



December 2017

GENERIC DRUGS

FDA Should Make Public Its Plans to Issue and Revise Guidance on Nonbiological Complex Drugs

Accessible Version

Why GAO Did This Study

Generic versions of brand-name drugs provide substantial cost savings for patients and the U.S. health care system. FDA, an agency within the Department of Health and Human Services (HHS), has approved generic versions of NBCDs. Some industry stakeholders have asserted that, because it is difficult to assess equivalence for these complex drugs, there could be safety and efficacy problems that might not appear until after generic versions are on the market.

GAO was asked to assess FDA's process for reviewing generic versions of NBCDs. Among other things, this report (1) identifies the scientific challenges the review of generic versions of NBCDs may present and (2) identifies and evaluates the steps FDA has taken that may help address the challenges related to the review of generic NBCDs. GAO studied the literature and examined FDA product-specific guidance. GAO reviewed information related to the five NBCDs for which FDA had approved a generic version prior to fiscal year 2017. GAO also interviewed FDA officials and a nongeneralizable selection of 19 stakeholders, including brand-name drug sponsors, sponsors of generic versions of NBCDs that have and have not received FDA approval, and external expert groups.

What GAO Recommends

FDA should announce its plans to issue and revise product-specific guidance for drugs that are nonbiological and complex. HHS concurred with GAO's recommendations.

View [GAO-18-80](#). For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov

GENERIC DRUGS

FDA Should Make Public Its Plans to Issue and Revise Guidance on Nonbiological Complex Drugs

What GAO Found

Certain drugs, referred to as nonbiological complex drugs (NBCD), have a more complex chemical structure than most other drugs. As a result, it can be more difficult to identify the physical and chemical properties of these NBCDs and, thus, more difficult to demonstrate that generic versions of these drugs are equivalent to their brand-name counterparts—a requirement for their approval by the Food and Drug Administration (FDA). To assess the equivalence of generic versions of NBCDs, drug company sponsors and FDA may need to take more steps compared with generic versions of noncomplex drugs. All but 2 of the 19 stakeholders GAO interviewed agreed that it is challenging to demonstrate equivalence. However, they disagreed about the extent of the challenges and whether those challenges could be overcome. For example, while some brand-name drug sponsors suggest it may be impossible to show that the active ingredient is equivalent between a brand-name and generic complex drug, some generic drug sponsors believe it can be done through advanced scientific methods.

GAO identified several steps that have been taken that may help address the challenges associated with reviews to determine equivalence of generic NBCDs to their brand-name counterparts. However, stakeholders disagreed about whether these steps have been sufficient. For example, to facilitate the entry of generic drugs on the market, including NBCDs, FDA issued product-specific guidance documents to industry, providing recommendations on how to demonstrate equivalence for certain products. While some stakeholders cited product-specific guidance as helpful, representatives of four brand sponsors said the guidance does not adequately address the scientific complexities of NBCDs. Further, guidance for some NBCDs was revised numerous times without any advance notification to industry, according to representatives of generic drug sponsors. Internal control standards for the federal government on communication state that sharing quality information with external parties is necessary to achieve an entity's objectives. FDA's good guidance practices regulation also specifies that the agency will publish a list of possible topics for guidance development or revision for the next year.

Although FDA publishes such a list annually, it does not include product-specific guidance documents. The lack of advance communication on guidance issuance and subsequent revisions can create setbacks for generic drug sponsors. For example, according to such sponsors, it may take considerable time, effort, and other resources for them to update their applications to market a generic drug in response to unexpected changes in guidance. This could delay or prevent the entry of some generics to the market.

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Abbreviations

ANDA	abbreviated new drug application
FDA	Food and Drug Administration
GDUFA	Generic Drug User Fee Amendments of 2012
HHS	Department of Health and Human Services
NBCD	nonbiological complex drug
NDA	new drug application

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December 14, 2017

Congressional Requesters

Generic drugs can provide substantial cost savings for patients and third-party payers and account for nearly 89 percent of prescriptions filled in the United States.¹ On average, generic drugs have retail prices that are 75 to 90 percent lower than the retail prices of their brand-name counterparts.² For patients with insurance coverage, lower costs are in the form of lower co-payments and other out-of-pocket costs. Third-party payers such as insurance companies and government health programs benefit from the significantly lower purchase prices for these drugs. While estimates vary, studies have found that generic drugs have collectively saved patients and public and private payers billions of dollars.³

A generic drug is essentially a copy of an approved brand-name drug. Typically, a drug company, or sponsor, seeking to market a generic drug in the United States submits an abbreviated new drug application (ANDA) to the Food and Drug Administration (FDA) for review to demonstrate that its product is the same as the brand version in certain ways.⁴ Specifically, ANDAs include data showing generic drugs are pharmaceutically equivalent (have the same active ingredient and other key characteristics) and bioequivalent (generally deliver the same amount of active ingredient in the same amount of time) to a brand-name drug.⁵

Most drugs are chemically synthesized and can be thoroughly characterized. That is, their molecular structure, size, shape, weight, and

¹Association for Accessible Medicines, *Generic Drug Access & Savings in the U.S.*, (Washington, D.C., 2017).

²GAO, *Generic Drugs Under Medicare: Part D Generic Drug Prices Declined Overall, but Some Had Extraordinary Price Increases*, [GAO-16-706](#) (Washington, D.C.: Aug. 12, 2016), 1.

³GAO, *Drug Pricing: Research on Savings from Generic Drug Use*, [GAO-12-371R](#) (Washington, D.C.: Jan. 31, 2012), 1.

⁴A drug sponsor is a person or entity, such as a drug company, that takes responsibility for developing a drug.

⁵See 81 Fed. Reg. 69580, 69637-8 (Oct. 6, 2016) (to be codified at 21 C.F.R. § 314.3(b) (2017)) (revising and relocating the definitions of pharmaceutical equivalents and bioequivalence).

other physical and chemical properties can be readily identified in a laboratory setting. Such data are used to demonstrate that a generic drug has the same active ingredient and performs in the same manner as a brand-name drug. There are some drugs, however, for which the demonstration of equivalence is more complicated. For this subset of drugs—that some refer to as nonbiological complex drugs (NBCD)—the characterization of their physical or chemical properties is complicated by the complexity of the drug’s active ingredient or formulation. Although chemically synthesized, NBCDs are similar to biological products in that they are not easily characterized.⁶

Although FDA has categorized certain drugs as complex based on a variety of factors, according to agency officials, FDA does not identify NBCDs as a separate type of drug and does not have an official definition of them for regulatory purposes. Further, there is no pharmaceutical industry consensus on the definition of NBCDs. For the purposes of our report, NBCDs refers to drugs that are nonbiological products for which it can be difficult to demonstrate that potential generics are equivalent to brand-name products due to their complexity, for example, those with a complex active ingredient or formulation.

Despite the complexity of NBCDs, drug companies have worked to create generic versions. As of August 2017, FDA has reviewed and approved generic versions of six NBCDs through the ANDA pathway. However, some industry stakeholders have raised concerns, noting that, in their view, if a drug has not been fully characterized, then a generic version cannot be shown to be equivalent to its brand-name counterpart. They assert that there could be safety and efficacy problems that might not appear until after the generic drug is on the market.

You asked us to assess FDA’s process for reviewing generic versions of NBCDs. In this report we:

1. identify the scientific challenges FDA and generic sponsors may face during the review of generic versions of NBCDs and

⁶Biological products are derived from living organisms and generally are complex structures that are not easily characterized. Some biological products are isolated from natural sources—human, animal, or microorganism—and include such products as blood, vaccines, and human tissues, among others. Biological products may also be produced using recombinant DNA technology.

the factors FDA has considered in its approval decisions for these drugs,

2. identify and evaluate the steps FDA has taken that may help address any challenges related to the review of generic NBCDs, and
3. describe stakeholders' views on additional steps that have been proposed to address these challenges.

For all three of our objectives, we conducted a literature search for relevant publications that were published from January 2010 through December 2016.⁷ We conducted a structured search of research databases using various combinations of relevant search terms including, “nonbiologic complex drug,” “NBCDs,” and “complex drug.” Our inclusion criteria included journal articles and book chapters. We excluded editorials, news articles, and articles summarizing a conference or workshop. In addition, we reviewed articles that were recommended by stakeholders, but which did not appear in our initial search. We reviewed the identified materials and focused on those that addressed the development and FDA’s review of ANDAs for generic NBCDs and any associated challenges. After applying our inclusion and exclusion criteria, we identified 29 publications. We synthesized information from these publications to identify a list of NBCDs, a list of challenges FDA or generic sponsors face in the review of generic versions of NBCDs, and a list of steps that have been or could be taken that may help address those challenges, as explained further below.

- List of NBCDs. We reviewed the 29 publications to construct a list of drugs that were identified as NBCDs by the authors. We shared this list with the Non-Biological Complex Drugs Working Group and with the National Institutes of Health’s Nanotechnology Characterization Lab—which both have experience with NBCDs—and then revised our

⁷We excluded materials published during or before 2010 because a preliminary review of the search results (which were not time limited) revealed that materials published prior to the enactment of the Biologics Price Competition and Innovation Act of 2009 focused on NBCDs in the context of the hypothetical pathways for the approval of follow-on biologics. See Pub. L. No. 111-148, tit. VII, 124 Stat. 804 (2010) (codified at 42 U.S.C. §§ 201 *et seq.*). This law, enacted in March 2010, created an abbreviated licensure pathway for biologics. The materials in our search results published after this law reflect current law and regulation.

list based on their review.⁸ We also confirmed that FDA considers each of the 28 drugs on our final list to be nonbiological and complex. See appendix I for the final list of drugs we identified as NBCDs.

- Review Challenges and Steps to Address Them. We synthesized information from the 29 publications into a list of challenges that FDA or drug sponsors may face during the review of ANDAs for generic versions of NBCDs, as well as the steps taken—and additional steps that could be taken—that may help address those challenges. We then interviewed representatives of four sponsors of brand-name NBCDs and an association representing brand-name drug sponsors (which we refer to as “brand sponsor representatives”); four sponsors of generic versions of NBCDs that FDA approved prior to fiscal year 2017, five sponsors of generic versions of NBCDs that had not yet received FDA approval as of May 2017, and an association representing generic drug sponsors (which we refer to as “generic sponsor representatives”); and four other groups with knowledge of this topic, (which we refer to as “external expert groups”), resulting in a total of 19 stakeholder interviewees.⁹ The views of these interviewees are not generalizable, but provided us with a range of perspectives on NBCDs. For a list of the stakeholders we interviewed, see appendix II. The perspective of brand sponsors may be overrepresented in our work because there was overlap between the authors of literature review publications and brand-name sponsors. To mitigate any potential bias, we asked all stakeholders to provide their perspectives on the list of challenges, steps taken, and additional steps that could be taken. We also generally asked each stakeholder to describe any additional challenges, steps taken, and additional

⁸The Non-Biological Complex Drugs Working Group consists of experts from industry, academia, and knowledge institutes, including the Nanotechnology Characterization Lab, the University of Geneva, and two brand-sponsors of NBCDs: Allergan and Vifor Pharma Ltd. The stated mission of the Working Group is to ensure that appropriate science-based approval and post-approval standards are created and globally introduced for NBCDs to the benefit and safety of patients. There are four drugs on the final list we constructed that the Nanotechnology Characterization Lab identified as NBCDs, but the Non-Biological Complex Drugs Working Group does not consider to be NBCDs. We retained these four drugs on our final list.

