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Background

FDA recently published a proposed rule titled 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. This proposed rule has been years in the making. FDA originally considered this topic in June 2000, but delayed further consideration due to ongoing litigation. FDA pursued this topic again in 2013 establishing a docket to allow for the nomination of drug products or categories of drug products that were demonstrably difficult to compound. That docket remained open through a 2015 Pharmacy Compounding Advisory Committee (PCAC) meeting, wherein PCAC offered criteria that should be considered to make this determination. Following subsequent meetings to clarify those criteria, FDA established a new public docket for such nominations in 2017. Recently, on March 19, 2024, FDA filed a proposed rule in the Federal Register clarifying the first three dosage forms which it considers Demonstrably Difficult for Compounding in 503A pharmacies and 503B Outsourcing Facilities, how these decisions were made, criteria for evaluating future drug products or categories of drug products and detailing who may submit drug products or drug categories for evaluation.

Who does this apply to?

The proposed rule calls for the development of two separate lists- one for 503A pharmacies, and another for 503B Outsourcing Facilities. The three dosage forms currently under scrutiny (discussed below) apply to both 503A and 503B facilities, though the proposed rule makes it clear that this may not always be the case. Future additions to the list could apply just to 503A pharmacies depending on the characteristics of the drug product or category of drug products relative to the capabilities of 503A pharmacies as perceived by PCAC and FDA.

What are the criteria by which drug products or categories of drug products are considered?

FDA proposes six criteria for consideration when determining whether drug products or categories of drug products may be demonstrably difficult to compound:

1. Complex formulation
    a. Characteristics that make a formulation complex may include those to which particle size is critical to the safety or efficacy of the drug product or those that require specific excipients or specific quantities of excipients to achieve a certain release rate.
2. Complex drug delivery mechanism
    a. Characteristics that make a drug delivery mechanism complex may include drugs that require a specific onset, rate, and extent through specific regions of the GI tract or formulations that contain liposomes, among other considerations.
3. Complex dosage form
    a. Characteristics that make a dosage form complex include those in which the container closure systems may interact with the compounded drug and impact its intended usage. This criteria might also apply to dosage forms such as coated beads, osmotic-controlled release systems, and liposomes, among others.
4. Bioavailability achievement complexity
    a. Characteristics that make achieving appropriate bioavailability complex are wide ranging according to the proposed rule. The proposal cites entire classes of drugs such as Biopharmaceutics Classification System (BCS) Class 2 and Class 4 drugs generally as being of concern.
5. Compounding process complexity
    a. Characteristics that make a compounding process complex include those that require specialized facilities, equipment, or a complex series of steps. The proposal lists processes such as granulation, extrusion, coating, and compression as a few examples of potentially complicated compounding processes.
6. Physiochemical or analytical testing complexity
    a. Examples of drug products or categories of drug products with physiochemical or analytical testing complexity may include those that require testing such as x-ray powder diffraction, or nuclear magnetic resonance to determine constituents of the formulation.

Are there drug products or categories of drug products that the FDA considers to be demonstrably difficult to compound?

Currently, FDA's proposed rule lists three drug products or categories of drug products that are demonstrably difficult to compound for both 503A and 503B facilities. These are:

1. Oral solid modified-release drug products that employ coated systems (MRCs)
    a. This includes dosage forms in which active pharmaceutical ingredients (APIs) are released by diffusion and osmotic systems or dosage forms in which APIs must be released at specified rates, patterns, or onsets throughout the GI tract to product their effect.
2. Liposome drug products (LDPs)
    a. This includes drug products in which the API is contained in or intended to be contained in liposomes.
3. Drug products using hot melt extrusion (HMEs)
    a. Hot melt extrusion is a process through which APIs and inactive ingredients are combined at temperatures above their glass transition and/or melting points. At that point shear is applied to the melted mixture as it is pushed through an orifice and emerges as an amorphous phase with uniform content.

FDA states that they are “not aware of any marketing of compounded drugs in the three proposed categories of drug products for human use” at this time. Accordingly, FDA does not expect an impact on products currently made by compounders. However, FDA invited individuals and organizations to nominate other drug products and categories of drug products to add to the Demonstrably Difficult list in the future.

Are there drug products or categories of drug products that the FDA elected NOT to include on the demonstrably difficult to compound lists at this time?

FDA elected not to include three other nominated drug products or categories of drug products on the list at this time. FDA noted, though, that these categories of products may be addressed in future rulemaking.

1. Drug products that employ transdermal or topical delivery systems
2. Metered dose inhalers
3. Dry powder inhalers

FDA did not give a specific justification for the omission of these three categories within the proposal.

What are the implications of this proposed rule?

While your pharmacy may not be compounding MRCs, LDPs, or HMEs, this proposed rule is still of vital importance to your business. FDA intends to use this framework to determine whether other products or classes of products are demonstrably difficult to compound in the future. This very likely will include products and classes of products compounded and dispensed frequently in your pharmacy, such as hormones. We are concerned that the proposed framework lacks necessary substantive detail and gives FDA entirely too much discretion to simply say "trust us; we know when we see it." As such, we suggest that you study the framework set forth in the proposed rule closely.

- Are the criteria well-defined?
- Is there enough explanation within the criteria to give compounders sufficient information to evaluate and defend their own formulations and compounding processes?
- Are the criteria reasonably framed or tailored to accepted standards of compounding practice?

If you have concerns regarding the framework and/or products addressed in the proposed rule, we strongly suggest that you file comments to the proposed rule as detailed below.

How can I get involved?

FDA will accept comments on the proposed rule until June 18.2024. As noted above, we encourage you to closely consider the proposed rule and file comments detailing your concerns.

The proposed rule may be viewed here: Federal Register :: 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

- A link to file comments to the proposed rule and view previously-filed comments may be found on that page.
- Additionally, to view or comment on nominated drug products or categories of drug products, you can head to https://www.regulations.gov and search for Docket No. FDA–2017–N–2562.

For further information or questions, please feel free to reach out to us by heading to www.fagronacademy.us!