B, provided the other conditions in that section are met. The Agency’s interpretation also furthers the broader purposes of the Act by (1) helping to protect patients from risks of compounding from bulk drug substances where there is no clinical need to do so and (2) protecting the integrity of the drug approval process. FDA intends to use the analysis discussed below in determining whether there is a clinical need for a nominated bulk drug substance.

The Agency does not interpret supply issues, such as backorders, to be within in the meaning “clinical need” for compounding with a bulk drug substance. We note that section 503B of the FD&C Act already allows compounding from bulk drug substances if the drug product compounded from such bulk drug substance is on the FDA drug shortage list at the time of compounding, distribution, and dispensing. Similarly, FDA does not interpret considerations of cost to be within the meaning of “clinical need.”

2. Inclusion of a Bulk Drug Substance on the 503B Bulks List

There may be situations in which FDA’s finding of clinical need is limited to the use of the bulk drug substance to make drug products with certain attributes, such as specific strengths, routes of administration, or dosage forms. In such a case, the Agency may tailor the proposed entry on the 503B Bulks List to the use of the bulk drug substance to compound a drug product with those attributes. For example, if the Agency were to find a clinical need for a bulk drug substance to be used to compound a drug product for topical use, it may limit the entry of that bulk drug substance on the 503B Bulks List to use of the substance to compound drug products for topical use.

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310
311 Additionally, when a bulk drug substance that is a salt or ester of an active moiety is listed, FDA
312 intends to include only that particular salt or ester on the 503B Bulks List. The base compound
313 and other salts or esters of the same active moiety are different bulk drug substances and would
314 therefore not be included.

315
316 FDA's evaluation of the nominated substances will be, necessarily, far less rigorous and less
317 comprehensive than the Agency's review of drug products as part of the new drug approval
318 process. The new drug approval process is conducted based on extensive data submitted in new
319 drug and abbreviated new drug applications, which are not available for the nominated
320 substances. Additionally, the Agency's review during the drug approval process includes
321 premarket evaluation of the specific drug product (i.e., the finished dosage form containing the
322 active ingredient and any inactive ingredients); its proposed labeling; the applicant's chemistry,
323 manufacturing, and controls information; and a premarket assessment of the establishments
324 where approved drug products will be manufactured. The Agency will not have the same type,
325 quality, or amount of information about the compounded drug product when it evaluates whether
326 there is a clinical need to compound using the nominated bulk drug substance.

327
328 Therefore, the inclusion of a drug substance on the 503B Bulks List should not, in any way, be
329 equated with or considered an FDA approval, endorsement, or recommendation of any drug
330 product compounded using the substance. Nor should it be assumed that drug products
331 compounded using substances on the 503B Bulks List have been proven to be safe and effective
332 under the standards required for Agency approval. Any person who represents that a
333 compounded drug product made with a bulk drug substance that appears on the 503B Bulks List
334 is FDA-approved, or otherwise endorsed by FDA generally, or for a particular indication, will
335 cause the drug to be misbranded under section 502(a) and/or 502(bb) of the FD&C Act.

B. Analysis for Evaluating Nominated Bulk Drug Substances

1. Overview of Proposed Analysis

340
341 FDA intends to use a two-part analysis, described more fully in section III.B.ii, below, in
342 evaluating substances nominated for placement on the 503B Bulks List to determine whether
343 there is a clinical need.

344
345 For Part 1 of this two-part evaluation, FDA intends to determine whether the bulk drug substance
346 is a component of an FDA-approved product. For purposes of this inquiry, FDA will generally
347 consider a bulk drug substance to be a component of an FDA-approved drug product if the bulk
348 drug substance is the same as the active pharmaceutical ingredient in an FDA-approved drug
349 product.¹⁹

350
351 If the bulk drug substance is not a component of an FDA-approved product, FDA will proceed to
352 Part 2 of its evaluation to determine whether the substance is clinically necessary.

353

¹⁹ The active pharmaceutical ingredient is as defined in the approved product labeling.

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354 If the bulk drug substance is a component of an FDA-approved drug, FDA intends to conduct a
355 threshold review based on the following questions:

- 356
357 (a) Is there a basis to conclude, for each FDA-approved product that includes the nominated
358 bulk drug substance, that (i) an attribute of the FDA-approved drug product makes it
359 medically unsuitable to treat certain patients for a condition that FDA has identified for
360 evaluation, and (ii) the drug product proposed to be compounded is intended to address
361 that attribute?
362 (b) Is there a basis to conclude that the drug product proposed to be compounded must be
363 produced from a bulk drug substance rather than from an FDA-approved drug product?

