CITIZEN PETITION: APPROVAL AND THERAPEUTIC EQUIVALENCE OF SAFE AND EFFECTIVE FOLLOW-ON HARDER-TO-COPY COMPLEX DRUGS

Submitted by Sidley Austin LLP
On Behalf of Vifor Pharma
January 9, 2020

Table of Contents

ACTION REQUESTED 1

STATEMENT OF GROUNDS 4

I. Introduction and Overview 4

A. The DCAP Reliance on the ANDA Pathway Does Not Work for Harder-to-Copy Complex Drugs 4

B. The 505(b)(2) Approval Pathway is Appropriate for Follow On Harder-to-Copy Complex Drugs and Can Support Therapeutic Equivalence Ratings 6

II. The ANDA Pathway Is Not Appropriate for Harder-to-Copy Complex Drugs and Instead FDA Should Clarify that Applications Should Be Submitted Pursuant to FDCA Section 505(b)(2) 9

A. The FDCA Provides for Two Abbreviated Pathways Depending on Whether Clinical Data is Necessary to Ensure Safety and Efficacy 9

B. The Challenges of Attempting to Approve Harder-to-Copy Complex Drugs Via the ANDA Pathway are Widely Recognized by FDA and Other Stakeholders 10

C. FDA Efforts to Approve Follow-On Versions of Harder-to-Copy Complex Drugs Via the ANDA Pathway are Ad Hoc and are Outside the Plain Language of the FDCA 14

D. FDA's Current Approach is Challenging and Costly for the Agency and Stakeholders 16

III. FDA Should Issue Guidance Making Clear that Therapeutic Equivalence Ratings for Follow-On Harder-To-Copy Drugs Require Clinical Studies to Show Same Clinical Efficacy and Safety Profile 18

A. The History of Therapeutic Equivalence Makes Clear that Same Clinical Efficacy and Safety Profile are Critical Considerations 18

B. Drugs Approved Under FDCA Section 505(b)(2) May Receive Therapeutic Equivalence Ratings As Long As Demonstrated to Have the Same Clinical Efficacy and Safety Profile 20

C. The Interchangeable Biosimilar Pathway Provides a Model for Demonstrating that a Follow-On Harder-to-Copy Complex Drug is Therapeutically Equivalent to the RLD 22

IV. Conclusion 24

ENVIRONMENTAL IMPACT 24

ECONOMIC IMPACT 24

CERTIFICATION 25

SIDLEY

SIDLEY AUSTIN LLP
787 SEVENTH AVENUE
NEW YORK, NY 10019
+1 212 839 5300
+1 212 839 5599 FAX

+1 212 839 5613
SBASS@SIDLEY.COM

AMERICA • ASIA PACIFIC • EUROPE

ACTION REQUESTED

Sidley Austin LLP submits this Citizen Petition on behalf of Vifor Pharma ("Vifor") to urge the Food and Drug Administration ("FDA" or the "Agency") to take critical steps regarding the approval and therapeutic equivalence of safe and effective follow-on harder-to-copy complex drugs. Vifor is a fully integrated specialty pharmaceutical company and a global leader in the treatment of iron deficiency, which is a widespread ailment and an underlying condition in many chronic diseases. Vifor develops and manufactures a number of complex iron drugs, including the intravenous iron replacement drugs Ferinject®/Injectafer® and Venofer®, the oral iron preparation Maltofer®, and the phosphate binder Velphoro®.[1]

Specifically, Vifor requests that FDA make clear to its stakeholders that the Abbreviated New Drug Application ("ANDA") approval pathway under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") is not appropriate for follow-on versions of certain harder-to-copy complex drugs identified by FDA.[2] Any FDA effort to approve these follow-on harder-to-copy complex drugs under Section 505(j) of the FDCA is contrary to the plain language of the statute and poses significant safety risks to patients. Instead, approvals and therapeutic equivalence determinations for harder-to-copy complex drugs must be made pursuant to FDCA Section 505(b)(2) and must include clinical studies. Vifor's request is consistent with FDA's authority to construe the standard of safety and effectiveness under FDCA Section 505(b)(2) and would support FDA's Drug Competition Action Plan ("DCAP") by facilitating competition and ensuring the availability of safe and effective follow-on drugs for patients.[3]

Vifor's request to FDA has two parts. ***First***, Vifor asks that FDA issue guidance, and publicly affirm, that the ANDA approval pathway is not appropriate for harder-to-copy complex drugs already identified by FDA. The statute does not permit FDA to require clinical studies pursuant to the ANDA pathway, and such studies are necessary to show that a follow-on harder-to-copy complex drug will have the same clinical effect and safety profile as the reference drug. Many of these drugs pose a risk of immunogenicity. Clinical studies are critical

---

[1] Vifor licenses these products for manufacturing in the United States, except for Maltofer®. In the U.S., Ferinject® is marketed as Injectafer®.

[2] *See* FDA, Statement from FDA Commissioner Scott Gottlieb, M.D. (Jan. 3, 2018), https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm591184.htm. In this statement, Former Commissioner Gottlieb refers to certain complex drugs as "hard to copy".