⁹The brand-name drug sponsors we interviewed included one sponsor of an NBCD for which there was an FDA-approved generic version and three sponsors of an NBCD for which there were not. The generic sponsors we interviewed were the first to receive approval for generic versions of four of the five NBCDs approved prior to fiscal year 2017. We also interviewed a generic sponsor for one NBCD that was not the first to receive approval. Finally, we selected five additional generic sponsors to interview that had submitted ANDAs for NBCDs, but had not received approval because of challenges demonstrating equivalency.

steps that we did not identify as part of our literature review. We also reviewed FDA documents—including product-specific guidance documents and stakeholder comments on the guidance documents, and documents associated with FDA's implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA).¹⁰ In addition, we interviewed FDA officials.

To identify the factors that FDA used in its approval decisions, we searched FDA's online database of official information about FDA-approved brand-name and generic drugs—Drugs@FDA—to identify the drugs from our list of NBCDs that had a generic version approved prior to fiscal year 2017, the fiscal year during which we conducted our work.¹¹ For each of the drugs with an FDA-approved generic version, we reviewed FDA documents—including public documents associated with FDA's review of drug applications, responses to Citizen Petitions, press releases, product-specific guidance documents, and slide presentations—that discussed the factors the agency considered when reviewing ANDAs for these products.¹² We also interviewed FDA officials and representatives of three generic drug sponsors that received the first ANDA approvals for an NBCD about FDA's review process.¹³

Finally, to evaluate the steps FDA has taken that may help address the challenges of reviewing generic NBCD applications, we assessed the extent to which FDA adhered to its good guidance practices regulation and *Standards for Internal Control in the Federal Government* in relation

¹⁰Pub L. No. 112-144, tit. III, 126 Stat. 993, 1008 (2012) (codified as amended at 21 U.S.C. §§ 379 *et seq.*). Guidance documents are documents prepared for sponsors, other industry stakeholders, and the public that describe the agency's interpretation of, or policy on, a regulatory issue.

¹¹www.accessdata.fda.gov/scripts/cder/daf/index.cfm, accessed September 25, 2017.

¹²Citizen Petitions are submitted by external stakeholders that ask the agency to take or refrain from taking an action. For example, a petitioner can ask the agency not to approve a drug application unless certain conditions are met.

¹³We were unable to interview representatives of the first generic sponsor for one of the five NBCDs with an FDA-approved generic version because the company that first obtained FDA approval is no longer in business, and we could not identify appropriate representatives to interview. Further, one sponsor received approval for the first generic version of two of the five NBCDs with an FDA-approved generic version. Thus, we interviewed three generic sponsors about the factors FDA considered in its approval decisions for four NBCDs.

to the agency's issuance of product-specific guidance documents.¹⁴ We also reviewed the status of product-specific guidance documents for our list of NBCDs that did not yet have an FDA-approved generic. We then compared the initial issuance date for each product-specific guidance to data from FDA on when the agency first received an ANDA for each drug. To assess the reliability of these data, we reviewed related documentation and traced a selection of the data to source documents. We found these data to be sufficiently reliable for the purposes of our reporting objectives.

We conducted this performance audit from August 2016 to December 2017 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

FDA Oversight of Drugs

FDA, an agency within the Department of Health and Human Services (HHS), oversees the approval of brand-name and generic drugs for marketing in the United States. The approval of brand-name drugs is based on FDA's review of a new drug application (NDA) containing data on the safety and effectiveness of the drug as determined through clinical trials and other research.¹⁵ In order to market a generic version of a drug in the United States, sponsors must submit an ANDA to FDA, and the agency must approve the application.¹⁶ Generic drug applications are termed "abbreviated" because generally they are not required to include

¹⁴21 C.F.R. § 10.115 (2016). Internal control is a process effected by an entity's oversight body, management, and other personnel that provides reasonable assurance that the objectives of an entity will be achieved. GAO, *Standards for Internal Control in the Federal Government*, [GAO-14-704G](#) (Washington, D.C.: September 2014).

¹⁵The statutory provisions governing NDA submission procedures and requirements are at section 505(b) of the Federal Food, Drug, and Cosmetic Act (hereinafter "the Act"). See 21 U.S.C. § 355(b).

¹⁶The statutory provisions governing ANDA submission procedures and requirements are at section 505(j) of the Act. See 21 U.S.C. § 355(j).

preclinical study data (studies involving animals) and clinical trial data (studies involving humans) to establish safety and effectiveness, as is required of NDAs. Instead, generic drug sponsors may rely on FDA's previous finding that the brand drug is safe and effective by demonstrating that their drug generally delivers the same amount of the same active ingredients in the same amount of time as the brand, also known as bioequivalence. Additionally, ANDA sponsors must demonstrate that the drug is the same as a brand-name drug in the following ways:

- contains the same active ingredient;
- is identical in strength, dosage form, and route of administration; and
- is labeled for conditions of use approved for the brand-name drug.¹⁷

FDA's review of an ANDA may span several review cycles before the agency makes a decision regarding its approval.¹⁸ For example, an additional review cycle may occur if, to ensure the equivalence of the generic drug to the brand-name drug, FDA asks a sponsor to supply additional data, analyses, or other information to address concerns identified in its review. FDA requests this additional information through a complete response letter, which is a written communication to a sponsor from FDA that usually describes all of the deficiencies that the agency has identified that must be satisfactorily addressed before the application can be approved. After receiving a complete response letter, a sponsor may address the deficiencies identified in the letter and resubmit the application to FDA for another review.

The Generic Drug User Fee Amendments of 2012, known as GDUFA, was enacted to address the growing volume of generic drug applications

¹⁷Note that upon approval of a sponsor's petition, the FDA may consider a type of ANDA submission called a "petitioned ANDA" for a drug product with modifications of certain of these characteristics. See 21 U.S.C. § 355(j)(2)(C). Once an ANDA (other than a petitioned ANDA) is approved, FDA will consider the generic drug to be therapeutically equivalent (i.e., having the same clinical effect and safety profile as its brand counterpart) and, therefore, be suitable for substitution with the brand drug.

¹⁸The first review cycle begins when FDA receives an application from a generic drug sponsor and ends when FDA issues an action letter that informs the sponsor of the agency's decision about an application. If FDA does not approve the application during the first review cycle, it issues a letter describing any problems identified in the application that prevented it from being approved. A new review cycle begins if the application is resubmitted to FDA.

that are submitted to FDA for approval through the ANDA pathway.¹⁹ Legislation, known as GDUFA II, was enacted in August 2017 to reauthorize the generic drug user fee program through fiscal year 2022.²⁰ GDUFA and GDUFA II provide supplemental resources to FDA by giving it the authority to collect user fees from the generic drug industry in addition to its regular appropriations. They also authorize the collection of these fees for regulatory science research projects, to help the agency and industry to address gaps in the evaluation and development of generic drugs created by rapid changes in science and technology.

Prior to each user fee authorization, FDA negotiates with representatives of the generic drug industry to identify goals for how FDA should spend those user fees over the next 5-year authorization period. Once FDA and the industry reach agreement, the Secretary of Health and Human Services submits letters containing these commitments to Congress. These commitment letters contain performance goals for FDA's review activities. Specifically, FDA has agreed to implement program enhancements and meet certain performance goals related to the timely review of ANDAs. These goals are intended to improve the efficiency, quality, and predictability of generic drug program activities that, in turn, could accelerate FDA's review of generic applications.²¹ In its most recent letter, known as the GDUFA II Commitment Letter, FDA has also agreed to develop a list of generic drug regulatory science projects with industry input and report on its website the extent to which those projects support efficient review and timely approval of ANDAs.²² As it has in the past, FDA is expected to report annually to Congress on its progress in achieving goals identified in these commitment letters.

¹⁹Pub. L. No. 112-144, tit. III, 126 Stat. 993, 1008 (2012) (codified as amended at 21 U.S.C. §§ 379 *et seq.*).

²⁰FDA Reauthorization Act of 2017, Pub. L. No. 115-52, tit. III (Aug. 18, 2017).

²¹See Food and Drug Administration, *Human Generic Drug User Fee Act Program Performance Goals and Procedures Fiscal Years 2013-2017*, accessed September 18, 2017, <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf>. See also Food and Drug Administration, *GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022*, accessed September 18, 2017, <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf> (hereinafter GDUFA II Commitment Letter).

²²GDUFA II Commitment Letter, p. 18.

In addition, as part of its efforts to streamline the generic drug approval process, FDA assists the industry with identifying the most appropriate methods for generating evidence needed to support ANDA approval by publishing product-specific guidance documents, either as draft or final versions.²³ These guidance documents describe FDA’s current thinking and expectations on how to develop generic drug products that are therapeutically equivalent to their brand-name counterparts. FDA may periodically revise these documents to provide updated information to the industry and public.

Nonbiological Complex Drugs

According to agency officials, FDA does not have an official definition of NBCDs for regulatory purposes. However, the agency has categorized certain drug products as complex based on a variety of factors as outlined in the GDUFA II Commitment Letter. (See table 1.)

