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OUTSOURCING FACILITIES ASSOCIATION

June 18, 2024

Dockets Management Staff (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2023–N–0061 for "Drug Products or Categories of Drug Products that Present Demonstrable Difficulties for Compounding Under Sections 503A or 503B of the Federal Food, Drug, and Cosmetic Act."

I. Introduction

The Outsourcing Facilities Association ("OFA") is the trade association representing FDA-registered outsourcing facilities ("503Bs") operating pursuant to Section 503B of the Federal Food, Drug, and Cosmetic Act ("FD&C Act"). OFA's members provide compounding and repackaging services to patients, healthcare providers, and healthcare facilities, and strive to ensure the specific needs of both providers and patients are met with safe and effective compounded and/or repackaged medications under the current Good Manufacturing Practices ("cGMP") standards and guidance of the FDA. OFA has been actively following U.S. Food and Drug Administration's (the "FDA") implementation of the Compounding Quality Act ("CQA") and has brought together members of industry to advocate for a safe, reasonable and practical application of the CQA.

On March 20, 2024, FDA issued a proposed rule, which both establishes criteria for the lists of drug products or categories of drug products that present demonstrable difficulties for compounding ("DDC Lists") under the FD&C Act and identifies the first three categories of drug products on both DDC lists: oral solid modified-release drug products that employ coated systems ("MRCs"), liposome drug products ("LDPs"), and drug products produced using holt melt extrusion ("HMEs") (collectively, the "Proposed Drug Categories"). *See* Drug Products or Categories of Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A or 503B of the Federal Food, Drug, and Cosmetic Act, FDA–2023–N–0061–0001 (Mar. 20, 2024) (the "Proposed Rule"). In the Supplementary Information to the Proposed Rule, FDA seeks comment on whether each Proposed Drug Category should be listed on the 503A or 503B DDC Lists.

Accordingly, OFA respectfully submits this comment in opposition to the Proposed Rule.

II. The Proposed Rule Fails to Observe the Required Rulemaking Procedures

As an initial matter, the Proposed Rule fails to satisfy the required rulemaking procedures because it does not contain necessary information, it is the product of a failed rulemaking process, and it fails to articulate any standard by which drugs or drug categories are to be listed on DDC Lists. This section addresses each of these deficiencies in greater detail below.

A. The Proposed Rule Omits Statutorily Required Information

The Proposed Rule is procedurally deficient because it omits three types of information statutorily required by Section 503B of the FD&C Act.

First, the Proposed Rule is entirely devoid of evidence demonstrating the compounding difficulties that justify the inclusion of each drug or drug category on the DDC List. The plain text of Section 503B directs the Secretary to develop a list of "drugs or categories of drugs that present demonstrable difficulties for compounding that are reasonably likely to lead to an adverse effect on the safety or effectiveness of the drug or categories of drugs. *See* Section 503B(a)(6). Without such rational and/or evidence, the Proposed Rule does not provide adequate notice for comment. As such, OFA is unable to comment on the proposed "Demonstrable Difficulties" or their safety/efficacy impacts because the Agency has not demonstrated any such difficulties.

Second, the Proposed Rule does not identify any "compounding conditions." Section 503B clearly contemplates that there are conditions necessary to prevent the drug or category of drugs from presenting demonstrable difficulties, and, if the conditions are followed by an outsourcing facility, then the outsourcing facility may compound such drugs or categories of drugs irrespective of their respective inclusion on the DDC List. *See* Section 503B(a)(6) ("The drug . . . is compounded in accordance with all applicable conditions identified on the [DDC List] as conditions that are necessary to prevent the drug or category of drugs from presenting the demonstrable difficulties described in subparagraph (A)."). Here, the Proposed Rule fails to identify any such "compounding conditions."

Third, because the Proposed Rule fails to include any such compounding conditions, the Proposed Rule necessarily lacks evidence demonstrating that the compounding conditions would mitigate the "adverse effect on the safety or effectiveness of the drug or category of drugs, taking into account the risks and benefits to patients."

Together, the three deficiencies identified above deprive the public of a meaningful chance to participate in the rulemaking process, as required by 5 U.S.C. § 553(c) of the APA. *See also GPA Midstream Ass'n v. United States Dep't of Transp.*, 67 F. 4th 1188, 1197 (D.C. Cir. 2023) (citing *Owner-Operator Independent Drivers Ass'n, Inc. v. Fed. Motor Carrier Safety Admin.*, 494 F.3d 188, 199 (D.C. Cir. 2007) (explaining that an agency "must disclose critical information justifying the proposal in time for public comment"). Accordingly, the Proposed Rule fails to observe the rulemaking procedures.