[3] FDA, FDA Drug Competition Action Plan, https://www.fda.gov/drugs/guidance-compliance-regulatory-information/fda-drug-competition-action-plan (last visited Dec. 12, 2019).

to ensure patient safety. FDA's guidance should therefore make clear that follow-on versions of such drugs will be reviewed and approved pursuant to FDCA Section 505(b)(2).

Second, Vifor asks that FDA's planned guidance on therapeutic equivalence for follow-on drugs approved pursuant to Section 505(b)(2)[4] make clear that a follow-on harder-to-copy complex drug may be determined to be therapeutically equivalent to its reference listed drug ("RLD"), when the two drugs meet the existing criteria, namely, they have: (1) the same active ingredient; (2) the same route of administration, dosage form, and strength; (3) the same clinical effect and safety profile; and (4) been shown to be bioequivalent. In this context, FDA should reiterate that demonstrating that a follow-on harder to copy complex drug has the same active ingredient and will have the same clinical effect and safety profile requires data from clinical studies.

It is absolutely critical for patient welfare that a follow-on drug designated as therapeutically equivalent *actually* have the same clinical effect and safety profile in patients as the RLD. In accordance with relevant state law, such drugs can be substituted at the pharmacy level for a prescribed reference product without specific direction from a health care provider. This is a process that has worked well in lowering drug costs for a wide range of small-molecule drugs. However, the risks associated with substitution are significantly higher with harder-to-copy complex drugs. Many of these products pose considerable risks of immunogenicity.[5] Studies have repeatedly shown that even minor modifications in manufacturing process can lead to serious adverse events. Therapeutic equivalence determinations should therefore only be made with incontrovertible evidence – derived from clinical studies – that the products will actually have the same clinical effect and safety profile in a patient.

In fact, requiring clinical studies would be consistent with FDA's approach to other complex therapeutic products and could be modelled on FDA's well-designed pathway for approval of interchangeable biosimilars. As detailed in FDA's recent guidance document, Guidance for Industry, Considerations in Demonstrating Interchangeability with a Reference Product (hereinafter, the "Interchangeability Guidance"), approval of an interchangeable biosimilar requires a stepwise approach, and may include data from clinical studies to eliminate residual uncertainties about whether the proposed substitutable biosimilar "can be expected to produce the same clinical result as the reference product in any given patient."[6]

---

[4] FDA, Statement from FDA Commissioner Scott Gottlieb, M.D., on the Agency's Efforts to Enhance the Utility of the Orange Book to Foster Drug Competition (Jan. 30, 2019), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-efforts-enhance-utility-orange-book-foster-drug.

[5] *See*, *e.g.*, FDA Draft Guidance, Drug Products, Including Biological Products, that Contain Nanomaterials, at 24 (Dec. 2017), https://www.fda.gov/media/109910/download; A. Shah and MA Dobrovolskaia, *Immunological Effects of Iron Oxide Nanoparticles and Iron-based Complex Drug Formulations: Therapeutic Benefits, Toxicity, Mechanistic Insights, and Translational Considerations*, 14(3) NANOMEDICINE 977-90 (2018) (Tab 1); M. Dobrovolskaia et al., *Immunological Properties of Engineered Nanomaterials*, 2(8) NAT NANOTECHNOL 469-78 (2007) (Tab 2); A. Ilinskaya et al., *Understanding the Immunogenicity and Antigenicity of Nanomaterials: Past, Present and Future*, 299 TOXICOL APPL PHARMACOL 70-77 (2016) (Tab 3); A. Smith et al., *The Skin As a Route of Allergen Exposure: Part I. Immune Components and Mechanisms*, 17 CURR ALLERGY ASTHMA REP. 17 (2017) (Tab 4).

[6] FDA, Guidance for Industry, Considerations in Demonstrating Interchangeability with a Reference Product, at 2 (May 2019), https://www.fda.gov/media/124907/download.

The DCAP goal of facilitating competition by bringing safe and effective follow-on products to market is important. Vifor urges FDA to take the steps discussed herein to ensure that any follow-on harder-to-copy complex drugs provide a safe and effective option for patients.

STATEMENT OF GROUNDS

I. Introduction and Overview

A. The DCAP Reliance on the ANDA Pathway Does Not Work for Harder-to-Copy Complex Drugs

FDA's current focus on increased competition and lower prices for prescription drugs as part of its DCAP[7] relies on the concept of therapeutic equivalence. In general, a drug product that is designated as a therapeutic equivalent of an RLD in FDA's publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"), can be substituted for the RLD under state substitution laws. The availability of a therapeutic equivalent thus leads to greater competition and a concomitant reduction in drug prices.[8]

For the most part, FDA's DCAP relies on the ANDA pathway under Section 505(j) of the FDCA for approval of therapeutically equivalent drug products. In this context, the Agency has highlighted the "record-breaking" numbers of ANDA approvals[9] as well as steps it has taken to facilitate the ANDA review process.[10] Vifor believes that these efforts are a worthy effort to increase availability of competitively priced small molecule drugs. The ANDA pathway works well for follow-on small molecule drugs and facilitates therapeutic equivalence determinations.

