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October 11, 2016

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

Re: Comments on Draft Guidance Documents for Industry:

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

Docket IDs: FDA-2016-D-1309 and FDA-2016-D-1267

Dear Sir or Madam:

The Pew Charitable Trusts is pleased to offer comments on the draft guidance documents issued by the Food and Drug Administration (FDA) in July 2016 related to compounded drug products that are essentially copies of commercially available or approved drugs under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), respectively. Pew is an independent, nonpartisan research and policy organization with a longstanding focus on drug quality and safety, including that of compounded drugs.

Importance of the FDA Approval Process

The FDA-approval process is critical to protecting patient safety, thus compounding copies of approved drugs is only appropriate when the drug is in shortage, or when a modification to the approved product is necessary to meet a patient's unique clinical needs.

For a drug product to be FDA-approved, it goes through rigorous testing to ensure that the product is effective and safe for use. The process starts with extensive research and testing designed to ensure that the compound can be used safely. When a product is deemed safe enough for testing in humans, three phases of clinical trials, monitored by the FDA, are required to further demonstrate safety and effectiveness. These trials serve an important public health function by identifying the drugs for which the risks outweigh the benefits before they are broadly marketed to patients. Historical data show that, generally, only one in 10 products that enter human testing (phase 1 clinical trials) will be approved for patients.[1] It is important that public policy continue to uphold this testing regime to better ensure that only those drugs that are safe and effective make it to patients.

The approval process is not only important for testing new chemical compounds. When a pharmaceutical manufacturer wants to use an existing drug in a new way – for example, a different dosage form, or in combination with another product – it must demonstrate that this altered version of

[1] Michael Hay et al., "Clinical Development Success Rates for Investigational Drugs," *Nature Biotechnology* 32, no. 1 (2014): 40–51, doi:10.1038/nbt.2786.

the product is also safe and effective. A change in formulation can affect the way a drug is absorbed in the body, so a manufacturer must conduct bioequivalence testing to demonstrate that the new form is available in the body in the same way and results in the same drug concentration as the original product, and thus that it too is safe and effective for use. When generic manufacturers make copies of approved products, they also must perform bioequivalence studies to ensure that the generic formulation is absorbed in the same way as the branded product. Similarly, if a manufacturer wants to market a product that is a combination of two previously approved drugs, testing on the combined drug is required to demonstrate, for example, that the two compounds are stable in combination and do not interact negatively with each other.

Another important feature of the FDA approval process is that finished form products are accompanied by product labeling that provides a detailed summary of pharmacology, clinical data, precautions, dosage information, and other relevant material. Experts, including physicians, toxicologists, and pharmacologists, review the data from the clinical trials and develop labeling instructions to inform providers about the drug's appropriate use. This labeling is designed to inform providers about appropriate use of a product, including precautions, warnings, and contraindications.

After FDA approval, drug products are produced in facilities that adhere to Current Good Manufacturing Practices (cGMP), the most robust quality standards in pharmaceutical manufacturing, to help ensure consistent product quality.[2] The manufacturing controls for approved products go beyond the general cGMP that also apply to outsourcing facilities; for approved products, FDA review includes a product-specific assessment of chemistry, manufacturing, and controls to verify that the manufacturing process ensures consistent quality, purity, and strength. Finally, approved drugs are subject to post-marketing surveillance through adverse event reporting. All of these protections help to ensure that the risks of drug products are known, and that they are outweighed by the benefit to patients.

Compounding Copies of Approved Drugs

Compounding plays an important role in health care for patients whose medical needs cannot be met by an approved drug. For example, patients who are allergic to a component of a commercially available product will need a compounded version without the offending ingredient, and patients who cannot swallow pills may need a compounded liquid formulation.

There are, however, inherent risks in using compounded drugs. Because compounded drugs are supposed to be customized to meet a patient need, they are not subject to the same rigorous safety and quality testing as FDA approved drugs. Without this testing, patients and their providers may not know the risks a compounded drug poses. For example, a compounded formulation of an FDA-approved drug may or may not be absorbed in the body in the same way as the approved product. In addition, quality standards for compounding pharmacies, primarily regulated by states, vary significantly and are not as robust as those applied to pharmaceutical manufacturers and compounding outsourcing facilities. Because of these risks, compounding should not become an alternative to FDA-approved manufacturing.