364
365 If FDA answers “no” to either threshold question, the Agency does not intend to include the
366 nominated bulk drug substance from the 503B Bulks List. If the Agency answers “yes” to both
367 questions, it intends to proceed to Part 2 of the analysis.

368
369 The Agency intends to use Part 2 to evaluate bulk drug substances that are components of FDA-
370 approved drugs if the questions in Part 1 are answered in the affirmative, and to evaluate bulk
371 drug substances that are not components of FDA-approved drug products. The Agency proposes
372 to conduct a balancing test, described more fully below, under which FDA would consider each
373 factor in the context of the others and to balance them, on a substance-by-substance basis, to
374 determine whether the substance is appropriate for inclusion on the 503B Bulks List. The
375 balancing test includes the following factors:

- 376
377 (a) The physical and chemical characterization of the substance;
378 (b) Any safety issues raised by the use of the substance in compounding;
379 (c) The available evidence of effectiveness or lack of effectiveness of a drug product
380 compounded with the substance, if any such evidence exists; and
381 (d) Current and historical use of the substance in compounded drug products, including
382 information about the medical condition(s) that the substance has been used to treat
383 and any references in peer-reviewed medical literature.

384
385 Under Parts 1 and 2 of its analysis, FDA intends to evaluate the nominated bulk drug substances
386 in the context of information provided by the nominators about the drug products proposed to be
387 compounded and the proposed uses of those drug products. The Agency may also consider
388 additional uses of the bulk drug substances that were not described in the nomination, such as
389 those that are described in public comments submitted to the Agency or that are otherwise
390 identified during the Agency’s review, if the Agency concludes they may be relevant to its
391 decision whether to place a bulk drug substance on the 503B Bulks List. The Agency may
392 request additional information from nominators or persons who have submitted relevant docket
393 comments to help inform its review.

394 395 2. *Explanation of Analysis*

396 397 a. Part 1

398 399 i. Subpart 1(a): Need for a Compounded Drug?

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400
401 Under Subpart 1(a), FDA intends to consider whether there is a basis to conclude, for each FDA-
402 approved product that includes the nominated bulk drug substance, that (i) an attribute of the
403 FDA-approved drug product makes it medically unsuitable to treat certain patients for a
404 condition that FDA has identified for evaluation, and (ii) the drug product proposed to be
405 compounded is intended to address that attribute.

406 Unless an attribute of the FDA-approved drug is medically unsuitable for certain patients, and a
407 drug product compounded using a bulk drug substance that is a component of the approved drug
408 is intended to address that attribute, there is no clinical need to compound using that bulk drug
409 substance. Rather, it would unnecessarily expose patients to the risks associated with drug
410 products that do not meet the standards applicable to FDA-approved drug products for safety,
411 effectiveness, quality, and labeling and would undermine the drug approval process.
412 Accordingly, unless FDA can answer “yes” to the two questions in Part 1(a) of its analysis, the
413 Agency intends to find there is no clinical need for compounding using the bulk drug substance.

414 In the Part 1(a) threshold test, FDA will focus on the rationale for compounding from a bulk drug
415 substance that appears in the nomination or that FDA otherwise identifies. For example, several
416 nominations state that patients need a drug product compounded using the bulk drug substance
417 because the FDA-approved drug that includes the bulk drug substance as a component also
418 includes inactive ingredients or additional active ingredients that are inappropriate for the patient
419 population. Other nominations state that the FDA-approved drug is for use by routes of
420 administration or in dosage forms that are inappropriate for the patient population. For these
421 examples, FDA will evaluate whether the inactive ingredients, additional active ingredients, the
422 route of administration, or the dosage forms are attributes of the FDA-approved products that
423 make them unsuitable and impart unacceptable risk for certain patients for the conditions that
424 FDA is evaluating. If so, FDA will consider whether the compounded drug products are
425 intended to address those attributes by, for example, excluding the inactive ingredients or
426 additional active ingredients or using a different route of administration or dosage form.
427

