FDA Releases Draft Guidances on Compounded Drugs, Helps to Answer "When are they Copies?"

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Some of us remember the television commercial and poster, created by the then-audio cassette company, Memorex, asking "is it live, or is it Memorex?" Forty years later, the Food and Drug Administration (FDA) could paraphrase the slogan to ask, "Is a compounded drug product essentially a copy of an approved drug product?" FDA recently released two draft guidance documents for industry, entitled "Compounded Drug Products that are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act [(FDCA)]"[1] and "Compounded Drug Products that are Essentially Copies of a Commercially Available Drug Product Under Section 503B of the [FDCA]." While the drafts are not legally binding on industry or the agency, they offer FDA's current thinking on the ever-evolving issue of pharmacy compounding. Industry has 90 days to submit comments to FDA on the two documents.

Compounded drugs have been a topic of broad interest, in part due to the tension between the potential benefits compounded drugs may provide to certain patients and, on the other hand, the potential dangers presented, because FDA does not evaluate or approve them for safety, effectiveness, and quality. Many pharmaceutical companies argue that compounders not only circumvent FDA regulatory approval controls (and thereby avoid the costs associated with new drug applications), but also undermine the commercial and innovative interests of pharmaceutical companies.

This Bulletin highlights many of the key points in the guidance documents and identifies the agency's central positions and concerns related to "commercially available drug products."

Key Background[2]

Section 503A of the FDCA

- Under Section 503A, drug products compounded for an identified individual are exempt from specific sections of the FDCA, including certain current good manufacturing practice (GMP) requirements, labeling requirements, and new drug approval requirements.[3]

- A drug may be compounded only if the licensed pharmacist or physician preparing the product "does not compound regularly or in inordinate amounts . . . any drug products that are essentially copies of a commercially available drug product."[4] Therefore, there is a question of what is meant by the phrase, "essentially a copy of a commercially available drug product."[5]

- The statutory provision states that "essentially a copy of a commercially available drug

1 The guidance documents are accessible at http://www.fda.gov/RegulatoryInformation/Guidances/UCM510154 (last accessed July 24, 2016) and http://www.fda.gov/RegulatoryInformation/Guidances/UCM510153 (last accessed July 24, 2016), respectively.

2 We will provide a general overview of the applicable laws for background and context. However, the focus of this Bulletin is on the two recent July draft guidance documents.

3 21 U.S.C. § 353a(a).

4 *Id.* at (b)(1)(D).

5 There are other conditions that must be met for a compounded drug product to qualify for the exemptions, but they are not discussed here.

product" does not include a drug product in which there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially-available drug product.[6]

Section 503B of the FDCA[7]

- According to Section 503B, drug products compounded by outsourcing facilities are exempt from certain sections of the FDCA, including specific labeling requirements, new drug approval requirements, and particular drug supply chain security requirements.[8]
- A drug may be compounded by an outsourcing facility only if "[t]he drug is not essentially a copy of one or more approved drugs."[9]
- In this case, the statute defines "essentially a copy of an approved drug" as:
  - (A) a drug that is identical or nearly identical to an approved drug, or a marketed drug not subject to certain prescription drug provisions and not subject to approval in an application submitted under section 505, unless, in the case of an approved drug, the drug appears on the drug shortage list at the time of compounding, distribution, and dispensing; or
  - (B) a drug, a component of which is a bulk drug substance that is a component of an approved drug or a marketed drug that is not subject to certain prescription drug provisions and not subject to approval in a new drug application, unless there is a change that produces for an individual patient a clinical difference, as determined by the prescribing practitioner, between the compounded drug and the comparable approved drug.[10]

FDA's Draft Guidance Documents

503A Draft Guidance

- When evaluating whether a drug product meets the conditions in 503A (and is, thus, exempt from certain requirements), FDA will first evaluate whether a compounded drug product is "essentially a copy of a commercially available drug product." If it is, the agency intends to determine whether the drug product was compounded regularly or in inordinate amounts.[11] As previously noted, FDA recognizes that compounding might be appropriate where the physician prescriber believes that the compounded medication provides a significant difference in benefit from the commercially-available drug product for a particular patient.
- *"Commercially Available Drug Product"*[12]
  - Commercially-available drugs are those on the market and are generally subject to FDCA requirements related to new drug approval, labeling, and GMP requirements.
  - A drug product is not commercially available if:

6 *Id.* at (b)(2).
7 For additional information on past 503B guidance, see AGG Bulletin at http://www.agg.com/Key-FDA-Guidance-Documents-For-Section-503B-Outsourcing-Facilities-12-17-2014/ (last accessed July 24, 2016).
8 21 U.S.C. § 353b(a).
9 *Id.* at (a)(5). Again, there are other conditions that must be met for a compounded drug product to qualify for the exemptions not discussed here.
10 *Id.* at (d)(2).
11 COMPOUNDED DRUG PRODUCTS THAT ARE ESSENTIALLY COPIES OF A COMMERCIALLY AVAILABLE DRUG PRODUCT UNDER SECTION 503A OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT, Page 4, http://www.fda.gov/RegulatoryInformation/Guidances/UCM510154 (last accessed July 24, 2016). This Bulletin's focus is on the general issue of what is meant by "copies of commercially available drug products." We will not review FDA's guidance related to whether a drug product is compounded regularly or in inordinate amounts.
12 *Id.* at 5.

- the drug product has been discontinued and is no longer marketed; or
- the drug product appears on the FDA drug shortage list and is in "currently in shortage" status.

- *"Essentially a Copy"*[13]
  - A drug product is essentially a copy of a commercially-available drug product if:

1. The compounded drug product has the same active pharmaceutical ingredient (API) as the commercially-available drug product.
   - For example, FDA recognizes that a drug product compounded without a particular inactive ingredient may produce a significant difference for a patient who has an allergy. However, FDA states that Congress did not intend for compounders to use the fact that some patients may have allergies as a basis to compound a drug without the inactive ingredient for other patients who do not have the allergy. Such a drug would be a copy.
2. The API has the same, similar, or an easily substitutable dosage strength.
   - Two drugs will have a similar dosage strength if the dosage strength of the compounded drug is within 10% of the dosage strength of the commercially-available drug product.
   - Regarding "easily substitutable dosage strength," in some cases, the same or similar dosage strength can be achieved by administration of fractional or multiple doses of a drug product. The patient could simply take less or more of a non-compounded drug. So, in such a case, compounding should not be done, because the compounded drug would have an easily substitutable dosage strength and, thus, is essentially a copy of an approved drug product.
3. The commercially-available drug product can be used by the same route of administration as prescribed for the compounded drug.
   - FDA generally will not consider a compounded drug to be essentially a copy if it has a different route of administration.[14]

503B Draft Guidance

- As noted, the statute allows compounding by an outsourcing facility only if the drug is not essentially a copy of one or more approved drugs. Therefore, FDA attempts to define certain terms to offer guidance to industry. It also provides two appendices, as flowcharts, to illustrate how it will make a determination in a particular case.
- *Definitions*
  - Approved drug means a drug product that is approved under section 505 of the FDCA (i.e., either as a new drug application or an abbreviated new drug application) and does not appear on a list of drugs that have been withdrawn or removed from the market because of safety or efficacy concerns.
  - Marketed drug not subject to section 503(b) and not subject to approval in an application submitted under section 505 means any non-prescription drug product marketed without an approved application.

13 *Id.* at 5-7.

14 FDA provides as an example an injectable drug sold in a vial that is labeled for intra-muscular use, but the drug can also be drawn from the vial by a smaller needle for subcutaneous administration. In this type of case, a compounded drug product with the same API and similar or easily substitutable strength prescribed for subcutaneous administration would generally be considered a copy and, thus, should not be compounded.

FDA refers to these products in the guidance as "covered OTC [over-the-counter] drug products."

- *Compounded Drugs and Approved Drugs*

1. Compounded Drugs that are Identical or Nearly Identical to an Approved Drug

    - FDA will consider a compounded drug to be identical or nearly identical to an approved drug if it has the same:
        - (a) active ingredient(s),
        - (b) route of administration,
        - (c) dosage form,
        - (d) dosage strength, *and*
        - (e) excipients.