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[2] For more comparing the safety measures followed by pharmaceutical companies that manufacture drugs with those used by compounding pharmacies, see these publications: The Pew Charitable Trusts, Pharmaceutical Compounding: Quality Standards for Different Scales (July 2015), available at: http://www.pewtrusts.org/~/media/assets/2015/09/drugcompounding_infographic.pdf?la=en (accessed 10/06/16); Clinical IQ, Quality Standards for Large-Scale Compounding Facilities, available at: http://www.clinicaliq.com/wp-content/uploads/2015/06/clinicaliq_compounding-quality-standards.pdf (accessed 10/05/16).

Allowing compounded drugs to be a marketed substitute for FDA-approved products undermines the critical protections built-into the drug-approval framework and creates a significant disincentive to take products through the FDA approval process. Thus federal law appropriately prohibits compounders from copying an approved drug, unless the drug is in shortage.

Comments

The comments below highlight where FDA's proposed policy preserves incentives for manufacturers to take drug products through the approval process, and where improvements would better prevent compounding from undermining the approval regime. Rather than comment on each guidance document separately, we address the guidances topically, capturing comments on the 503A and 503B guidances separately within each topic area where necessary.

Definitions of essentially copies:

Overall, FDA's draft guidance documents define "essentially a copy" of a commercially available drug (for 503A) or an approved drug product (for 503B) in a manner that will effectively and appropriately limit the circumstances in which copies of FDA-approved products may be compounded.

With respect to both 503A and 503B facilities, FDA's proposed guidance makes clear that if a compounder combines two products that are essentially copies of commercially available/approved drugs, the resulting combined product is also a copy. This helps to ensure that combining products cannot be used to circumvent the rules around making copies when the combination does not provide a therapeutic benefit for patients. In circumstances where a combination of two drugs does provide a clinical benefit to the patient, the compounder can still make the combination product if the clinical need is documented.

503A:

The draft guidance defines a drug product as essentially a copy of a commercially available drug product if: it includes the same active pharmaceutical ingredient(s); its dosage strength is the same, similar, or easily substitutable, and it is given by the same route of administration as compared to the commercially available product. FDA's proposed definition is appropriately broad to ensure that patients receive compounded copies only when a prescriber determines that it is necessary to produce a significant difference for the patient.

The inclusion of "same, similar, or easily substitutable" dosage strength in the FDA's proposed definition of "essentially a copy" will help prevent marketing of compounded products that are only marginally different from commercially available products and would not result in a significant difference to a patient. FDA interpreted same or similar to be within 10 percent of the dosage strength of the commercially available drug. With the exception of pediatric patients, the proposed 10 percent variation in dosage strength is a reasonable standard because it typically does not result in a clinically significant difference. For pediatric patients, this threshold may be too high, as even smaller variations in dosage strength can result in significant differences for infants with very low body weight.

Additionally, by clarifying that drugs that use the same API in similar dosage strength and form will be considered copies if they have the same route of administration, FDA will capture minor changes in drugs' formulations in the definition of a copy. For example, compounding a commercially available capsule into a tablet would be compounding a copy because the two products have the same route of administration. However, if the change in formulation from capsule to tablet makes a significant difference for the patient, the prescriber will document that difference, and the patient will receive the

compounded tablet. FDA's definition of a copy protects patients from receiving compounded products (in this example, the compounded tablet) if they will not result in a true difference for the patient compared to the commercially available drug.

503B:
Section 503B of the FD&C Act includes a two-part definition of when a compounded drug product is essentially a copy of one or more approved drugs. The first component only applies when the approved drug is in shortage. The second component applies in other circumstances when a product is compounded using active ingredients that are also contained in approved drugs. In the draft guidance, FDA has appropriately interpreted the first part of the definition very narrowly, and the second part more expansively.

