Understanding the List of Difficult to Compound Drug Products

Presentation to the National Academy of Sciences, Engineering, and Medicine Committee re

Clinical Utility of Treating Patients with Compounded "Bioidentical Hormone Replacement Therapy"

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Overview of Presentation

- History of the Difficult to Compound List
- Statutory procedures for developing the List
- FDA’s proposed criteria for evaluating nominations for the List
- FDA’s next steps

The Difficult to Compound List Originated in Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act)

- To qualify for the exemptions under section 503A, a compounded drug product may not be a “drug product identified by the Secretary by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product” (section 503A(b)(3)(A) of the FD&C Act).

Section 503B Also Prohibits Compounding Drugs on a Difficult to Compound List

- To qualify for the exemptions under section 503B, an outsourcing facility may not compound a drug identified "on a list published by the Secretary … 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 category of drugs, taking into account the risks and benefits to patients, or … [the drug] is compounded in accordance with all applicable conditions… that are necessary to prevent the drug or category of drugs from presenting the demonstrable difficulties [identified]" (section 503B(a)(6) of the FD&C Act).

Procedure for Developing the Lists

Both 503A and 503B:

- Require FDA to develop the list of difficult to compound drugs through regulations, which means notice and comment rulemaking; and
- Before issuing regulations on demonstrably difficult to compound drugs, FDA must consult the Pharmacy Compounding Advisory Committee (PCAC).

- The FD&C Act creates some exemptions from these requirements that FDA has not yet used, and is not likely to use:
  - Under section 503A, FDA need not consult the PCAC if "the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health" (section 503A(c)(1) of the FD&C Act).
  - Under section 503B, FDA can create an interim list of drugs that are difficult to compound after notice in the Federal Register and opportunity for comment (section 503B(c)(3).

Difficult to Compound List History

- FDA first began to develop the list of difficult to compound drugs in 2000 when the law only contained section 503A.
- At a PCAC meeting in July of 2000, FDA described its proposed criteria and some of the categories of drugs that it was considering for the list.
- FDA suspended efforts to develop the list after the Supreme Court, in 2002, found certain provisions of section 503A to be unconstitutional.

Difficult to Compound List History, cont'd

- In 2013, in the DQSA, Congress amended section 503A to remove the unconstitutional provisions and revalidated the rest of section 503A, including the provisions on difficult to compound drugs. The DQSA also included section 503B which created the category of compounding outsourcing facilities.
- Immediately after passage of the DQSA in 2013, FDA resumed development of the list by soliciting nominations from the public. Seventy-one drugs or categories of drugs were nominated in response to the notice.
- In July, 2017, FDA opened a new docket to allow additional nominations for the list, and some additional drugs or categories of drugs have been nominated.
- FDA convened an internal agency working group to develop the criteria it would use to evaluate whether a drug product or category of drug products is demonstrably difficult to compound under sections 503A and 503B, and to lead the evaluation of the nominated drugs.

Difficult to Compound List History, cont'd

- In June 2015, FDA consulted with the PCAC to get the PCAC's views on proposed the criteria for evaluating drug products or categories nominated for the list, and since then has consulted PCAC on 6 drug categories:
  - Metered dose inhalers (Mar. 9, 2016 PCAC)
  - Dry powder inhalers (Mar. 9, 2016 PCAC)
  - Drug products that employ transdermal or topical delivery systems (Nov. 3, 2016 PCAC)
  - Oral solid modified release drug products that employ coated systems (May 9, 2017)
  - Liposome drug products (Nov. 21, 2017)
  - Drug products produced using hot melt extrusion technology (Nov. 21, 2017)

Several Reproductive Hormones Were Nominated for the Difficult to Compound List

- The nominated drugs included several hormone products:
  - bioidentical hormone pellets;
  - estradiol (oral and topical);
  - progesterone (oral and topical);
  - progesterone with estradiol (oral and topical)
  - testosterone pellets; and
  - estriol (dosage form not specified)
- FDA has not yet presented information on these drugs to the PCAC

FDA's Evaluation Criteria

FDA has developed six criteria that it proposes to use to develop the list of difficult to compound drugs:

1. Complexity of the formulation
2. Complexity of the drug delivery mechanism
3. Complexity of the dosage form
4. Complexity of achieving bioavailability
5. Complexity of the compounding process
6. Complexity of physicochemical or analytical testing

1. Complex Formulation

- Formulation in which the ingredients are required to have certain unique characteristics or properties that are necessary to achieve and maintain the proper performance of the drug product
- Examples may include:
  - Crystalline (including polymorphs) or amorphous forms
  - Chirality
  - Particle size
- As a result of consultation with the PCAC, FDA added to its explanation of this criterion the statement: "The compatibility and/or stability (physical and chemical) of the API(s) and/or excipients in the final dosage unit may be evaluated to determine if the compounded drug product has a complex formulation."