    - A compounded drug product that has all of these characteristics in common with an approved drug product is essentially a copy, unless the approved drug appears on FDA's drug shortage list at the time of compounding, distribution, and dispensing.

    - If the shortage is resolved before the outsourcing facility distributes the compounded drug, FDA does not intend to take enforcement action against an outsourcing facility filling orders that it received while the drug was on FDA's drug shortage list, provided the drug also appeared on the shortage list within 60 days of the outsourcing facility distributing/dispensing the drug. That is, FDA apparently allows an outsourcing facility to fill an immediate void but, once the shortage is resolved, there must be a limit to the compounding, and a presumptive reversion to use the approved drug product.

2. Compounded Drugs that Contain a Bulk Drug Substance that is a Component of an Approved Drug

    - If a component of the compounded drug is a bulk drug substance that is also a component of an approved drug, the compounded drug product is essentially a copy of an approved drug and cannot be compounded under 503B, unless there is a prescriber determination of clinical difference.

    - Because an outsourcing facility will provide physician office stock of the compounded drug without a specifically identified patient, the facility should obtain a statement from the practitioner that specifies the change between the compounded drug and the comparable approved drug and indicates that the compounded drug will be administered or dispensed only to a patient for whom the change produces a clinical difference.

        - *Example:* A physician who regularly treats a patient with an allergy to an inactive ingredient in a particular approved injectable drug product could order a compounded version, provided the doctor includes a statement on the order that removing the particular inactive ingredient produces a clinical difference for the patient and will provide the drug only to the patient with that particular clinical need.

    - FDA does not require a particular format for the provider statements, so long as it identifies the relevant change and the clinical difference it produces for a particular patient.

    - A lower price is not sufficient to establish that the compounded product is not essentially a copy of the approved drug.

- *Compounded Drugs and Covered OTC Drug Products*

1. Compounded Drugs that are Identical or Nearly Identical to a Covered OTC Drug Product

- Section 503B directly addresses copies of an approved drug. However, it does not provide similar exemptions if the compounded drug is identical or nearly identical to a covered OTC drug on FDA's drug shortage list. With limited exception, FDA intends to apply the same policy described above, namely that the agency will consider a compounded drug to be identical or nearly identical if it has the same:
  - (a) active ingredient(s),
  - (b) route of administration,
  - (c) dosage form,
  - (d) dosage strength, ***and***
  - (e) excipients.

2. Compounded Drugs that Contain a Bulk Drug Substance that is a Component of a Covered OTC Drug Product

   - A product is essentially a copy and cannot be compounded if a component of the drug product is a bulk drug substance that is also a component of a covered OTC drug, unless there is a change that produces a clinical difference for an individual patient, as determined by the prescribing practitioner, between the compounded drug and comparable ***approved*** drug. In contrast, FDA notes: "A clinical difference between the compounded drug and an unapproved drug (such as a covered OTC drug) does not exempt the compounded drug from the definition in section 503B(d)(2)(B)" and, thus, compounding should not occur.

AGG Observations

- FDA's draft guidance documents are, in our opinion, an attempt by the agency to find a balance where it reiterates the statutory presumption that a compounder will not compound essentially copies of commercially-available drugs, but recognizes instances where a physician believes a compounded medication may be more beneficial to a specific patient. The agency seeks to define terms to minimize confusion and, perhaps, an overreaching effort by some facilities or pharmacies to compound when not appropriate or consistent with the statute. The added recommendation that a physician include a statement on the order explaining the need to compound in a given case seems to be an example where the agency wants to ensure compounding is an exception, not the rule, when there are commercially-available drugs or essentially copies of such drugs on the market.

- The 503B guidance defines identical or nearly identical drugs to mean that the two drugs have the same active ingredient(s), route of administration, dosage form, dosage strength, and excipients. Because all of these characteristics must match, some may argue that the guidance does not go far enough in eliminating compounded drugs that are actually nearly identical, but may not meet the aforementioned characteristics.

- FDA's interpretation and implementation of Sections 503A and 503B continue to evolve, but it seems clear that the agency is trying to set some parameters and expectations where compounding may be appropriate (and not appropriate). As the guidance documents are in draft form and FDA is seeking comments, more is yet to come.

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