With respect to the first component of the definition in section 503B of "essentially a copy," which applies to a drug that is "identical or nearly identical" to an approved product that is in shortage, FDA proposes to consider a compounded product to fall within this component of the definition if it has the same active ingredients, route of administration, dosage form, dosage strength, and excipients as the approved product. FDA's narrow interpretation of identical or nearly identical products ensures that when drugs are compounded because they are in shortage, they are exact copies of the approved product. This is critical because it protects patient safety by helping to ensure that the results of the safety and efficacy studies that led to the drug's approval, and any post-market analysis, are as relevant as possible to the compounded version. For example, newborns have specific clinical needs for preservative-free formulations and small doses of active ingredient. When drugs for infant patients are in shortage, the compounded versions need to have the same active ingredients, strength, and preservative-free excipients to minimize risks to these patients of administering the compounded version.

In contrast, the second part of the 503B definition, which states that a compounded drug product is essentially a copy of an approved drug if "a component of [the compounded drug product] is a bulk drug substance that is a component of an approved drug or a marketed drug" should be interpreted more broadly. FDA proposes to consider a compounded product to be "essentially a copy" if it shares an active ingredient with an approved drug, whether that ingredient is sourced from a bulk drug substance or an approved drug. Therefore, when FDA-approved drugs are not in shortage, compounding products that are essentially copies of approved drugs would only be permitted when a prescriber determines that a clinical difference will result. For example, if a compounder dilutes product outside of the range described on the FDA approved drug label, FDA's proposed interpretation would require that a prescriber document the reason a patient's medical need cannot be met by the range studied in the clinical trials that led to the drug's approval. This will help to ensure that patients only receive compounded products when approved drugs will not meet their clinical needs.

Notably, some outsourcing facilities assist providers by reconstituting, diluting, or mixing approved products according to their FDA-approved labels. For example, if a hospital needs to use an injectable product that comes in a concentrated solution, it might contract with an outsourcing facility to dilute the product so it is available to providers in the dosage strengths needed for safe administration to patients. This type of activity does not pose the same threat to the approval process as manipulation of the product outside of the product label, because the outsourcing facility is preparing the product for use in the manner supported by the clinical trials that led to that product's approval. Accordingly, FDA should clarify in the draft guidance that a product is not "essentially a copy" if it is being reconstituted, diluted, or mixed consistent with FDA-approved product information. This exception should apply only

when an approved product is being manipulated into a usable form, not when the product is being compounded from bulk ingredients.

Statement of significant and clinical differences:
The statute requires compounders to ensure that a significant or clinical difference will result for patients before compounding versions of commercially available (in 503A) and FDA approved (in 503B) drug products. FDA proposes to generally defer to the judgment of the clinicians as expressed on a prescription or purchase order. Requiring that the clinical or significant difference be documented is a reasonable policy that allows FDA to oversee compounders' fulfillment of their statutory obligation without questioning the prescriber determination of difference.

The documentation from providers is important because it helps ensure that patients receive a compounded product only when there is a clinical need for a customized formulation. The required documentation of clinical difference will promote careful consideration of the risks and benefits of prescribing a compounded product over an approved drug. Over time, if the data could be captured, the documentation could potentially provide a sufficiently robust data source to incentivize taking a compounded product through the FDA drug approval process. For these reasons, the prescriber documentation requirement is a critical component in upholding the integrity of the FDA approval system and its overall goal of ensuring safe and effective drugs for patients.

Because of the protections built-into the approval process, FDA guidance should encourage compounders creating drugs that are essentially copies of approved products to start from approved products wherever possible to meet a patient's need. Combining two sterile products into a single bag may, for example, be justified if there is a clinical need to administer the products together. However, this need to administer the products together would not justify compounding the products from bulk ingredients. FDA's guidance should require that when a compounder is creating a product from bulk ingredients that could have been made starting with FDA-approved products, the documentation should justify why it was necessary to compound from bulk.

For some prescribers, this documentation may require adjusting work flow processes, including working around issues such as whether pharmaceutical purchasers in hospitals and other health care systems are properly licensed and authorized to document clinical differences. For compounded products that are essentially copies of approved drugs, and that are needed for a patient population on a consistent basis, formulary management and information technology systems, with a templated format that allows for the statement of clinical or significant difference, might be considered for efficient implementation of the documentation requirements, so long as the significant or clinical difference for patients is routinely evaluated by the requesting prescriber or prescriber group.