Table 1: Categories and Descriptions of Drug Products that the FDA Categorizes as Complex

Category	Examples
Complex active ingredients	Peptides, polymeric compounds, complex mixtures of active pharmaceutical ingredients, naturally sourced ingredients
Complex formulations	Liposomes and colloids
Complex routes of delivery	Locally acting drugs such as dermatological products and complex ophthalmological products and otic dosage forms that are formulated as suspensions, emulsions, or gels
Complex dosage forms	Transdermals, metered dose inhalers, and extended release injectables
Complex drug-device combinations	Auto injectors, metered dose inhalers
Other	Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement

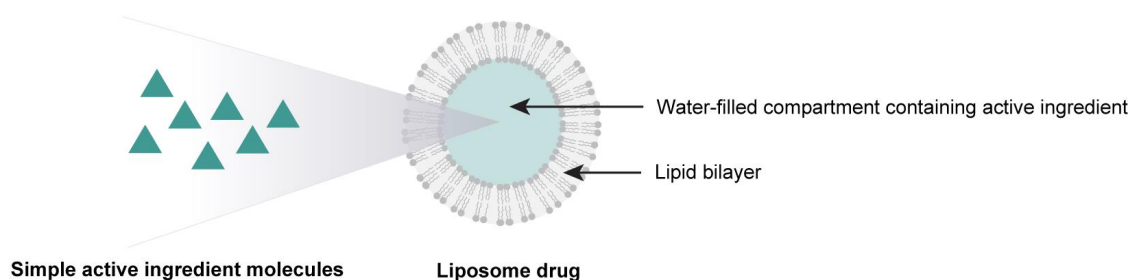
Source: Food and Drug Administration (FDA). | GAO-18-80

Our report focuses on generic drugs for which it can be difficult to demonstrate equivalence to the brand-name product due to their complexity, for example, those with complex active ingredients or

²³See 72 Fed. Reg. 30388-9 (May 13, 2007). According to FDA’s *Fact Sheet: FDA Good Guidance Practices*, the agency invites the public to comment on its draft Level 1 guidances—those that set forth the agency’s initial interpretations of new significant regulatory requirements; describe substantial changes in FDA’s earlier interpretation or policy; and deal with complex scientific or highly controversial issues—and reviews and considers the submitted comments in preparing the final documents. <https://www.fda.gov/aboutfda/transparency/transparencyinitiative/ucm285282.htm>, Accessed May 19, 2017.

complex formulations. Drugs with complex active ingredients include those for which the molecular structure is not homogeneous, but instead contains a mixture of different, closely related structures. This makes characterizing the active ingredient challenging because it may not be possible to fully isolate and quantify the individual structures in the active ingredient using analytical tests.²⁴ Drugs with complex formulations include those for which the interaction between a simple active ingredient and excipients contributes to the therapeutic performance of the drug.²⁵ One example of a drug with a complex formulation is one designed to be carried within a liposome. A liposome is a tiny, lipid-based vesicle made up of a bilayer membrane surrounding an aqueous (water-filled) inner compartment. A water soluble active ingredient is carried within the aqueous inner compartment of the vesicle. (See fig. 1.)

Figure 1: Illustration of a Drug with a Complex Formulation



Source: GAO. | GAO-18-80

Note: An example of a drug with a complex formulation is one designed to be carried within a liposome. A liposome is a tiny, lipid-based vesicle made up of a bilayer membrane surrounding an

²⁴For example, the multiple sclerosis drug Copaxone (glatiramer acetate injection) consists of a mixture of polypeptide chains, each containing the same four amino acids; in aggregate, the drug contains a specific ratio of these amino acids. According to an FDA document describing the agency's approach to approving a generic version of glatiramer acetate injection, the drug's amino acid chains vary in length and molecular weight and the sequences of the four amino acids in each chain may not be completely replicated from batch to batch of the drug. The heterogeneity of this mixture makes it challenging to fully identify the drug's physical and chemical properties.

²⁵Excipients are inactive ingredients that are not intended to provide therapeutic effects at the intended dosage, although they may act to improve product delivery, shelf life, stability, or palatability, among others.

aqueous (water-filled) inner compartment. A water soluble active ingredient is carried within the aqueous inner compartment of the vesicle. This illustration does not represent a specific drug.

For example, in the cancer drugs irinotecan liposome injection and vincristine sulfate liposome injection, the active ingredients (irinotecan hydrochloride and vincristine sulfate, respectively) are not complex. However, in each case the drug's therapeutic performance is dependent on the liposome (which is made up of inactive ingredients) that slowly releases the active ingredient.

Unlike FDA, some industry stakeholders consider NBCDs to be a distinct category of drug. However, there is no consensus definition among pharmaceutical industry stakeholders. Definitions in the literature we reviewed on NBCDs generally align with that put forth by the Non-Biological Complex Drugs Working Group.²⁶ Some stakeholders consider the Working Group's definition to be more restrictive than FDA's categorization of complex products as it only includes drugs with complex active ingredients or complex formulations. These stakeholders also stated that the definition implies that it is impossible to manufacture generic versions of NBCDs. However, other stakeholders disagreed with the creation of this definition at all, as they suggest it was developed specifically to question the validity of manufacturing generic versions of these drugs.

Generic Versions of NBCDs Pose Scientific Challenges during the Drug Development Process; FDA Considered Multiple Types of Equivalency Data in Its Approvals

Both the stakeholders we interviewed and the literature we reviewed pointed out that demonstrating pharmaceutical equivalence and bioequivalence to brand-name drugs are among the challenges facing sponsors of generic versions of NBCDs and FDA. However, there was

²⁶The Non-Biological Complex Drugs Working Group defines NBCDs as "medicinal products, not being a biological medicine, where the active substance is not a homomolecular structure, but consists of different (closely related and often nanoparticulate) structures that cannot be isolated and fully quantitated, characterized and/or described by physico-chemical analytical means. The composition, quality, and in vivo performance of NBCDs are highly dependent on the manufacturing processes of the active ingredient as well as (in most cases) the formulation."

disagreement about whether and how these challenges can be overcome. We found that in its approval of generic versions of 5 of 28 drugs prior to fiscal year 2017 that we identified as NBCDs, FDA considered a range of data when assessing equivalence to the relevant brand products.

Stakeholders We Interviewed Agreed that Demonstrating Equivalence between Brand and Generic NBCDs Is Scientifically Challenging, but Disagreed about Whether Challenges Can Be Overcome

In our literature review, we identified that demonstrating pharmaceutical equivalence and bioequivalence were among the scientific challenges FDA and generic sponsors encounter during the review of generic NBCDs.

Demonstrating pharmaceutical equivalence. According to the literature we reviewed, it is difficult to show in the case of NBCDs that the brand and generic active ingredients are equivalent if the drug's structure and other properties cannot be fully characterized. FDA officials, and all but 1 of the 18 stakeholders that commented, agreed that demonstrating pharmaceutical equivalence is challenging.²⁷ However, among these stakeholders there was disagreement over the extent of this challenge. Though the majority of stakeholders agreed demonstrating pharmaceutical equivalence is a challenge, representatives of three stakeholder groups (brand, generic, and external expert group) stated it is challenging, but only in certain circumstances.²⁸ Further, six generic sponsor representatives agreed this is a challenge that is possible to overcome. According to representatives of one generic sponsor, the use of advanced analytical tools enabled them to demonstrate pharmaceutical equivalence. Finally, in agreeing that demonstrating such equivalence can be challenging, FDA officials noted that with the advancement of

²⁷See app. II for a full list of stakeholders we interviewed. Though all stakeholders had the opportunity to comment on all of the challenges we identified in our literature review, some stakeholders did not comment on every challenge. In this case, 18 of 19 stakeholders commented on this challenge. One generic sponsor representative disagreed that demonstrating pharmaceutical equivalence is challenging and one external expert group informed us that it does not have a position on the issue.

²⁸For purposes of reporting, "brand sponsor representatives" and "generic sponsor representatives" include responses from individual brand or generic sponsors as well as the national associations that represent them.

science, problems that are currently challenging may not be challenging in the future.

Though stakeholders told us that there are some tools available to characterize drugs, there is disagreement as to what critical quality attributes—those essential to a drug’s performance and safety—should be measured in order to demonstrate pharmaceutical equivalence. Three brand sponsor representatives and representatives of one external expert group noted that although it is possible to measure many attributes of a drug, it is not clear whether the measurable attributes are the critical ones. Further, representatives of another external expert group told us that although there may not be adequate technology to fully characterize an NBCD, there are many attributes that can be characterized. There may also be many potential differences that can be identified between a generic NBCD and the brand name drug. However, according to representatives of this external expert group, these potential differences may not be critical. Two brand sponsor representatives suggested that the critical quality attributes of NBCDs were not well understood because it is not possible to adequately identify potential differences, and thus, difficult to demonstrate sameness in critical attributes. As a result, they said that demonstrating pharmaceutical equivalence is challenging, which could result in differences in safety and effectiveness between brand-name and generic versions of NBCDs.

Demonstrating bioequivalence. According to the literature we reviewed, it can also be difficult to show that a generic NBCD delivers the same amount of active ingredient in the same amount of time as the brand because conventional bioequivalence tests—measuring drug concentrations in blood plasma—may not be reflective of drug performance. For example, one NBCD we identified, cyclosporine emulsion, is an eye drop and acts directly on the eye.²⁹ As a result, only a small amount of the active ingredient is absorbed into the blood, making it difficult to measure the concentration of the drug in the blood plasma. Similar to pharmaceutical equivalence, FDA officials and all but one of the stakeholders we interviewed that commented on this challenge agreed that demonstrating bioequivalence for generic versions of NBCDs is

²⁹As of August 2017, no generic version of this brand-name drug had been approved by FDA.

challenging.³⁰ However, stakeholders disagreed about the extent of the challenge of demonstrating bioequivalence. Specifically, six stakeholders (including brand sponsor representatives, generic sponsor representatives, and representatives of external expert groups) indicated that this challenge could be considered on a case-by-case basis. Two of these stakeholders (representatives of one generic sponsor and one external expert group) said that the challenge can be overcome.

FDA officials agreed that demonstrating bioequivalence for generic versions of NBCDs can be challenging when analyzing the drugs we identified as NBCDs using the conventional bioequivalence approach, but said that they can rely on alternative methods. Specifically, FDA regulations provide for five ways that the FDA may assess bioequivalence beyond blood plasma concentration.³¹ Alternative methods include comparison of concentration of the drug in other bodily fluids and comparing clinical data of the patient response to two products. Further, generic sponsors are not required to perform tests in the human body to demonstrate bioequivalence for all drugs. For example, for solutions that are injected directly into the bloodstream and have the same active and inactive ingredients at the same concentration as the brand-name drug, bioequivalence is considered self-evident.³²

An additional challenge we identified in the literature stemming from issues in demonstrating bioequivalence is that the mechanism of action—that is, how the interaction between a drug and a target within the body (receptor, membrane, or tissue) produces a particular effect—for NBCDs may be unknown. Two brand and two generic sponsor representatives noted that knowing a drug's mechanism of action is important for establishing bioequivalence because such understanding is useful in identifying the appropriate studies to conduct. However, nine generic sponsor representatives we spoke to disagreed that an unknown

³⁰Representatives of one generic sponsor we interviewed only had experience with one NBCD and in this case, FDA waived the in vivo bioequivalence demonstration requirement as the drug is injected directly into the bloodstream. As a result, representatives of this sponsor did not comment as to whether demonstrating bioequivalence is a challenge for NBCDs. Another generic sponsor representative disagreed that demonstrating bioequivalence is a challenge. In addition, one external expert group informed us that it does not have a position on the issue.

³¹See 21 C.F.R. § 320.24 (2016). In addition, this regulation also provides that a sponsor may establish bioequivalence using any other approach deemed adequate by FDA.

³²See 21 C.F.R. § 320.22(b) (2016).

mechanism of action for a drug is a challenge. Representatives of one generic sponsor noted that brand sponsors may not understand their own drug's mechanism of action and therefore generic sponsors should not be required to demonstrate this. Representatives of one external expert group stated that this challenge should be considered on a case-by-case basis. FDA officials also indicated that an unknown mechanism of action can create a challenge for demonstrating bioequivalence for certain drugs.