B. The Proposed Rule Is a Direct Result of a Failed Process

The Proposed Rule is further flawed because it was not developed in consultation with an advisory

committee comprised of pharmacists and physicians with expertise in 503B compounding capabilities and operations. Although 503B facilities are not expressly identified in Section 503B(c)(2), expertise in their capabilities and operations is clearly required for promulgating a new rule affecting the regulated class. Yet not a single current or former advisory committee member has any experience or expertise in 503B compounding capabilities and operations. As such, the Proposed Rule is procedurally deficient.

C. The Proposed Rule Lacks Any Standard for Objectively Determining Whether Drug Products or Categories of Drug Products Present Demonstrable Difficulties for Compounding

The Proposed Rule makes no attempt to define or create any sort of standard allowing for the objective determination of whether specific drug products or categories of drug products present demonstrable difficulties for compounding under Section 503B of the FD&C Act. Instead, it merely identifies six criteria without any explanation as to why any of the six criteria render a drug product or category of drug product demonstrably difficult to compound.[1] This omission is a serious procedural error. The APA requires that a notice of proposed rulemaking include "either the terms of substance of the proposed rule or a description of the subjects and issues involved." *See* 5 U.S.C. § 553(b). As such, agencies have a "duty to 'identify and make available technical studies and data that it has employed in reaching the decisions to propose particular rules'" and FDA's "we know it when we see it approach" has no home in APA rulemaking. *See Solite Corp. v. EPA*, 952 F.2d 473, 484 (D.C. Cir. 1991) (quoting *Connecticut Light & Power Co. v. Nuclear Regulatory Comm'n*, 673 F.2d 525, 530 (D.C. Cir. 1982) ("An agency commits serious procedural error when it fails to reveal portions of the technical basis for a proposed rule in time to allow for meaningful commentary."). Indeed, the D.C. Circuit explained that "[t]o allow an agency to play hunt the peanut with technical information, hiding or disguising the information that it employs, is to condone a practice in which the agency treats what should be a genuine interchange as mere bureaucratic sport." *See Connecticut Light & Power Co. v. Nuclear Regulatory Comm'n*, 673 F.2d 525, 530 (D.C. Cir. 1982).

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[1] The Proposed Rule states, in pertinent part, as follows:

> FDA has identified six criteria it proposes to consider in determining whether drug products or categories of drug products present demonstrable difficulties for compounding under Sections 503A and 503B of the FFDCA (the "Proposed Listing Criteria"):
>
> 1. Complex formulation;
> 2. Complex drug delivery mechanism;
> 3. Complex dosage form;
> 4. Bioavailability achievement complexity;
> 5. Compounding process complexity; and
> 6. Physiochemical or analytical testing complexity.
>
> In evaluating drug products or categories of drug products for the DDC Lists, the Agency proposes to consider these criteria individually and collectively, and to take into account the risks and benefits to patients of the compounded drug product or categories of drug products. The criteria are not mutually exclusive. A drug product or category of drug products may meet one or more of these criteria that indicate it presents demonstrable difficulties for compounding.

See Proposed Rule at 19780.

Here, the only insight into FDA's proposed criteria comes from a 2015 PCAC Committee meeting transcript, which explains that the proposed criteria stem from a concept paper published in 2000:

> We also got a bunch of comments submitted to the docket on that concept paper. But then as a result of the litigation, the cases that were going through the courts, and after the Supreme Court decision held certain provisions of 503A unconstitutional, like we did on the bulks list, we suspended our efforts to implement these provisions of Section 503A.

See June 18, 2015 PCAC Transcript at 22. But, reliance on a concept paper predating the very industry targeted by the Proposed Rule ***by over a decade*** is flawed. No concepts predating the outsourcing facility industry's conception—and especially those relating to the difficulties outsourcing facilities would encounter when compounding substances—using standards that were not even contemplated yet by the Agency cannot be applied to the industry. Or, more simply, no meaningful comment could occur when the industry did not exist.