428 Whether there is an attribute of the FDA-approved drug product that makes it medically
429 unsuitable for some patients for the conditions that FDA has identified for evaluation and, if so,
430 whether the compounded drug product addresses that attribute, will be determined on a case-by-
431 case basis. For example, if an approved drug product contains peanut oil, patients with a peanut
432 allergy treated with the FDA-approved drug product may develop a serious allergic reaction.²⁰
433 Accordingly, FDA would likely determine that a proposal to produce a compounded drug
434 product without the peanut oil to address the condition described in the nomination would
435 proceed through Part 1(a). Or, if a drug product is approved with two active ingredients in a
436 fixed combination, but FDA has received or identified information indicating that it is known,
437 within that specialty, on the basis of competent evidence, that some patients need just one active
438 ingredient and are likely to have an adverse clinical reaction to the second active ingredient, and
439 there is no FDA-approved drug product containing the one active ingredient they need, then
440 FDA would likely determine that a proposal to compound the single-ingredient product from a
441 bulk drug substance would proceed through Part 1(a).

²⁰ See Footnote 21.

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442
443 In general, broad statements that a compounded drug product with an attribute that differs from
444 the FDA-approved drug is necessary for certain patients, without sufficient evidence that the
445 attribute makes the FDA-approved drug medically unsuitable for specific patients for the
446 condition that has been identified for evaluation, will not be adequate. For example, general
447 statements that a preservative-free drug needs to be compounded because some patients may
448 have an allergy to the preservative in the approved drug likely would not be an acceptable reason
449 for compounding from bulk drug substances, unless the preservative is well known to be a
450 clinically significant allergen for some patients who are administered the drug. Similarly, minor
451 changes in dosage form, such as from tablet to capsule, are unlikely to fulfill a clinical need that
452 cannot be met by the approved drug. Nor is the combination of multiple active ingredients to
453 allow for administration of fewer products likely to represent a clinical need for purposes of this
454 factor.

455
456 ii. Subpart 1(b): Need for a Drug Compounded from a Bulk Drug Substance?
457

458 Under Subpart 1(b), if there is an FDA-approved drug product that incorporates the nominated
459 bulk drug substance, FDA intends to consider whether there is a basis to conclude that the drug
460 product proposed to be compounded must be produced from a bulk drug substance rather than an
461 FDA-approved drug product. This is because in order to place a bulk drug substance on the
462 503B Bulks List, FDA must determine that there is a clinical need for outsourcing facilities to
463 compound a drug product *using the bulk drug substance*. Accordingly, the Agency intends to
464 find that there is no clinical need to compound using a bulk drug substance unless the nomination
465 identifies a drug product that must be produced from the bulk drug substance rather than from an
466 FDA-approved drug product.

467
468 To make this assessment, FDA intends to consider the difference or differences between the
469 proposed compounded drug product and the FDA-approved product. Whether the compounded
470 drug product must be prepared by starting from a bulk drug substance will be assessed case by
471 case, considering the proposed differences between the products, the basis provided by the
472 nominator for why it intends to use the bulk drug substance rather than the FDA-approved drug
473 to compound the proposed drug product, and other relevant information, including the type and
474 number of manipulations necessary to produce the proposed drug from the FDA-approved
475 product versus the bulk drug substance and their potential impact on the overall quality of the
476 resultant drug product. For example, FDA is likely to determine that a drug product that is being
477 proposed to be compounded without an active or inactive ingredient (e.g., an allergen) in the
478 approved product must be compounded from a bulk drug substance rather than the FDA-
479 approved drug because of the difficulties and complexities likely to be associated with removing
480 an ingredient from a finished drug product. In contrast, FDA is likely to determine that a drug
481 product that is being proposed to be compounded in a lower concentration than an FDA-
482 approved product (e.g., for a pediatric patient) should be compounded from the FDA-approved
483 product because a more dilute drug product can often be formulated from an approved drug
484 product with minimal, simple manipulations (e.g., adding a diluent to an approved drug).

485
486 b. Part 2
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488 For bulk drug substances that are components of an FDA-approved drug, FDA only intends to
489 proceed to Part 2 if the Agency answers “yes” to the questions in both subpart 1(a) and subpart
490 1(b). FDA’s analysis of bulk drug substances that are not components of FDA-approved drugs
491 will start with Part 2.
492