Additional scientific challenges. Finally, based on our examination of the literature, we identified two additional challenges that can arise during the review of generic NBCDs:

- *First, the processes used to manufacture NBCDs are complex and may be proprietary.* Therefore, a generic sponsor may not know the exact manufacturing steps a brand sponsor uses. We identified a number of studies indicating that because the quality and composition of NBCDs are highly dependent on complex manufacturing processes, small differences in those processes between the brand and generic sponsors may result in significant differences in the drugs' clinical effects. Twelve of the 19 stakeholders (including representatives of brand, generic, and external expert groups) we interviewed and FDA officials agreed that this is a challenge. Of those, four generic sponsor representatives stated that this is a challenge that could be overcome. For example, representatives of one generic sponsor noted that if a company had a starting point and knew the critical quality attributes of a product, it should be able to advance to the next step in the process. More specifically, if the start and end are known, companies could do the work in between to get to the end point. FDA officials noted that this is a challenge on a case-by-case basis and stated that there are other drugs not categorized as NBCDs that have complex manufacturing processes.
- *Second, there may be a need to compare the immunogenicity risk—the risk of an adverse immune response—of the generic version of an NBCD to the brand version.* FDA officials and all but three stakeholders that responded on this point agreed that this is a challenge, at least for certain products.³³ For example, representatives of one external expert group noted that immunogenicity is a concern that should be evaluated on a case-by-case basis. In the case of one NBCD that FDA approved—enoxaparin

³³One external expert representative did not answer this question.

sodium injection—the agency reviewed data on the immunogenicity risk of generic versions of the drug because development of antibodies to these products has a known association with a life-threatening adverse effect. Further, since low-molecular weight heparins, like enoxaparin sodium, are naturally derived, there is a potential for impurities that could increase the risk of product immunogenicity. Three generic sponsor representatives disagreed this is a challenge. Representatives of one of the three generic sponsors indicated that there should be no reason to think the immune response would be different in a generic as compared to its brand-name counterpart, particularly if there is no risk of an adverse immune response for the brand-name drug. The representative of another generic sponsor stated that it is not a challenge because of the technology available today compared to in the past. FDA officials also agreed that determining the immunogenicity risk of generic NBCDs is a challenge and stated that they take a risk-based approach when considering the need for clinical assessment of product immunogenicity.

FDA Used a Range of Equivalency Data to Approve Generic Versions of Five NBCDs

FDA approved generic versions of 5 of 28 drugs we identified as NBCDs prior to fiscal year 2017 and considered a range of data when assessing equivalence to the relevant brand product. (See table 2.)

Table 2: The Nonbiological Complex Drugs (NBCD) with a Generic Version Approved by FDA Prior to Fiscal Year 2017

Brand name ^a	Generic name	Selected indications	Year first generic approved	Number of FDA-approved generic versions
Diprivan	Propofol	Induces anesthesia	1999	3
Lovenox	Enoxaparin sodium injection	Blood clots	2010	3
Ferrlecit	Sodium ferric gluconate complex in sucrose	Iron deficiency anemia	2011	1
Doxil	Doxorubicin hydrochloride (liposomal)	Ovarian and other cancers	2013	2
Copaxone	Glatiramer acetate injection	Multiple sclerosis	2015	1

Source: GAO analysis of Food and Drug Administration (FDA) information. | GAO-18-80

^aAnother NBCD on our list, Renvela, had a generic version approved during fiscal year 2017.

In contrast to the typical assessment of sameness for less complex drugs, FDA considered a group of overlapping tests to determine equivalence between brand and generic versions of these five drugs. For four of the

five drugs (enoxaparin sodium injection, sodium ferric gluconate complex in sucrose, doxorubicin hydrochloride (liposomal), and glatiramer acetate injection), FDA relied on extensive characterization data to determine whether the proposed generic and brand drug were pharmaceutically equivalent.³⁴ Although the factors considered were specific to each drug, FDA reviewed data on such attributes as molecular weight distribution, particle characteristics, and composition of various drug components. FDA officials and representatives of the sponsors with approved generics we spoke with generally agreed that, because of the complexity of these products, the characterization data considered were more extensive than what the agency would typically consider for a less complex drug. FDA officials told us that for typical small-molecule drugs it is easy to demonstrate active ingredient sameness as there are established analytical methods to measure molecular structure. For complex products, it is important to review additional data to ensure a sponsor is able to consistently manufacture the same product. For generic versions of enoxaparin sodium injection and glatiramer acetate injection—which FDA officials told us contain the most complex active ingredients of the five drugs—the agency supplemented the characterization data by reviewing additional data from biological assays to determine or confirm active ingredient sameness, as well as other data. In the case of enoxaparin sodium injection, which is derived from a natural source (pig intestines), FDA also considered data from an animal model and other tests to evaluate impurities to confirm that the immunogenicity risk of the generic product was no greater than the brand. FDA officials told us that by relying on multiple confirmatory tests, the agency could mitigate the risk that the proposed generic product was different from the brand.

For three of the five drugs—propofol, sodium ferric gluconate complex in sucrose, and doxorubicin hydrochloride (liposomal)—FDA reviewed data from laboratory tests and tests conducted by generic sponsors in patients or healthy volunteers to assess bioequivalence. The agency waived the in vivo bioequivalence demonstration requirement for the two other drugs—enoxaparin sodium injection and glatiramer acetate injection—because they are solutions administered as an injection directly into the

³⁴For the fifth drug, propofol, the formulation is complex, but the active ingredient is not, according to FDA officials. Therefore, extensive characterization data were not needed to demonstrate active ingredient sameness.

bloodstream.³⁵ Thus, as for other injectable versions of complex and non-complex drugs with the same quality and quantity of active ingredients as their brand-name drugs, it was assumed that these generic drugs would deliver the same amount of active ingredient in the same amount of time as the brand.

FDA Has Taken Steps that May Help Address Scientific Challenges Related to Generic NBCDs, but Does Not Inform Sponsors of Its Plans to Issue Product-Specific Guidance

According to the literature we reviewed, FDA has taken steps that may help address the scientific challenges the review of generic NBCDs present. FDA has issued product-specific guidance to help generic sponsors understand how to demonstrate that their products are equivalent to brand-name drugs. However, stakeholders expressed concerns about its contents, timeliness, and lack of advance notice.

FDA Has Taken Steps That May Help Address Several Challenges the Review of Generic NBCDs Present

We identified two types of actions that FDA has taken which, according to the literature we reviewed, may help address the challenges the review of generic NBCDs present: using advanced analytical characterization methods and prioritizing certain types of GDUFA regulatory science research. FDA has relied on advanced analytical characterization methods to make approval decisions for generic NBCDs. For example, FDA established four “sameness” criteria for generic versions of glatiramer acetate injection that recommended that generic sponsors use advanced technology to provide data such as physicochemical characterizations including spectroscopic fingerprints and certain structural signatures that demonstrate the secondary structures of their

³⁵FDA may waive the requirement to demonstrate bioequivalence in the human body for certain drugs, including certain drugs that are solutions administered by injection that are formulated with the same active and inactive ingredients at the same concentration as the brand-name product. See 21 C.F.R. § 320.22(b) (2016).

proposed generic product.³⁶ FDA officials suggested that such advancements in the technology used for demonstrating drug equivalency have improved the scientific community's understanding of complex products. FDA officials said that though the demonstration of pharmaceutical equivalence for certain products may seem scientifically impossible now, such demonstration may be possible in as little as a month because of swift advancements in technology.

The stakeholders we interviewed generally agreed that there has been technological advancement in demonstrating drug equivalency, but noted that some challenges persist. For example, 5 of 10 generic sponsor representatives as well as representatives of three of four external expert groups that we interviewed agreed with FDA that scientific advancements have been beneficial in enhancing the ability to demonstrate equivalency for complex products.³⁷ However, two generic sponsor representatives described a challenge with using such advanced methods. According to one of these generic sponsor representatives, some brand NBCD sponsors have capitalized on the complexity of the data used to demonstrate equivalence in order to generate controversy that could delay approval and market acceptance of generic versions of these products. Another generic sponsor representative said that brand NBCD sponsors have tried to call into question the use of innovative approaches by using Citizen Petitions and other means to cast scientific doubt on the development and approval of affordable complex generics. All five brand sponsor representatives and one external expert group expressed different concerns. They questioned whether recent technological advances have been adequate to overcome the challenges the reviews of generic NBCDs present. Two brand sponsor representatives and one external expert group suggested that FDA's approach of relying on a

³⁶Spectroscopic fingerprints are measurements of the emission or absorption of radiant energy (e.g., infrared, X-rays, radio waves) by certain components of a drug using such tools as nuclear magnetic resonance spectrometers. The secondary structure of a polypeptide describes the three-dimensional folding of its amino acid chains.

³⁷Though stakeholders had the opportunity to comment on all of the steps taken, which we identified in our literature review, some stakeholders did not comment on every step taken. In this case, two generic sponsor representatives did not comment on the use of advanced analytical characterization methods and three generic sponsor representatives and one external expert group agreed that there has been technological advancement in demonstrating drug equivalency, but did not address the extent to which such advancements have been beneficial. For purposes of reporting, "brand sponsor representatives" and "generic sponsor representatives" include responses from individual brand or generic sponsors as well as the national associations that represent them.

group of overlapping tests to make approval decisions has not been sufficient to demonstrate equivalency for generic NBCDs. One brand sponsor representative said that because not all of the critical quality attributes for NBCDs are known, generic NBCD sponsors can only show similarity to an extent and noted that technology is not yet at the point where these products can be fully characterized.

The second step we identified that may help address the challenges the review of generic NBCDs present, according to the literature we reviewed, is FDA's prioritization of certain regulatory science research activities. FDA established the GDUFA Regulatory Science Research Program to support projects that could potentially enhance the development of generic drugs, and the agency annually creates a list of topics to help prioritize research activities. According to FDA's annual lists of regulatory science priorities for generic drugs, for each fiscal year from 2014 through 2017, FDA has made "equivalence of complex products" a GDUFA regulatory science research priority. FDA officials said that this initiative has provided for internal studies, external grants, and other external collaborations to help advance methods for demonstrating equivalency for complex products. (See table 3 for examples of such activities.)