Additionally, it is important to note that any drug products or categories of drug products that FDA deems to present demonstrable difficulties for compounding under sections 503B of the FD&C Act present the same difficulties for manufacturing. Even FDA recognizes that a Section 510-registered drug manufacturer may register a facility as an outsourcing facility and manufacturer of both approved drug products and compounded drug products. *See FDA's 503B Facility Guidance* and the Facility Definition Under Section 503B of the Federal Food, Drug, and Cosmetic Act Guidance for Industry at 6. As such, both Section 503B outsourcing facilities and Section 510 drug manufacturing facilities must both comply with cGMP, use validated methods and equipment, and meet certain USP standards. Thus, if the same drug or categories of drug products are compounded at a facility that is both an outsourcing facility and a Section 510-registered drug manufacturer using the same standards and equipment, how can there be a demonstrable difficulty to compound such a drug if the facility is acting as a 503B but no difficulty if manufacturing as a 510-registered facility?

Finally, we point out that Section 503B outsourcing facilities have invested additional resources to file ANDAs and 505(b)(2) NDAs for certain products.[2] Yet, the Proposed Rule's criteria fail to explain how a demonstrable difficulty exists in this scenario. As such, the Agency commits serious procedural error when it fails to reveal portions of the technical basis for a proposed rule in time to allow for meaningful commentary. More concerning, this demonstrates that the Proposed Rule is arbitrary and capricious because it allows FDA to deem a drug or category of drug products too difficult to compound even when facilities are operating under the same standards—or, worse yet, when it is the exact same facility.

III. The Proposed DDC Listing Criteria Fail to Provide Objective Standards for Determining Whether Specific Drug Attributes Present Compounding Difficulties Warranting DDC Listing

[2] *See* Comment from Exela Pharma Sciences, Docket Comment ID: FTC-2024-0018-6372 ("Exela has consistently supplied several drugs under the 503B pathway over the years. In fact, Exela went beyond the 503B pathway, and invested additional resources to file ANDAs and 505(b)(2) NDAs to obtain approval as a permanent solution . . . .").

The language used in the Proposed Listing criteria is confusing and ambiguous. For example, the word "complex" is used in each of the Proposed Listing criteria. Regarding the first four criteria, the word "complex" refers to certain drug attributes; regarding the final two criteria, the term refers to difficulties. Utilizing a term and applying the same term so that it has different meanings renders the criteria vague and confusing. By simply removing the word "complex" from the criteria provides more clarity, as demonstrated below:

> Criterion 1: Formulations using ingredients with physicochemical forms that determine drug performance.
>
> Criterion 2: Formulations that control API release without the use of device components.
>
> Criterion 3: Formulations with difficult to manufacture API delivery characteristics or drug delivery devices.
>
> Criterion 4: Formulations with difficult to manufacture bioavailability performance.
>
> Criterion 5: Formulations compounded through difficult to operate manufacturing processes.
>
> Criterion 6: Formulations requiring difficult to perform testing processes.

Because API delivery and bioavailability are synonymous, and the last two criteria mean *difficult to manufacture or test*, the six proposed criteria reduce to the following concerns:

1. Drugs may be difficult to compound where they have ingredients with certain physicochemical properties that affect API delivery to, or action at sites of action (Criterion 1).

2. Drugs may be difficult to compound where the bioavailability of their APIs is determined by designed formulation characteristics or combination device performance (Criteria 2-4).

3. Drugs may be difficult to compound or test where such activities are hard to conduct (Criteria 5-6).

Although the criteria seem driven by those concerns, the criteria do not address those concerns. This is because the criteria descriptions do not bridge the gap between any drug attributes and compounding difficulties, or define "difficult" at all: they provide no standard for determining whether specific drug attributes or compounding/testing systems pose difficulties that warrant DDC Listing.

For example, the first criterion focuses on drugs formulated with ingredients that have certain physicochemical properties that achieve or maintain intended drug performance ("physicochemically active drugs" or "PA Drugs"). Yet, the description of that criterion provides no standard that can be applied to determine whether any specific drug in a Proposed Drug Category is demonstrably difficult to compound because it contains an ingredient that makes the drug physicochemically active. Nor does the criteria description provide any examples of

physicochemical attributes of any specific PA Drugs that necessarily render the Drugs so difficult to compound that they should be DDC Listed.