493 In Part 2 of its evaluation, FDA intends to balance the four factors described below. Whether the
494 factors in Part 2 taken together weigh in favor of or against a finding of clinical need will inform
495 FDA’s proposal to include or exclude nominated bulk drug substances from the 503B Bulks List.
496

i. Subpart 2(a): Physical and Chemical Characterization

499 Under the first factor, the physical and chemical characterization of the bulk drug substance,
500 FDA intends to consider each substance's purity, identity, and quality. Based on attributes such
501 as the substance's molecular structure, stability, melting point, appearance, likely impurities, and
502 solubilities, FDA would determine whether the substance can be identified or compounded
503 consistently based on its physical and chemical characteristics. If a substance cannot be well-
504 characterized, or is not chemically and physically stable after compounding, or requires
505 conditions to prevent degradation that cannot be accomplished reliably, this factor would weigh
506 against its inclusion on the 503B Bulks List because there would be no assurance that its
507 properties and toxicities, when used in compounding, would be the same as the properties and
508 toxicities considered by the Agency.
509

510 With respect to bulk drug substances that are components of FDA-approved drug products, FDA
511 will have already determined the bulk drug substance in a particular drug product possesses
512 chemical and physical characteristics suitable for inclusion as an active ingredient in an FDA-
513 approved product. However, bulk drug substances that are components of FDA-approved drug
514 products may present different challenges. In addition to concerns related to purity of substances
515 from sources that have not been evaluated during the premarket approval process, there may be
516 physical and chemical characterization concerns, such as stability or bioavailability concerns,
517 when they are used to compound drug products, that differ from the approved product in their
518 formulation, route of administration, strength, or other features. FDA therefore intends to
519 consider whether such concerns are associated with use of the bulk drug substance to compound
520 a particular drug product.
521

ii. Subpart 2(b): Safety Issues Raised by Use of the Substance in Compounding

525 Under the second factor, FDA intends to consider the safety issues raised by the use of a
526 nominated bulk drug substance in compounding. With respect to nominated bulk drug
527 substances that are not components of FDA-approved drug products, based on FDA's review of
528 the substances nominated to date, it is unlikely that the substances will have been thoroughly
529 investigated in *in vitro* or in animal toxicology studies, or that there will be well-controlled
530 clinical trials to substantiate their safe use in humans. Thus, in evaluating these substances, the
531 Agency is likely to have at its disposal very limited information, or in some cases no
532 information, of the type and quality that is ordinarily required and evaluated as part of the drug
533 approval process.

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Therefore, to evaluate substances that are not components of FDA-approved drug products, the Agency intends to rely on information, such as reports in peer-reviewed medical literature, about each substance's pharmacology, acute toxicity, repeat dose toxicity, mutagenicity, developmental and reproductive toxicity, and carcinogenicity, or other data that relates to safety. The Agency may also rely on reports and abstracts in the literature or reported to FDA about adverse reactions associated with human use of the substances, or other appropriate information. FDA also intends to consider the availability of approved drug products or drug products that follow an over-the-counter monograph (OTC monograph products) as treatment options for the conditions being considered. The existence of such approved drug products or OTC monograph products would likely weigh against inclusion on the proposed list when the toxicity of the bulk drug substance appears to be significant or where there are other safety concerns associated with the use of the substance in compounded drug products.

With respect to bulk drug substances that are components of FDA-approved drug products, FDA will have already determined that a drug product that includes the bulk drug substance as a component is shown to be safe for its intended use under the conditions described in its approved product labeling. However, when a bulk drug substance that is a component of an FDA-approved drug product is used in compounding, differences between the resulting compounded drug product and the approved drug product may raise safety concerns (e.g., issues arising from different formulations, routes of administration, or strengths). Additionally, there may be relevant differences between the proposed uses or intended patient population of the FDA-approved drug and a compounded drug product (e.g., if the compounded drug product is specifically proposed for a pediatric population and the FDA-approved drug is indicated for adults). In evaluating the potential impact of such differences on the safety of the compounded drug product, FDA intends to rely on available safety information, such as peer-reviewed scientific literature, reports to FDA about adverse reactions relevant to the difference or differences, and FDA's expertise to evaluate safety risks associated with drug products proposed to be compounded from the nominated bulk drug substance.

iii. Subpart 2(c): Available Evidence of Effectiveness or Lack of Effectiveness

Under the third factor, FDA proposes to consider evidence of the substance's effectiveness or lack of effectiveness for an identified use, including but not limited to reports in peer-reviewed medical literature, if any such evidence exists. In the new drug approval process, applicants are required to demonstrate effectiveness under the substantial evidence standard described in section 505(d) of the FD&C Act. FDA recognizes that few, if any, of the substances nominated for the 503B Bulks List that are not components of approved drug products will have been studied in adequate and well-controlled investigations sufficient to satisfy the standard in the drug approval process. In evaluating these bulk drug substances, the Agency would consider relevant evidence concerning effectiveness that is available.