Table 3. Examples of FDA-Supported Regulatory Science Research Projects Related to Its Equivalence of Complex Products Priority Area

Grant or contract name^a
Development of bio-relevant in-vitro assay to determine labile iron in the parenteral iron complex product
In vitro in vivo correlations of parenteral microsphere drug products
Evaluation of dissolution methods for complex parenteral liposomal formulations
Development of a liposome doxorubicin product drug release assay
Development of hydrogel-based in vitro dissolution apparatus for microparticle formulations
Evaluation of in vitro release methods for liposomal amphotericin B
Development of physiologically based pharmacokinetic simulation for long-acting injectable microspheres
Computational drug delivery; leveraging predictive models to develop bioequivalent generic long-acting injections
Influence of raw materials, manufacturing variables, and storage conditions on release performance of long acting release microsphere products
Novel method to evaluate bioequivalence of nanomedicines
Investigation of peptide interactions in microsphere drug products
Advanced analytical techniques for mixed polymer drug-delivery systems
Critical process parameters for the preparation of amphotericin B liposomes
Pulsatile microdialysis for in vitro release of ophthalmic emulsions

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-18-80

^aThe information presented in this table was obtained directly from FDA. We did not edit grant or contract names to correct typographical or grammatical errors, and we reprinted the abbreviations and acronyms as they were provided by the FDA.

Eighteen of the 19 stakeholders that we interviewed expressed support for the GDUFA regulatory science priorities, but some expressed concern about whether the initiatives are sufficient to overcome the challenges the review of generic NBCDs present.³⁸ One brand sponsor representative suggested that the commissioning of regulatory science research for complex products highlights that there are challenges with approving these products through the ANDA pathway. In addition, some stakeholders expressed concerns about FDA's management of the GDUFA regulatory science initiatives. Two generic sponsor representatives advocated for FDA to provide greater transparency and stakeholder involvement in the prioritization of GDUFA research activities. One of these representatives suggested that, although FDA holds annual public meetings to discuss the GDUFA regulatory science initiatives with stakeholders, the agency has not been open to implementing stakeholder recommendations about specific research activities. In our own recent report examining FDA's implementation of GDUFA, we noted that FDA officials were cognizant of stakeholder concerns, but that FDA officials said that decisions about which projects to fund are an inherently governmental function and should be made internally to support public health.³⁹ We also reported that FDA officials plan to improve communications with industry about the priorities list. For example, in the GDUFA II Commitment Letter FDA pledges to conduct a public workshop annually to solicit input for its list of GDUFA II Regulatory Science initiatives. After considering this input, FDA plans to post the list on its website.

FDA Has Issued Product-Specific Guidance, but Stakeholders Expressed Concerns about Its Contents, Timeliness, and Lack of Advance Notice of Guidance Issuances and Revisions

FDA has issued product-specific guidance to industry for NBCDs (as well as for other complex products, and non-complex products), which,

³⁸One stakeholder did not comment on this step taken.

³⁹GAO, *Generic Drug User Fees: Application Review Times Declined, but FDA Should Develop a Plan for Administering Its Unobligated User Fees*, [GAO-17-452](#) (Washington, D.C.: May 25, 2017), 37.

according to the literature we reviewed, may help address the challenges the review of generic NBCDs present. However, stakeholders identified opportunities to improve various aspects of the guidance. Product-specific guidance documents provide a drug sponsor with recommendations for how to demonstrate equivalency for specific products, such as recommendations for how to design bioequivalence studies. In June 2010, FDA announced procedures by which the agency would make recommendations on the design of bioequivalence studies available to the public through issuing product-specific guidance documents online and by periodically announcing their availability in the Federal Register to ensure equal access to this information, rather than sharing that information with individual sponsors only if they requested it.⁴⁰ In 2014, FDA established an internal Bioequivalence Review Committee that meets monthly to identify drugs for which a product-specific guidance document should be developed, as well as to monitor the status of guidance undergoing initial development or revision. Officials told us that FDA seeks to develop an approval framework and share it with sponsors before an ANDA is submitted to facilitate industry's drug development programs and make the FDA review process more efficient.

FDA has issued product-specific guidance documents recommending the information needed to demonstrate equivalence for 17 of the 28 drugs on our list of NBCDs, as of August 2017. (See table 4.) In addition to the 5 for which FDA had already approved a generic version prior to fiscal year 2017, FDA had received an ANDA for 7 additional drugs and product-specific guidance has been issued for all 12 of these drugs.⁴¹

⁴⁰75 Fed. Reg. 33311 (June 11, 2010) (issued following announcement of draft guidance at 72 Fed. Reg. 30388 (May 31, 2007)).

⁴¹Three of the seven NBCDs for which FDA has received, but not yet approved, an ANDA prior to fiscal year 2017 appear on the agency's June 2017 *List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic*. FDA published that list to improve transparency and encourage the development and submission of ANDAs in markets with no competition. The agency also committed to expediting the review of generic drug applications in markets where there are fewer than three approved generic versions of a given product. FDA approved a generic version of another of these seven NBCDs—Renvela (sevelamer carbonate)—during fiscal year 2017.

Table 4: Status of FDA Guidance Development for Generic Versions of 28 Brand-Name Nonbiological Complex Drugs as of August 2017

	Status of guidance development	Number of drugs
Guidance issued	Generic version approved	5 ^a
	Generic application submitted, but no generic versions approved	7
	No generic applications submitted	5
No guidance issued	No generic applications submitted, brand is discontinued	4
	No generic applications submitted, brand is on the market	7
Total	Total	28

Source: GAO analysis of Food and Drug Administration (FDA) information. | GAO-18-80

^aIn addition to the five nonbiological complex drugs (NBCD) for which FDA approved a generic version prior to fiscal year 2017, FDA also approved a generic version of an additional NBCD—Renvela (sevelamer carbonate)—during fiscal year 2017.

FDA has not issued guidance for 11 of the 28 drugs we identified as NBCDs. In 4 of the 11 cases, the brand product has been discontinued. FDA officials told us that if a brand product is discontinued, the agency will not typically issue product-specific guidance unless there is specific interest from industry. Finally, for the 7 cases in which the brand product is still being marketed, but for which FDA has not yet issued a guidance document, officials told us that there is no significant use of the brand product on the market in 3 of the 7 cases. Thus, according to FDA officials, developing product-specific guidance is a low priority unless there is subsequent specific interest from industry. For the other 4 drugs, FDA officials told us that the agency plans to issue guidance as the science becomes available, noting that in most cases, the guidance documents are already under development.

Five generic sponsor representatives and one external expert group that we interviewed said that FDA's product-specific guidance has been helpful. Representatives of one external expert group suggested that generic drug sponsors learn a lot from FDA's guidance because it can serve as a roadmap for how to receive approval of a generic product. One generic sponsor representative cited such guidance as being particularly helpful when no generic version of the drug has been approved. However, both brand and generic sponsor representatives expressed concerns with the adequacy of FDA's guidance, but for different reasons. Four of the five brand sponsor representatives we interviewed said FDA's guidance does not adequately address the scientific complexities of NBCDs. One brand sponsor representative indicated that the criteria FDA

outlines in its guidance for one NBCD do not demonstrate product “sameness,” but rather product “similarity.” Another brand sponsor representative referred to FDA’s draft guidance for one NBCD as being “aspirational” because some of the methods needed to provide the data FDA recommended in the guidance have not been developed.

Additionally, five generic sponsor representatives and one external expert group expressed concerns that FDA does not provide enough detail in the guidance for drug sponsors. One generic sponsor representative suggested that, in addition to telling sponsors what data are needed for product approval, FDA should specifically outline what methods sponsors should use to generate the recommended data. FDA officials said that the agency is aware of these specificity concerns and suggested that FDA provides sufficient information in the guidance documents to help generic drug sponsors demonstrate equivalency. FDA officials acknowledged that there are some aspects of the process that are not included in their guidance, such as recommending a particular method when multiple methods can be used to provide certain data. As a result, generic drug sponsors are still expected to determine the appropriate method to use to demonstrate equivalency as FDA cannot test every possible way to measure a particular parameter. FDA officials noted that guidance is non-binding and sponsors have the option of developing better or alternative methods for demonstrating product equivalence for FDA’s review. However, two generic sponsor representatives told us that FDA expects sponsors to follow the guidance. One generic sponsor representative told us that any disclaimers in FDA guidance about alternative approaches being acceptable are merely “window dressing.” Another generic sponsor representative told us that typically, FDA is not willing to entertain approaches not in line with guidance. FDA officials stated that a generic drug can still be approved if the sponsor deviates from FDA’s guidance, though they told us that the vast majority of sponsors follow the guidance.

Several stakeholders also expressed concerns about FDA’s guidance-issuance process. First, six generic sponsor representatives said that FDA should issue draft guidance sooner, such as before ANDAs are submitted for a drug. FDA officials told us that for all five NBCDs with a generic version approved prior to fiscal year 2017, the agency had a general sense of the evidence it believed a generic sponsor would need to submit to satisfy the approval factors it would consider before a generic sponsor submitted the first ANDA for a given product. However, in four of five cases FDA did not release product-specific guidance documents to industry outlining how to demonstrate equivalence until after the first ANDA approval. (See table 5.) Instead, sponsors generally learned about

these factors through discussions with agency officials and through complete response letters—which outline changes a sponsor needs to make before FDA will approve an application—after submitting an ANDA.

Table 5: Timing of Product-Specific FDA Guidance Issuance in Relation to Generic Application Submission and Approval for the Five Nonbiological Complex Drugs with Generic Versions Approved Prior to Fiscal Year 2017

Drug name ^a	Submission of first approved generic application ^b	First generic approval	First publicly available product-specific guidance issued
Doxorubicin hydrochloride (liposomal)	June 2011	February 2013	February 2010
Enoxaparin sodium injection	August 2005	July 2010	October 2011
Glatiramer acetate injection	December 2007	April 2015	April 2016
Propofol	March 1997	January 1999	June 2016
Sodium ferric gluconate complex in sucrose	March 2006	March 2011	June 2013

Source: GAO analysis of Food and Drug Administration (FDA) information. | GAO-18-80

^aFDA approved a generic version of a sixth nonbiological complex drug—sevelamer carbonate—during fiscal year 2017.

^bFDA may have received an application for a generic version prior to receiving the applications that were ultimately the first to be approved. However, as required by 21 C.F.R. § 314.430 (2016), FDA will not disclose the existence or other information concerning an unapproved application unless that information is publically disclosed by the sponsor.

For the other 23 drugs on our list of NBCDs without a generic version approved prior to fiscal year 2017, FDA issued guidance before a generic sponsor submitted an ANDA in 8 cases. (See table 6.) For 2 of these 8 drugs, however, FDA issued guidance 1 year or less before the first ANDA was submitted, which may have been too late in the process to be helpful for generic sponsors, who generally told us that they begin developing their ANDAs years before submitting them to FDA. However, for 5 of the 8 drugs, FDA has issued a product-specific guidance document and no ANDAs have been submitted. For the remaining drug, FDA issued guidance more than 1 year before the first ANDA was submitted.

Table 6: Timing of FDA Guidance Issuance in Relation to Generic Application Submissions for 23 Brand-Name Nonbiological Complex Drugs as of August 2017

Status of guidance development	Number of drugs
Guidance issued	
Before approval of first generic version, but after first generic application submitted	4

Status of guidance development	Number of drugs
Before approval of first generic version and before first generic application submitted ^a	8
No guidance issued	11
Total	23

Source: GAO analysis of Food and Drug Administration (FDA) information. | GAO-18-80

^aThis category includes drugs for which a generic application has been submitted and those for which a generic application had not yet been submitted as of June 2017.