To be sure, the OFA agrees that the physiochemical form of some drug ingredients can have a material effect on API delivery to or performance at sites of action. The OFA does not agree, however, that all PA Drugs should be placed on a DDC List. The Proposed Listing Criteria fail to make any mention of how any one PA Drug is more difficult to compound than any other PA Drug or non-PA Drug or explain the requisite difficulty warranting the inclusion of any PA Drug on a DDC list. Nor does FDA explain why the use of any PA Drug in compounding under cGMP would be different from manufacturing using the exact same PA Drug. For instance, what if a 503B outsourcing facility compounded that product using FDA approved product as a starting material? Or utilizing the same validated method? Because the Proposed Rule fails to provide any such standards or explanations, it is arbitrary and capricious.

IV. The Proposed Rule Is Not Supported by Evidence Demonstrating Compounding Difficulties

FDA's explanations for including the three Proposed Categories on the DDC List fail to identify the specific compounding limitations rendering the proposed drug categories so difficult to compound so as to require inclusion on the DDC List. For example, FDA generally states that MRC formulations may have complex formulations, delivery mechanism, dosage forms, compounding processes, and analytical testing. FDA also identifies specific needs and safety risks associated with compounding MRC formulations. *See* 89 FR 19782. FDA's rationale, however, is framed in the ***hypothetical***—it does not provide any evidence that 503B outsourcing facilities in fact face difficulties compounding MRCs. Nor does FDA provide evidence that 503B facilities are incapable of properly compounding MRCs. Indeed, FDA does not even address the fact that 503B outsourcing facilities can develop the compounding capabilities if it is required to use validated methods and equipment. The same deficiencies identified in this section likewise apply to FDA's explanations for including LDPs and HMEs on the 503B DDC List. Accordingly, because FDA fails to provide sufficient evidence justifying the inclusion of the Proposed Categories on the 503B DDC list, finalizing the Proposed Rule in its current form would be arbitrary, capricious, and not in accordance with applicable law.

V. The Proposed Rule Fails to Issue Compounding Conditions

Even assuming, for argument's sake, FDA did include evidence warranting the inclusion of the Proposed Categories on the 503B DDC List, the Proposed Rule is still inconsistent with the FD&C Act unless and until the compounding conditions are issued along with evidence demonstrating that they would mitigate the "adverse effect on the safety or effectiveness of the drug or category of drugs, taking into account the risks and benefits to patients." *See* Section 503B(a)(6)(B) (the "Conditions and Evidence"). Failing to include the Conditions and Evidence not only cuts off the opportunity to compound the Proposed Drugs as expressly permitted by the FD&C Act, but it also demonstrates FDA lacks sufficient evidence supporting the effectiveness of the compounding conditions. Accordingly, FDA's failure to include the Conditions and Evidence is arbitrary, capricious, and not in accordance with the APA and FD&C Act.

VI. The Evidence in the Proposed Rules Suggests There Is No Need to Place MRCs, LDPs, or HMEs on any DDC List.

The Supplemental Information to the Proposed Rule suggests there is no present basis for including MRCs, LDPs, or HMEs on the 503B DDC List. For instance, when commenting on the listing of MRCs, FDA stated:

> The Agency is not aware of compounded MRCs for human use . . . . FDA is also not aware of a rationale for why a patient would have a medical need for compounded MRCs, as opposed to an FDA-approved product, nor is it aware of any actual or potential benefit that would outweigh the risks to patient safety that would be presented by compounded MRCs.

See 89 FR 19782. The Agency uses identical language to describe the status of HME compounding. *See* 89 FR 19785. With respect to the listing of LDPs, FDA acknowledged that it is "not aware of compounded LDPs for human use . . . . FDA is also not aware of any actual or potential benefit that would outweigh the risks to patient safety that would be presented by compounded LDPs." *See* 89 FR 19784. Critically, with respect to all Proposed Drug Categories, FDA acknowledged that it "find[s] no additional incremental benefits of proposing to establish the criteria or to place these three categories of human drug on the DDC Lists in this proposed rule." *See* Preliminary Regulatory Impact Analysis Initial Regulatory Flexibility Analysis Unfunded Mandates Reform Act Analysis, Docket No. FDA-2023-N-0061.

VII. FDA Failed to Prepare a Preliminary Regulatory Impact Analysis

FDA is attempting to side-step preparing a regulatory flexibility analysis by certifying that doing so is unnecessary. Specifically, FDA contends that the Proposed Rule will not have a significant economic impact on a substantial number of small entities.