For example, for substances that are not components of approved drug products, but have been widely used for a long period of time, the literature may include anecdotal reports of effectiveness for a particular use or reports of clinical trials suggesting possible effectiveness.

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580 Conversely, the literature may contain anecdotal or clinical evidence that a substance did not
581 show effectiveness for a particular use in a reasonably designed trial. Further, information about
582 other available treatments may affect FDA's evaluation. For a bulk drug substance that is
583 proposed to be used to compound drug products to treat a serious or life-threatening disease,
584 there may be more serious consequences associated with ineffective therapy, particularly when
585 there are approved drug products that may be appropriate for treatment. In those cases, the
586 existence of drug products approved to treat the condition would likely weigh against inclusion
587 on the 503B Bulks List, and the availability of no or minimal effectiveness data, trials that do not
588 demonstrate effectiveness, would weigh more heavily against placement on the list in FDA's
589 balancing of the relevant factors.

590
591 With respect to bulk drug substances that are components of FDA-approved drug products, FDA
592 will have already determined that a drug product that includes the bulk drug substance as a
593 component is effective for its indicated use under the conditions described in its approved
594 labeling. Additionally, in Part 1(a) of the analysis, the Agency will already have considered
595 whether there is a basis to conclude that an attribute of the FDA-approved drug product makes it
596 unsuitable to treat certain patients for the medical condition described in the nomination.
597 However, when the bulk drug substance that is a component of an FDA-approved drug product is
598 used in compounding, differences between the compounded drug product and the FDA-approved
599 drug product may raise effectiveness concerns arising, e.g., from a different formulation, route of
600 administration, or strength. Additionally, effectiveness concerns may be raised by differences
601 between the FDA-approved drug product and the compounded drug product in terms of their
602 proposed uses or intended patient population. FDA intends to consider whether such
603 effectiveness concerns are associated with use of the bulk drug substance to compound a
604 particular drug product.

iv. Subpart 2(d): Historical and Current Use in Compounding

605
606
607
608 Under the fourth factor, FDA intends to consider the historical and current use of the substance
609 in compounding drug products, which may include the length of time the substance has been
610 used in compounding; the medical conditions it has been used to treat; the patient population it
611 has been used to treat; how widespread its use is and has been, including use in other countries;
612 whether it is typically used to compound drugs that healthcare providers maintain in their offices
613 in advance of identifying individual patients; and relevant references in peer-reviewed medical
614 literature. Documentation of this information may include reference to past medical textbooks or
615 medical specialty professional organization guidelines that describe the use of the drug.
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617 The longer a substance has been used in compounding drug products and the broader its use,²¹
618 particularly to compound drug products for office stock,²² the more this factor will generally
619 weigh in favor of inclusion of the substance on the list. In contrast, if FDA’s analysis suggests
620 that the historical and current use of the substance in compounding has been minimal or non-
621 existent, or the nominator has not provided information supporting its historic use in
622 compounding, the more this factor would generally weigh against inclusion of the substance on
623 the 503B Bulks List.
624

625 In weighing this factor for bulk drug substances that are components of FDA-approved drug
626 products, FDA intends to consider evidence, if available, of whether the substance has been used
627 to compound drug products that are intended to address an attribute of the FDA-approved drug
628 product that makes it unsuitable to treat certain patients for the condition that FDA has identified
629 for evaluation.

²¹ For example, in the description of Part 1(a) of this analysis, we noted that an example of a situation in which an attribute of the approved drug product may make it medically unsuitable to treat certain patients for the condition identified for evaluation is when a patient who has a peanut allergy needs to be treated with an approved drug that contains peanut oil. In general, this factor would weigh more heavily in favor of including of the bulk drug substance on the 503B Bulks List if there is information that a significant portion of the population of the United States has a peanut allergy and therefore uses a compounded drug rather than the approved drug, compared to information that a bulk drug substance is to be compounded to treat few patients with an uncommon, non-urgent condition.