FDA does not consistently share information about its plans to issue and revise guidance with the public. FDA officials told us that, on a quarterly basis, the agency posts new product-specific guidance documents or revisions to existing product-specific guidance documents on its website but does not provide prior notice to industry that a product-specific guidance document is being developed or is under revision.⁴² Initial issuance of product-specific guidance or revisions to existing product-specific guidance without advance notice to industry is inconsistent with federal internal control standards for external communication, which state that agencies should externally communicate the necessary quality information to achieve the agency's objectives.⁴³ This lack of prior notice is also inconsistent with FDA's good guidance practices regulation, which states that once a year, FDA will publish, both in the Federal Register and on the Internet, a list of possible topics for future guidance development and revision during the next year.⁴⁴ FDA does publish such a list annually and may update this list during the year on a case-by-case basis. However, it does not include product-specific guidance documents in this annual guidance agenda.

As part of GDUFA II, FDA has committed to issuing most product-specific guidance for noncomplex products at least 2 years prior to the earliest lawful ANDA filing date for NDAs containing new chemical entities approved on or after October 1, 2017. However, because the science for

⁴²"Product-Specific Guidances for Generic Drug Development," U.S. Food and Drug Administration, accessed September 27, 2017, <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>. This web page also contains a list of all existing product-specific guidance documents, in addition to the newly issued and revised guidance documents. FDA officials told us that the agency generally publishes new product-specific guidance documents as draft, not final, guidance.

⁴³GAO-14-704G, Principle 15.

⁴⁴21 C.F.R. §10.115(f)(5) (2016).

demonstrating equivalency is not always available for complex products, FDA officials told us that they have not committed to a specific time frame for providing complex product guidance, instead committing to issue such guidance as soon as scientific recommendations are available. Officials told us that in order to resolve open scientific issues, FDA may need to conduct research or laboratory investigations, which may take longer than the time it takes to develop guidance for noncomplex products.

Several stakeholders described challenges that arise when FDA unexpectedly issues or revises such guidance after a sponsor has already begun its drug development work. Four generic sponsor representatives said that during ANDA development or FDA review for several NBCDs, relevant guidance was either initially issued or revised multiple times without any advance public notice. The representatives independently equated this to FDA “moving the goalposts” or “moving targets.” Nine generic sponsor representatives indicated that guidance revisions may create setbacks for sponsors, who were developing their ANDAs to meet prior equivalency standards. For example, one generic sponsor representative told us that if FDA changes the guidance in relation to a human bioequivalence study, a sponsor that has already conducted a study in line with the prior guidance document may be unable to recruit additional human subjects, which can cause a delay or cause a sponsor to question whether to continue pursuing the ANDA. This representative also noted that, for some brand-name drugs, there is a limited supply available on the market, so finding additional doses against which to compare a proposed generic can be challenging. Further, a sponsor may need to manufacture additional batches of its proposed generic product, which involves time and production line space in the sponsor’s manufacturing establishment. Another generic sponsor representative concurred that unanticipated guidance issuance or revisions can create logistical challenges, noting that some complex liposomal drugs are only administered once a month, so having to repeat a study with such a product would be time consuming and expensive. A third generic sponsor representative also noted that unnecessary testing on humans—which may occur if a bioequivalence study needs to be redone—raises ethical concerns.

FDA officials told us that they do not include product-specific guidance documents in the annual guidance agenda or otherwise publicly announce the status of initial issuance or planned revisions for a number of reasons. First, officials told us that the relative volume of product-specific guidance documents issued or revised in a given year is much larger than the more general guidance documents included on the

guidance agenda.⁴⁵ According to the annual report of FDA's Office of Generic Drugs, during calendar year 2016 FDA issued or revised 249 product-specific guidance documents.⁴⁶ In comparison, the 2016 Center for Drug Evaluation and Research guidance agenda lists 104 guidance documents that the Center was planning to issue or revise in calendar year 2016.

Second, officials told us that the process of drafting and internally reviewing product-specific guidance documents is more fluid than for other more general guidance documents that are included on the guidance agenda. According to FDA officials, the amount of time it takes to initially draft or revise a product-specific guidance document varies greatly due to the scientific complexity of the issues involved. Officials told us that some product-specific guidance documents may be identified as being in need of revision and subsequently revised before the next annual guidance agenda is issued. Alternatively, drafting or revising product-specific guidance documents may require consultation with other FDA offices. As a result, FDA officials told us that they may think that a guidance document will be ready for initial issuance or revised issuance in a certain time frame, but they may not always meet this estimated time frame. Officials said that if FDA published a list of product-specific guidance documents to be issued or revised in the next year and then did not publish all of the guidance documents on the list within the estimated time frame, then sponsors may become frustrated and not trust the subsequent accuracy of the list. However, FDA's good guidance practices regulation notes that the agency will publish a list of possible topics for guidance development and revision during the next year. Because the regulation uses the word "possible," the list could include topics on which the agency ultimately does not issue or revise guidance within the year. In comparing the 2016 Center for Drug Evaluation and Research guidance agenda—which includes the more general guidance topics—to the 2017 agenda, we found that 46 of 104 guidance topics appeared on both agendas. While FDA does not always issue or revise all of the general guidance documents that it intended for a given year, its publication of

⁴⁵Examples of general guidance topics that do appear on the guidance agenda include: ANDA Submissions – Identifying Reference Products; Assessing Adhesion for ANDAs with Transdermal Delivery Systems and Topical Patches; and Submission of ANDAs for Certain Highly Purified Synthetic Peptide Drug Products.

⁴⁶U.S. Food and Drug Administration, *Office of Generic Drugs 2016 OGD Annual Report: Ensuring Safe, Effective and Affordable Medicines for the American Public* (Silver Spring, Md.: January 2017).

possible general guidance topics provides a greater degree of transparency than is provided to sponsors interested in the development of product-specific guidance.

Finally, FDA officials told us that they do not publicly announce the status of product-specific guidance document development, either on the annual guidance agenda or otherwise, because it could create uncertainty for industry. They said that announcing revisions were underway without outlining what the revisions were and when they would be completed, could lead sponsors to submit questions to FDA, which could not be answered at that time and would be burdensome for the agency. Further, if a sponsor is actively developing a product and then learns that FDA may issue or revise a relevant guidance, FDA officials said that the sponsor might put its development efforts on hold while awaiting the guidance issuance, which could delay generic entry. However, four generic sponsor representatives suggested that the unanticipated issuance or revision of such guidance may already be delaying generic entry. One of these generic sponsor representatives told us that after the sponsor had already submitted its ANDA for iron sucrose injection, FDA issued a product-specific guidance and then revised it. The representative told us that the company decided to stop pursuing this ANDA given the complexity of the drug and uncertainty about whether FDA would change its guidance again. As of August 2017, FDA has not approved a generic version of iron sucrose injection.

Despite FDA officials' concerns about the potential challenges associated with publicly announcing anticipated guidance issuance or revision, eight generic sponsor representatives were supportive of greater transparency about when the agency planned to initially issue or revise existing product-specific guidance.⁴⁷ Five generic sponsor representatives told us that such transparency could be helpful in that a sponsor could decide to postpone bioequivalence or other studies if it knew revised guidance was forthcoming. Three generic sponsor representatives said that such information could help with planning or resource allocation. For example, knowing that a guidance document was being revised could result in a sponsor making different decisions on procuring materials for testing because of concerns that they may expire too soon. By postponing such activities, a sponsor may reach the market sooner because it could

⁴⁷Representatives of the two additional generic sponsors did not respond to our questions on this point.

prepare to quickly conduct the necessary studies once the new guidance was issued, rather than wasting time and other resources on a study that needs to be repeated. At present, in response to the unanticipated issuance or revision of product-specific guidance, sponsors may need to repeat their development work, which could delay generic entry, or may decide to abandon development efforts entirely, which could lead to fewer generic sponsors on the market and thus reduced savings for the health care system.

Additional Steps Have Been Proposed to Address the Challenges Presented by the Review of Generic NBCDs, but Stakeholder Views Are Mixed

In addition to the steps FDA has already taken, we identified five additional steps that have been proposed to address the challenges the reviews of generic NBCDs present based on our literature review and stakeholder interviews. However, we also found that stakeholder support for each proposal was mixed.

Clinical trials for safety and effectiveness. The first additional step we identified would require generic sponsors to conduct clinical safety and effectiveness trials as part of the approval process for generic NBCDs as is required for NDAs, but not ANDAs. Four of five brand sponsor representatives and one of four external expert groups we interviewed expressed support for this proposal, but four of these stakeholder groups indicated that clinical safety and effectiveness trials may not be needed in every case.⁴⁸ According to one brand sponsor representative and one external expert group, physicochemical parameters—such as measurements of a drug’s particle size and ability to dissolve—may not be enough to demonstrate that generic versions of some NBCDs are

⁴⁸For purposes of reporting, “brand sponsor representatives” and “generic sponsor representatives” include responses from individual brand or generic sponsors as well as the national associations that represent them. Though all stakeholders had the opportunity to comment on all of the additional steps that could be taken that we identified, some stakeholders did not comment on every proposal. In this case, of the three other external expert groups we interviewed, two did not comment on this proposal and one disagreed that clinical trials should be required. Further, the fifth brand sponsor representative told us that clinical bioequivalence trials, rather than clinical trials for safety and effectiveness, should be part of the approval process for many generic versions of NBCDs.

equivalent to the brand. Two brand sponsor representatives and one external expert group suggested that a separate approval pathway based on a “stepwise” or “similarity” approach, akin to the biosimilar pathway, is needed for reviewing generic versions of NBCDs.⁴⁹ One of these sponsor representatives suggested that a stepwise approach would allow for “head-to-head” clinical trials to assess differences in safety and effectiveness between the brand and generic versions of NBCDs.

Two of the 10 generic sponsor representatives we interviewed specifically objected to the creation of a new approval pathway for generic NBCDs and these sponsor representatives, along with 6 others, were opposed to requiring clinical trials for the approval of generic NBCDs. Two generic sponsor representatives said that requiring clinical trials for safety and effectiveness for generic versions of all NBCDs was not a feasible solution because it creates a financial disadvantage for generic sponsors, given the costs of such trials. FDA officials noted that, by statute, FDA cannot require a generic sponsor to conduct clinical safety and effectiveness trials as part of an ANDA submission; however, the agency says it already has authority to require submission of such data through a different abbreviated approval pathway—the 505(b)(2) pathway.⁵⁰ FDA

⁴⁹The Biologics Price Competition and Innovation Act of 2009 created an abbreviated licensure pathway for biologics that are demonstrated to be, among other things, “highly similar” (biosimilar) to or “interchangeable” with an FDA-licensed biologic. A sponsor of a potential biosimilar submits an application to FDA that provides information demonstrating biosimilarity based on, among other things, data from: analytical studies; animal studies; and a clinical study or studies. FDA has the discretion to waive certain studies for a given application. See Pub. L. No. 111-148, tit. VII, § 7002, 124 Stat. 804, 805 (2010) (codified at 42 U.S.C. § 262(k)).