2. Complex Drug Delivery Mechanism

- The way in which the drug product is targeted for delivery and/or released from the dosage form in the body to achieve the desired therapeutic effect
- Examples may include:
  - Coated beads
  - Polymeric matrices
  - Liposomes

3. Complex Dosage Form

- Physical dosage units with characteristics that are difficult to consistently achieve and maintain
- Examples may include:
  - Propellant based aerosolized products
  - Dry powder inhalers
- As a result of consultation with the PCAC, FDA added to its explanation of this criterion the statement: “Complex dosage form also refers to container closure systems that may interact with the compounded drug and affect its intended use, either through physical (inconsistent dose administration) or chemical interactions between the compounded drug and the container closure system.”

4. Bioavailability

- The rate and extent to which the active ingredient, or its active moiety, is absorbed into the body and becomes available at the site of action
- Examples may include:
  - Characteristics of the API or compounded drug product resulting in inconsistent bioavailability

5. Compounding Process Complexity

- Compounding the drug product requires multiple, complicated, or interrelated steps and/or specialized facilities and/or equipment to achieve the appropriate drug product
- Examples may include:
  – Creating multi-particulate dosage forms of solid oral beads (requires wet granulation, extrusion, spheronization, fluid bed drying, coating or curing before they are processed into the final dosage form)

6. Physicochemical or Analytical Testing Complexity

- The challenges presented with confirming the end product testing for batch-to-batch uniformity, potency, purity, and quality of a drug product
- Examples may include:
  - Specialized analytical instruments and/or training for identifying constituents of complex mixtures by nuclear magnetic resonance, mass spectrometry, and/or X-ray powder diffraction
  - Cell-based assays for performance characterization

Application of the Criteria

FDA has said:

- The criteria are not mutually exclusive; a drug product, or category of drug products, may meet one or more of these criteria;
- The criteria will be considered individually and collectively when evaluating whether a drug product or category of drug products is demonstrably difficult to compound; and
- No single criterion will be considered dispositive.

FDA Is Actively Working on a Proposed Rule on Difficult to Compound Drugs

- In connection with the Office of Management and Budget's Spring Unified Agenda, on May 24, 2019, FDA announced that it is developing a proposed rule
  - to establish the criteria it will use to evaluate whether drug products and categories of drug products are demonstrably difficult to compound under sections 503A and 503B of the Act, and
  - to identify certain categories of drugs that it views as being demonstrably difficult to compound
- The Spring Unified Agenda is a semiannual compilation of information about regulations under development by federal agencies across the government that addresses recent regulatory actions and future priorities. Inclusion on the agenda means FDA is actively working on the proposed rule, but does not guarantee when the proposed rule will be published.

How does this relate to the work of the Committee?

- The Committee has been asked to, among other things:
  - Describe the physical and chemical characteristics of compounded BHRT drug products (e.g., active ingredient, inactive ingredient(s), dosage forms, routes of administration, strengths);
  - Review and assess the available evidence (or lack of evidence) regarding the safety and effectiveness of compounded BHRT drug products; and
  - Based on the available evidence, summarize findings and make recommendations with respect to the clinical utility of compounded BHRT drug products and whether the available evidence of safety and effectiveness supports use of compounded BHRT drug products to treat patients.
- Any recommendation regarding the safety or effectiveness of compounded BHRT products depends on how confident you are that they can be compounded correctly over the life of the product, and that depends in part on how difficult they are to compound.

Sample Questions to Ask Related to Difficulties in Compounding BHRT

- Does the safety or effectiveness of BHRT products depend on achieving complex formulation characteristics (e.g., particle size, polymorphism, solubility)?
- Do the formulations depend on complex drug delivery systems and can these be made correctly by most pharmacists consistently?
- Are the BHRT products provided in complex dosage forms such as combination products in which the active ingredients must be maintained in a specific proportion over the life of the product to ensure safety and effectiveness?
- How difficult is it to ensure bioavailability of the products and how is it determined whether a specific formulation is bioavailable?
- Are the compounding processes for BHRT complex? Do they require specialized equipment or facilities not likely to be found in most compounding facilities?
- Is the release testing conducted adequate to ensure that the compounded BHRT products actually are what they purport to be or is more complex testing necessary to ensure they will perform as intended?