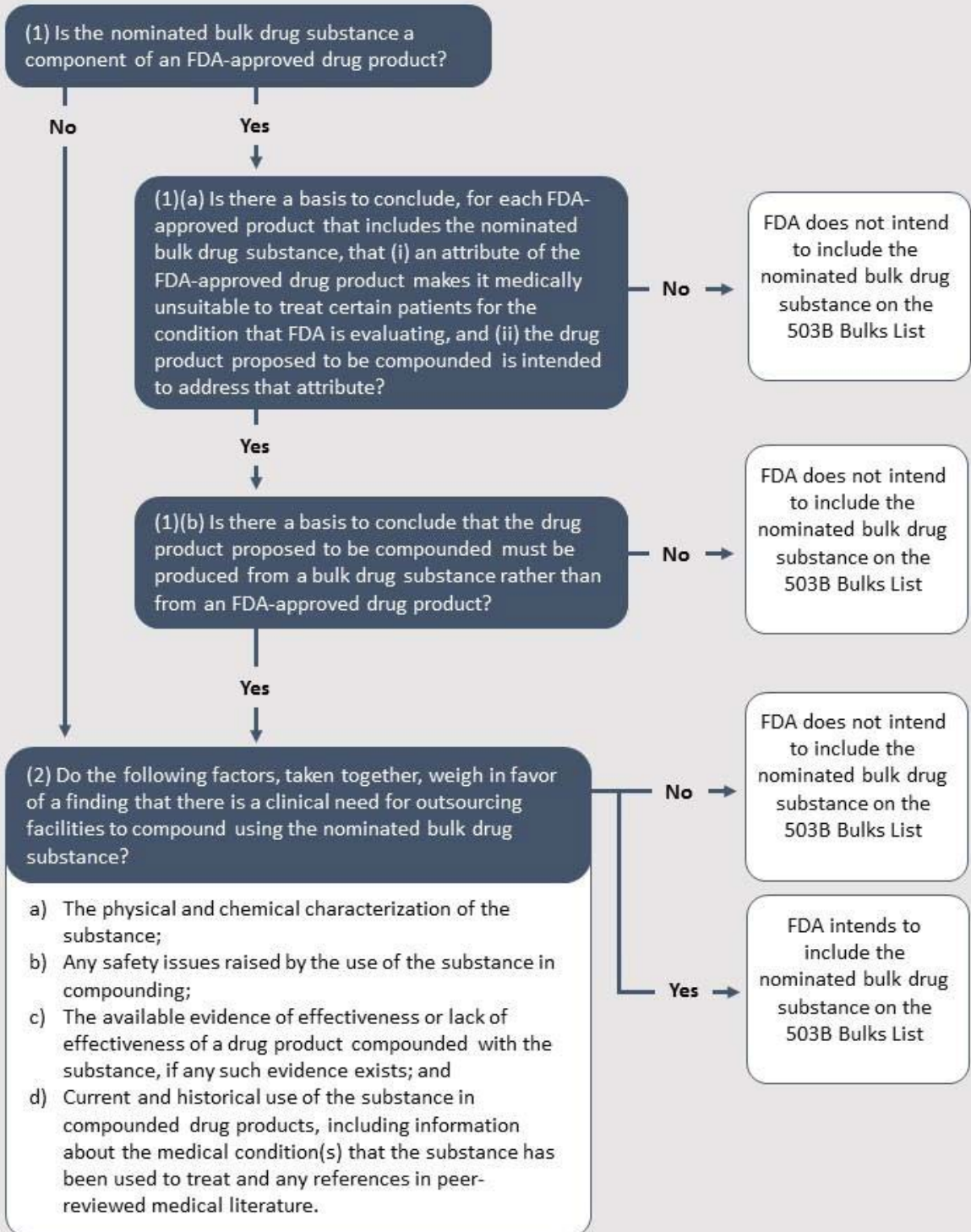
²² In conducting this analysis, the Agency proposes to note the extent of compounding drug products using a nominated bulk drug substance for office stock, because outsourcing facilities are the only entities that can distribute compounded drug products without first receiving prescriptions for identified individual patients. In contrast, compounding under section 503A must be based on the receipt of a valid prescription for an identified individual patient. Section 503A(a). See FDA’s guidance for industry *Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act*.

For example, if there is information that the drug compounded from the nominated bulk drug substance is maintained in physicians’ offices to treat patients who present with infections in emergency situations, this factor may weigh more heavily in favor of including the bulk drug substance on the list, compared to information that a bulk drug substance is used to compound a drug product that does not need to be administered in the office in non-emergency situations.

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**APPENDIX A:
HOW FDA GENERALLY INTENDS TO EVALUATE BULK DRUG SUBSTANCES THAT HAVE BEEN
NOMINATED FOR INCLUSION ON THE 503B BULKS LIST**



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