One particularly important component of FDA's proposed guidance is that it that restricts the prescriber's statement of significant or clinical difference to the *therapeutic* benefits that a compounded product produces for a patient as compared to a commercially available or approved product, not differences in price. Escalating prescription drug prices is an important problem because of the effects on both patient access and health care costs. However, compounding products solely for the purpose of

creating low-cost versions of FDA-approved drug products unnecessarily exposes patients to safety risks.[3]

Drug shortages:
During drug shortages, patient access to critical medications is essential. Compounding drug products that are identical copies of commercially available and approved drugs is an important way to provide access during a shortage.

As the statute contemplates, outsourcing facilities can provide access during significant disruptions in the supply chain. Similarly, products compounded under section 503A may also provide an important alternative for expedited access to drugs in shortage, particularly when outsourcing facilities will need additional time to provide the product. FDA's proposal to permit compounders regulated under section 503A to make copies of approved drugs during drug shortages may help alleviate the public health impact of drug unavailability.

However, whether copies of shortage products are produced in 503A or 503B facilities, it is critical that compounding cease when shortages are resolved. Section 503B sets the expectation that if an outsourcing facility is copying a drug because the drug is in shortage, the approved product must be in shortage "at the time of compounding, distribution, and dispensing." This protection ensures that as soon as patients can access an approved product, they are switched to that product. It also maintains incentives for the drug manufacturer to resume production. Restricting distribution of the compounded product when the approved drug is once again available (with some reasonable window to anticipate the lag before the approved product is broadly available to patients) also mitigates the incentive for compounders to create large stockpiles of compounded product to compete with the manufactured product once it is back on the market.

For these reasons, if FDA is going to exercise enforcement discretion to permit 503A facilities to compound drugs in shortage, it should also consider restrictions similar to those placed on 503B facilities to prevent distribution of the compounded product once the approved product is back on the market. We read the draft guidance to potentially permit 503A facilities to compound drugs in shortage in anticipation of prescriptions and then, even once the approved product is on the market, to distribute that product instead of the approved product as patients present prescriptions to fill (restricted only by the limitations on anticipatory compounding, currently proposed to be 30 days).

Regular or inordinate amounts:
503A:
The statute prohibits compounding copies of approved drugs "regularly or in inordinate amounts." This restriction applies to compounded drugs that are copies of approved products and for which there is not a significant difference for a patient. Therefore, it is appropriate that FDA interpret this language narrowly to ensure that patients preferentially receive approved drugs. Limiting the number of compounded drugs that are essentially copies of commercially available products to four or fewer a month, as FDA has proposed, is a clear and enforceable threshold. This restriction applies to the most concerning type of compounding – compounded copies that compete directly with approved products yet produce no significant difference for patients. Recognizing that four prescriptions will be a small

[3] "Compounding Is Not a Safe Solution to Rising Drug Prices," The Pew Charitable Trusts, September 28, 2016. http://www.pewtrusts.org/en/research-and-analysis/analysis/2016/09/28/compounding-is-not-a-safe-solution-to-rising-drug-prices

percentage of compounds for some facilities, and a large percentage for others, the value of a clear, enforceable standard weighs against any concern about the equity of the four-prescription rule. Compounding facilities should monitor their production volume to ensure they have not exceeded compounding these products in regular or inordinate amounts.

Recordkeeping:

503A:

FDA's guidance on recordkeeping, specifically maintaining records demonstrating compliance, is critical to helping to ensure that the overall public health goals of the statute are achieved. We suggest that the draft guidance also specify that prescriptions for compounded drug products be kept separately, or otherwise in a form from which they are easily distinguishable, from those for commercially available products. This will allow for records of compounded products, including prescriber notations of significant difference, to be readily accessible and retrievable.

Restricting the compounding of drugs that are essentially copies of commercially available and approved drugs to valid patient need (demonstrated through a determination of significant clinical difference), and disruptions in the supply chain, are in the best interests of public health and safety. Thank you for your efforts to protect patients through robust implementation of the Drug Quality and Security Act, and for your consideration of these comments.

Sincerely,

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