⁵⁰See 21 U.S.C. § 355(j)(2)(A). In addition to the NDA and ANDA regulatory pathways, FDA may also approve drugs for marketing in the United States through the 505(b)(2) pathway. Under this pathway, sponsors must submit full reports of safety and effectiveness, but may rely on research conducted by a third party, without that party's permission, in order to meet the approval requirements. (The statute specifies that the 505(b)(2) pathway is to be utilized when an applicant relies on investigations that “were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted” 21 U.S.C. § 355(b)(2).) For example, the 505(b)(2) application may rely on information from approved products in the scientific literature, in addition to studies conducted by the 505(b)(2) drug sponsor. Sponsors may use this pathway when seeking approval of a modified drug that would not be permitted under the ANDA pathway because it requires review of clinical data to test or establish the safety or effectiveness of a product. Examples of such modifications include a change in dosage form (e.g., a change from a solid oral dosage form to a transdermal patch), change in strength (e.g., change to a lower or higher strength), a change in route of administration (e.g., change from an intravenous to a spinal canal injection), or substitution of an active ingredient.

officials said that, if they believe that a clinical safety and effectiveness trial is needed for approving a product, they would direct the sponsor to submit its application through the 505(b)(2) pathway. FDA officials said that the ANDA and 505(b)(2) pathways provide the agency with adequate flexibility for approving complex generic products and, as a result, they do not believe that a separate approval pathway for generic NBCDs is needed.

While three generic sponsor representatives we interviewed agreed that the 505(b)(2) pathway provides the agency with flexibility for approving complex products, one of these representatives and six other generic sponsor representatives expressed concerns with this pathway. First, the 505(b)(2) pathway is more costly to the sponsor in terms of user fees. In fiscal year 2017, a 505(b)(2) applicant submitting clinical data as part of its application would pay an application fee of more than \$2 million, while an applicant submitting an ANDA would pay an application fee of about \$70,000. Second, drugs approved through the 505(b)(2) pathway may not always be rated as therapeutically equivalent to the brand version as they are not considered to be generic drugs and thus are not required to be pharmaceutically equivalent or bioequivalent. This is problematic for generic NBCD sponsors because, according to generic sponsor representatives, products not rated as therapeutically equivalent by FDA cannot be marketed as substitutable with the brand version. As a result, generic sponsor representatives told us they would need to engage in special marketing efforts with pharmacists, clinicians, and other providers, whereas with drugs approved through the ANDA pathway, automatic substitution at the pharmacy level may occur and so no additional marketing would be needed.

Stakeholder involvement in guidance development. The second additional step that we identified is that FDA should seek and incorporate feedback from a variety of stakeholders as it develops guidance for generic NBCDs. Some publications from our literature review suggested that this proposal could support the development of comprehensive guidance that ensures the safety and effectiveness of generic NBCDs. All of the brand and seven generic sponsor representatives we interviewed, as well as three external expert groups supported stakeholder involvement in the development of guidance. Four of the brand and five generic sponsor representatives were supportive of FDA holding advisory committee or public meetings to discuss guidance development because it could encourage collaboration among experts from different areas to help solve scientific problems. However, there was disagreement about which stakeholders should be involved in these discussions. Brand

sponsor representatives were supportive of their own involvement in the guidance development process, noting that brand sponsors have the most knowledge of their specific products.

However, three generic sponsor representatives expressed concerns about involving the brand NBCD sponsors in this process. One of these generic sponsor representatives suggested that such involvement would provide brand sponsors with an opportunity to shape public opinion against generic products. This representative also said that generic sponsors might not be comfortable participating in a public meeting about developing guidance for a specific product because such participation would show which products a sponsor is currently developing, which is something a sponsor may not want to share publicly. Another generic sponsor representative cautioned that greater stakeholder involvement in guidance development too early in the process could “turn over the keys” to the brand sponsor in terms of defining the requirements necessary for generic approval, as generic sponsors might not yet have the data necessary to contribute to the guidance development process.

FDA officials disagreed that additional steps to seek and incorporate stakeholder feedback on guidance development are necessary, noting that there is no shortage of opportunities for stakeholders to provide comments and feedback. FDA officials noted that stakeholders already can and do provide feedback to FDA on guidance development through public comment periods on draft guidance documents, Citizen Petitions, and public meetings, such as the annual GDUFA Regulatory Science meetings. Further, FDA officials stated that the agency will not engage in closed-door meetings with individual drug sponsors unless it is in relation to the sponsor’s own application. This ensures that no particular stakeholder receives information ahead of others, which could provide that stakeholder with an unfair advantage. Finally, FDA officials told us that, although stakeholders can provide comments at any time, FDA does not solicit comments on a potential guidance before a draft version of the guidance document is released because of concerns that any comments received would be too broad.

Greater communication between FDA and generic drug sponsors.

The third additional step that we identified would facilitate greater communication between FDA and generic sponsors during reviews of ANDAs for complex products. As part of the GDUFA II Commitment Letter, FDA proposes enhancements to the existing ANDA pathway for complex generic products, which includes the drugs we identified as NBCDs as well as additional products. The enhanced ANDA pathway is

intended to provide sponsors of generic complex products the opportunity to have product development meetings, pre-submission meetings, and mid-cycle review meetings with FDA to discuss their applications as opposed to communicating through written correspondence, which some stakeholders have identified as inefficient.⁵¹ According to the GDUFA II Commitment Letter, the goals of the enhanced pathway are to clarify regulatory expectations early in product development; assist applicants in developing more complete submissions; promote a more efficient and effective ANDA review process; and reduce the number of review cycles before granting approval.

Both brand and generic sponsor representatives, as well as representatives of two external expert groups that we interviewed expressed support for this proposal. Some stressed that, due to the complex nature of challenges associated with NBCDs, clear and prompt exchanges are essential, but are currently lacking. Generic sponsor representatives emphasized that to this point, meetings have rarely been granted. Seven generic sponsor representatives indicated that it is challenging to communicate efficiently and effectively with FDA through the current ANDA review process, noting that communication between FDA and generic sponsors often occurs through written correspondence, which is slow. According to one generic sponsor representative, it can take 6 months for FDA to respond to a question.⁵² Generic sponsor representatives stressed that in instances in which they were able to communicate with FDA through teleconferences and meetings, this increased the efficiency and success of the review process. For example, one generic sponsor representative noted that it becomes much simpler to clear up any questions and confusion through phone calls, if they are granted by FDA. The generic sponsor representative further indicated that the length of time it may take FDA to respond to a meeting request may contribute to the delayed entry of generic drugs into the marketplace. Therefore, this generic sponsor representative and another said that meetings proposed under the GDUFA II Commitment Letter should

⁵¹According to the GDUFA II Commitment Letter, FDA will strive to grant or deny meeting requests and conduct meetings within certain time frames. For example, for fiscal year 2018, FDA has a goal of granting or denying 90 percent of product development meeting requests within 30 days from receipt of the request.

⁵²According to FDA officials, in 2016 the agency responded to more than 90 percent of controlled correspondences—a correspondence submitted to FDA by or on behalf of a generic drug manufacturer or related industry requesting information on a specific element of generic drug product development—within 2 months.

improve the review process because this approach provides generic NBCD sponsors with the opportunity to have “scientist-to-scientist” conversations with FDA. Another generic sponsor representative cited a 90-minute meeting it had with FDA that the representative estimated was the equivalent of 20-25 written messages back and forth.

Although stakeholders we interviewed generally supported greater communication, some expressed skepticism concerning the adequacy and implementation of this proposal. Four brand sponsor representatives expressed concerns about whether this proposal can sufficiently address the challenges the review of generic NBCDs present. One of these brand sponsor representatives noted that the enhanced ANDA pathway does not address the fundamental issue that, in this sponsor’s opinion, these drugs are impossible to characterize. In addition, one generic sponsor representative expressed skepticism concerning the implementation of the enhanced pathway. This representative suggested that the extent to which the enhanced ANDA pathway addresses the challenges the reviews of NBCDs present will not become clear until the program is implemented.

Public availability of equivalency data. The fourth additional step that we identified calls for making publicly available the data submitted as part of an ANDA that demonstrate equivalence between generic and brand NBCDs. Three brand sponsor representatives, three generic sponsor representatives, and one external expert group we interviewed were supportive of this proposal. One of the brand sponsor representatives indicated that publicly releasing these data would help inform health care providers’ treatment decisions. The external expert group also suggested that such transparency is needed to help support science-based discussions on the regulatory approval process.

However, one brand sponsor representative, four generic sponsor representatives, and one external expert group opposed this proposal and suggested that it is infeasible. Two generic sponsor representatives said that this proposal would put the sponsors whose data were released at a financial disadvantage because it would invite competition from other generic sponsors. In addition, FDA officials raised concerns about this proposal citing a number of legal constraints on the agency’s ability to disclose such information.

Greater post-market monitoring. The final additional step we identified would require greater post-market monitoring for generic NBCDs. Although FDA has already implemented a post-market surveillance

program for all generic products, some publications from our literature review suggested that greater post-market monitoring is needed for generic NBCDs to detect potential differences in safety and effectiveness between brand and generic versions. Four brand sponsor representatives and one external expert group agreed that greater post-market monitoring may be needed for generic versions of NBCDs, but three of these stakeholders suggested that such additional monitoring would only be needed on a case-by-case basis. For example, these stakeholders suggested that for products for which a dangerous adverse event is possible but has a low incidence rate, greater post-market monitoring of generic versions may be necessary. Moreover, one brand sponsor representative and one external expert group questioned whether current monitoring activities are sufficient for NBCDs, as they focus on safety and not effectiveness.

However, FDA officials and several other stakeholders disagreed that greater post-market monitoring activities are needed for any generic NBCDs. FDA officials and eight generic sponsor representatives suggested that the current post-market monitoring systems are adequate and generic NBCDs should not be treated differently than other generic products. In addition, one generic sponsor representative suggested that any extra post-market monitoring could pose additional problems by casting doubt on FDA's approval decisions for these drugs. Finally, FDA officials told us that they conduct monitoring of potential generic effectiveness differences, in addition to their post-market monitoring of potential safety concerns. A group of FDA staff meets monthly to discuss concerns raised by providers, other groups, or by articles in the literature that suggest potential generic substitutability issues. If the group identifies potential issues in need of further investigation, officials told us that such issues would be pursued through FDA's scientific investigation and research planning activities.