Under the Regulatory Flexibility Act ("RFA"), 5 U.S.C. §§ 601-612, as amended, where an agency publishes a general notice of proposed rulemaking, "the agency shall prepare and make available for public comment an initial regulatory flexibility analysis," which must describe the impact of the proposed rule on small entities. *See* 5 U.S.C. § 503(a); *see also Aeronautical Repair Station Ass'n, Inc. v. Fed. Aviation Admin.*, 494 F.3d 161, 174–75 (D.C. Cir. 2007). Section 603 of the RFA requires agencies to include in each initial regulatory flexibility analysis five categories of information. However, such an analysis is not required if "the head of the agency certifies that the rule will not, if promulgated, have a ***significant economic impact*** on a substantial number of small entities." *See* 5 U.S.C. § 605(b) (emphasis added).

Here, FDA is proposing to certify that the Proposed Rule will not have a significant economic impact on a substantial number of small entities. Underlying this proposed certification is an assumption that the only costs the Proposed Rulemaking will impose are the "small costs to read and understand the rule." In making its determination that the proposed rule will not have a significant impact on a substantial number of small businesses, FDA calculated the estimated costs of the proposed rule by looking for evidence of marketing of the three categories of human drug products it proposes to include on the DDC lists. FDA asserts that it found no evidence of any such

marketing, and, necessarily then, compounders would not incur costs to discontinue marketing any existing products that the proposed rule would identify as demonstrably difficult to compound.[3]

The Agency identified 79 outsourcing facilities in the United States. If the Proposed Rule was neither fatally flawed nor arbitrary and capricious, the Proposed Rule would contain the compounding conditions under which outsourcing facilities could compound individual DDC Listed drugs (required by 503B(a)(6)(B)). Such compounding conditions would likely be requirements for specialized equipment or facilities and engineering controls—all such conditions would be of substantial cost to compounders, many of which are small entities. Because the Proposed Rule is fatally flawed and arbitrary and capricious and adequate notice was not provided to sufficiently comment on the true costs of the Proposed Rule, we refer to annual operational costs associated with United States Pharmacopeia compliance as estimated for a 30-chair infusion clinic with USP Chapters <797> and <800> pharmacy cleanrooms for non-hazardous and hazardous drugs.[4] The authors found that "recurring annual costs for a 30-chair fully compliant infusion clinic were calculated to be $785,207. One-time costs associated with initial construction and renovations were estimated to be $1,365,207–$1,535,207 and $965,207–$1,005,207, respectively." Thus, there will be costs associated with the Proposed Rule, and these costs certainly will have a ***significant economic impact*** on small entities—at least 79 by FDA's count. And, it is quite clear that FDA has not taken these costs into account in its economic impact analysis. Nor, has FDA taken into consideration the economic impact that a negative list, such as the DDC, will have on patient access to life saving medications, the costs of those drugs increasing due to less patient access, and the direct impact negative lists have on drug shortages.

VIII. Conclusion

The Proposed Rule cannot be finalized at this time. It was proposed with deliberate disregard of applicable rulemaking procedures. Accordingly, OFA respectfully requests that FDA take the following course of action:

1. *Include on PCAC members with experience in Section 503B compounding or cGMP requirements relating to Section 503B compounding.* In its present form, PCAC does not have the requisite knowledge to make decisions and/or recommendations regarding drug products that may create demonstrable compounding difficulties for outsourcing facilities.

2. *Propose DDC Listing criteria containing objective standards for determining whether specific drug attributes present compounding difficulties warranting DDC Listing.* Without any such objective standards it is unclear what or why certain drugs or categories of drug substances warrant inclusion on the DDC list.

[3] Arguably, FDA did not find evidence of any "marketing" because it is unclear what specific drugs fit into the categories of drugs it seeks to include on the DDC list.

[4] Kusoski C, Booth J, Salch S, Jozefczyk H, Kennerly-Shah J. Costs associated with United States pharmacopeia compliant infusion clinics. Journal of Oncology Pharmacy Practice. 2022;28(1):141-148. doi:10.1177/10781552211048871

3. *FDA must identify compounding conditions which, if followed, negate the DDC List criteria.* The Proposed Rule will remain inconsistent with the FD&C Act unless and until such compounding conditions are identified. *See* Section 503B(a)(6)(B).

4. *Perform a Regulatory Flexibility Analysis*. The inclusion of the Proposed Categories will cause a significant economic impact on small entities that FDA did not consider.

Respectfully submitted,

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Lee H. Rosebush, Chairman OFA

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