Conclusions

The review of applications for generic NBCDs is by its nature challenging for both drug sponsors and FDA. Nonetheless, the agency has reviewed applications for generic versions of drugs that are both nonbiological and complex and, satisfied of their equivalence to their brand-name counterparts, approved generic versions of five prior to fiscal year 2017. However, for four of these five drugs, FDA did not issue the relevant product-specific guidance documents until after generic versions were approved. Moreover, FDA has not provided sponsors with advance notice

as to when guidance documents will be issued or revised. This practice is inconsistent with federal internal control standards as well as FDA's good guidance practices regulation, which calls for the agency to annually publish possible topics for future guidance development and revision during the next year. It is understandable that the agency's thinking on how to establish equivalence or address other challenges will evolve over time. Certainly, generic sponsors and FDA may both be learning and moving forward on parallel tracks, particularly as science advances, and sponsors cannot be fully apprised of FDA's views on a continuous basis. However, by not informing sponsors of the agency's plans to issue or revise product-specific guidance documents, FDA could be impeding generic sponsors' planning, preventing them from making as fully informed decisions as possible. When guidance is unexpectedly issued or revised, sponsors may need to repeat their development work, delaying market entry and the availability of more affordable versions of NBCDs. Such an approach is not in the interest of public health.

Recommendations for Executive Action

We are making the following two recommendations to FDA.

The Commissioner of FDA should, in order to increase transparency, publicly announce the agency's plans for issuing new product-specific guidance for a drug that is nonbiological and complex within the next year. (Recommendation 1)

The Commissioner of FDA should, in order to increase transparency, publicly announce planned significant revisions to an existing product-specific guidance for a drug that is nonbiological and complex within the next year. (Recommendation 2)

Agency Comments

We provided a draft of this report to HHS for comment. In its written comments, which are reproduced in appendix III, HHS concurred with our recommendations and said it will identify the most appropriate mechanism to notify the public of its plans to issue and to revise product-specific guidance for nonbiological complex drugs. HHS also provided technical comments, which we incorporated as appropriate.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies to appropriate congressional committees; the Secretary of Health and Human Services; and other interested parties. In addition, the report will be available at no charge on the GAO website at <http://www.gao.gov>.

If you or your staff have any questions about this report, please contact me at 202-512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix IV.

A handwritten signature in black ink, reading "Marcia Crosse". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Marcia Crosse
Director, Health Care

List of Requesters

The Honorable Greg Walden
Chairman
The Honorable Frank Pallone Jr.
Ranking Member
Committee on Energy and Commerce
House of Representatives

The Honorable Michael Burgess
Chairman
The Honorable Gene Green
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives

The Honorable Diana DeGette
Ranking Member
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives

The Honorable Gus Bilirakis
House of Representatives

The Honorable G.K. Butterfield
House of Representatives

The Honorable Fred Upton
House of Representatives

Appendix I: List of Nonbiological Complex Drugs

As part of our work, we constructed a list of drugs that some consider to be nonbiological complex drugs (NBCD). We constructed this list by reviewing publications that identified specific drugs as NBCDs and then shared this list with the Non-Biological Complex Drugs Working Group and with the National Institutes of Health’s Nanotechnology Characterization Lab—which both have experience with NBCDs, and we revised our list based on their review. ¹ We also confirmed that FDA considers each of the drugs on our final list to be both nonbiologic and complex. There are four drugs on the list that the Nanotechnology Characterization Lab identified as NBCDs, but the Non-Biological Complex Drugs Working Group does not consider to be NBCDs: Diprivan, Estrasorb, Oraqix, and Invega Sustenna. Representatives of the Working Group told us that for these four products, their complexity does not lead to significant challenges in demonstrating pharmaceutical equivalence.

Table 7: List of 28 Nonbiological Complex Drugs Included in the Scope of Our Study

Brand-name drug approved for U.S. market	Generic name	Selected indication(s)
1. Abraxane	Paclitaxel	Lung, breast, and other cancers
2. Ambisome	Amphotericin B (liposomal)	Fungal infections
3. Amphotec	Amphotericin B (lipid complex)	Aspergillus
4. Copaxone	Glatiramer acetate injection	Relapsing forms of multiple sclerosis
5. DaunoXome	Daunorubicin citrate	AIDS related Kaposi’s sarcoma
6. DepoCyt	Cytarabine (liposomal)	Lymphomatous meningitis
7. DepoDur	Morphine sulfate (liposomal)	Pain treatment following major surgery
8. Dexferrum	Iron dextran	Iron deficiency anemia
9. Diprivan ^a	Propofol	Anesthesia and sedation
10. Doxil	Doxorubicin hydrochloride (liposomal)	Ovarian and other cancers

¹The Non-Biological Complex Drugs Working Group consists of experts from industry, academia, and knowledge institutes, including the Nanotechnology Characterization Lab, the University of Geneva, and two brand-sponsors of NBCDs: Allergan and Vifor Pharma Ltd. The stated mission of the Working Group is to ensure that appropriate science-based approval and post-approval standards are created and globally introduced for NBCDs to the benefit and safety of patients.

**Appendix I: List of Nonbiological Complex
Drugs**

Brand-name drug approved for U.S. market	Generic name	Selected indication(s)
11. Estrasorb ^a	Estradiol hemihydrate	Vasomotor symptoms associated with menopause
12. Exparel	Bupivacaine (liposomal)	Post-surgical analgesia
13. FeraHeme	Ferumoxytol	Iron deficiency anemia in patients with chronic kidney disease
14. Feridex	Ferumoxides	Magnetic resonance imaging contrast agent
15. Ferlecit	Sodium ferric gluconate complex in sucrose	Iron deficiency anemia
16. Fragmin	Dalteparin sodium	Blood clots
17. InFed	Iron dextran	Iron deficiency anemia
18. Injectafer	Ferric carboxymaltose	Iron deficiency anemia
19. Innohep	Tinzaparin sodium	Blood clots
20. Invega sustenna ^a	Paliperidone palmitate	Schizophrenia/schizoaffective disorders
21. Lovenox	Enoxaparin sodium injection	Blood clots
22. Marqibo	Vincristine sulfate (liposomal)	Acute lymphoblastic leukemia
23. Onivyde	Irinotecan hydrochloride (liposomal)	Pancreatic cancer
24. Oraqix ^a	Lidocaine; prilocaine	Local anesthetic for dental procedures
25. Renvela	Sevelamer carbonate	Controls serum phosphorus in patients with chronic kidney disease on dialysis
26. Restasis	Cyclosporine	Ocular inflammation associated with keratoconjunctivitis sicca
27. Venofer	Iron sucrose	Iron deficiency anemia with chronic kidney disease
28. Visudyne	Verteporfin	Macular degeneration and pathologic myopia and ocular histoplasmosis

Source: GAO analysis of literature and Food and Drug Administration information. | GAO-18-80

^aThere are four drugs on this list that the Nanotechnology Characterization Lab identified as nonbiological complex drugs (NBCD), but the Non-Biological Complex Drugs Working Group does not consider to be NBCDs. Representatives of the Working Group told us that for these four products, their complexity does not lead to significant challenges in demonstrating pharmaceutical equivalence.

Appendix II: List of Stakeholders Interviewed

Table 8: List of Stakeholders GAO Interviewed

Brand Sponsor Representatives	1. Allergan
	2. Celgene
	3. Pharmaceutical Research and Manufacturers of America
	4. Teva Pharmaceutical Industries
	5. Vifor Pharma Ltd.
Generic Sponsor Representatives	1. Amneal Pharmaceuticals
	2. Amphastar Pharmaceuticals, Inc.
	3. Association for Accessible Medicines
	4. Biocon Limited
	5. Dr. Reddy's Laboratories Ltd.
	6. GeneraMedix Inc. ^a
	7. Momena Pharmaceuticals, Inc. ^b
	8. Mylan
	9. Navinta LLC
	10. Sun Pharmaceutical Industries Ltd
External Expert Groups	1. American Association of Pharmaceutical Scientists
	2. Nanotechnology Characterization Lab
	3. Non-Biological Complex Drugs Working Group
	4. U.S. Pharmacopeial Convention

Source: GAO. | GAO-18-80

^aAlthough GeneraMedix Inc is no longer in business, we were able to interview two former employees of this sponsor who were knowledgeable about the Food and Drug Administration's review and approval of the first generic version of one of the nonbiological complex drugs (NBCD) on our list, sodium ferric gluconate.

^bAlthough Momena was not itself an abbreviated new drug application (ANDA) sponsor, it worked closely with the ANDA sponsor Sandoz on the development of two NBCDs.

Appendix III: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

NOV 2 2017

Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Ms. Crosse:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "*Generic Drugs: FDA Should Announce Plans to Issue and Revise Guidance on Nonbiological Complex Drugs*" (GAO-18-80).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

A handwritten signature in cursive script that reads "Barbara Pisaro Clark".

Barbara Pisaro Clark
Acting Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: GENERIC DRUGS: FDA SHOULD ANNOUNCE PLANS TO ISSUE AND REVISE GUIDANCE ON NONBIOLOGICAL COMPLEX DRUGS (GAO-18-80)

The U.S. Department of Health and Human Services (HHS) appreciates the opportunity from the Government Accountability Office (GAO) to review and comment on this draft report.

Recommendation 1

The Commissioner of the Food and Drug Administration (FDA) should, in order to increase transparency, publicly announce the agency's plans for issuing new product-specific guidance for a drug that is nonbiological and complex within the next year.

HHS Response

HHS concurs with GAO's recommendation and will identify the most appropriate mechanism to notify the public of new product-specific guidance for nonbiological complex drugs that may be issued in the next year.

Recommendation 2

The Commissioner of FDA should in order to increase transparency, publicly announce planned significant revisions to an existing product-specific guidance for a drug that is nonbiological and complex within the next year.

HHS Response

HHS concurs with GAO's recommendation and will identify the most appropriate mechanism to notify the public of planned significant revisions to product-specific guidance for nonbiological complex drugs that may be issued in the next year.

Appendix IV: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7114 or crossem@gao.gov.

Staff Acknowledgments

In addition to the contact named above, individuals making key contributions to this report include Geri Redican-Bigott (Assistant Director); Katherine L. Amoroso (Analyst-in-Charge); Sam Amrhein; Sandra George; Karen Howard; Saida B. Hussain; Matthew Nattinger; Rebecca Parkhurst; and Jennifer Rudisill. Pille Anvelt and JoAnna Berry also made contributions to the report.

Appendix V: Accessible Data

Agency Comment Letter

Text of Appendix III: Comments from the Department of Health and Human Services

Page 1

Marcia Crosse Director, Health Care

U.S. Government Accountability Office 441 G Street NW

Washington, DC 20548 Dear Ms. Crosse:

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Barbara Pisaro Clark

Acting Assistant Secretary for Legislation

Attachment

Page 2

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Strategic Planning and External Liaison

James-Christian Blockwood, Managing Director, spel@gao.gov, (202) 512-4707
U.S. Government Accountability Office, 441 G Street NW, Room 7814,
Washington, DC 20548