FDA and other stakeholders have long recognized that the ANDA pathway, which does not allow submission of data from clinical studies in support of approval,[11] poses significant challenges for approving safe and effective follow-on versions of harder-to-copy complex drugs.[12] Despite this, and as outlined further below, FDA continues to operate outside the bounds of the statute in its effort to force approvals of follow-on harder-to-copy complex drugs through the Section 505(j) pathway. The set of harder-to-copy complex drugs in this context

---

[7] FDA, FDA Working to Lift Barriers to Generic Drug Competition (June 21, 2017), https://www.fda.gov/NewsEvents/Newsroom/FDAVoices/ucm612018.htm. Under the DCAP, FDA is taking a number of steps to facilitate approval of generic drugs, including publishing a list of off-patent, off-exclusivity branded drugs without approved generic drugs. *See* FDA, FDA Tackles Drug Competition to Improve Patient Access (June 27, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm564725.htm.

[8] *See, e.g.*, IMS Institute for Healthcare Informatics, *Price Declines After Branded Medicines Lose Exclusivity in the U.S.* (Jan. 2016), https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/price-declines-after-branded-medicines-lose-exclusivity-in-the-us.pdf (Tab 5).

[9] FDA, FDA in Brief: FDA Highlights Record-breaking Number of Generic Drug Approvals in October (Nov. 9, 2018), https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm625627.htm.

[10] FDA, FDA in Brief: FDA Takes New Actions to Reduce the Time that it Takes for Safe and Effective New and Generic Drugs to Reach the Market (Sept. 24, 2018), https://wayback.archive-it.org/7993/20190423050356/https://www.fda.gov/NewsEvents/Newsroom/FDAInBrief/ucm621466.htm. *See also*, FDA, Guidance for Industry, ANDA Submissions – Content and Format (June 2019), https://www.fda.gov/media/128127/download.

[11] Sections 505(j)(2)(A)(vi) (an ANDA is not required to contain full reports of safety-and-effectiveness investigations) and 505(j)(2)(A)(viii) of the FDCA ("The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)").

[12] *See* FDA, Statement from FDA Commissioner Scott Gottlieb, M.D. on New Steps to Facilitate Efficient Generic Drug Review to Enhance Competition, Promote Access and Lower Drug Prices (Jan. 3, 2018), https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm591184.htm. In this statement, Former Commissioner Gottlieb refers to certain complex drugs as "hard to copy".

has been identified by FDA as including: (1) drugs containing nanomaterials,[13] as well as (2) drugs containing complex active ingredients and/or formulations.[14] In the scientific community, certain of these harder-to-copy complex drugs are also known as non-biological complex drugs ("NBCDs"), as discussed further below.[15] For purposes of this Citizen Petition, Vifor adopts FDA's nomenclature and will refer to these categories collectively as "harder-to-copy complex drugs."

The ANDA pathway requires that the sponsor demonstrate that a potential generic product is pharmaceutically equivalent – i.e. the same as – and bioequivalent to the RLD. Harder-to-copy complex drugs pose a challenge because they are composed of non-homomolecular material, often have an unknown mode of action, and it is difficult to fully characterize the products.[16] As described in more detail below, these characteristics mean that it is difficult – if not impossible – to demonstrate full pharmaceutical equivalence and bioequivalence to a reference drug. As a result, any follow-on drug approved via the ANDA pathway will *de facto* not be the same as the reference product and therefore will likely not have the same clinical effect and safety profile.

The very significant challenges involved in approving follow-on versions of certain complex drugs was the subject of a request by Congress in 2015 to the Government Accountability Office ("GAO"). Specifically, Congress asked the GAO to undertake an assessment of FDA's "regulatory pathway for reviewing generic versions of nonbiologic complex drugs (NBCDs)",[17] a category which describes drugs with complex active ingredients, such as nanomaterials and/or complex formulations that cannot be fully characterized. Among other things, the GAO was asked to recommend any changes to the ANDA process necessary to ensure the safety and effectiveness of generic versions of NBCDs.[18] The resulting report publicly released by GAO in early 2018 recognizes the substantial challenges involved in approving follow-on drugs with complex active ingredients and/or complex formulations

[13] *See* FDA Draft Guidance for Industry, Drug Products, Including Biological Products, that Contain Nanomaterials, *supra* note 5, at 6.

[14] *See, e.g.*, L. Hussaarts et al., *Equivalence of Complex Drug Products: Advances in and Challenges for Current Regulatory Frameworks*, 1407 Ann. N.Y. Acad. Sci. 39-49 (2017) (authors, including those from FDA, identify a range of harder-to-copy complex drugs) (Tab 6). Former FDA Commissioner Gottlieb described such complex drugs in his comments at FDA's July 18, 2017 public meeting, "Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access." There, Dr. Gottlieb stated that, for many complex drugs, "the traditional requirements used to demonstrate sameness may not be appropriate when it comes to complex drugs that can't be easily measured in the blood, or where the drug's therapeutic affect is delivered locally to a particular organ, rather than systemically, through the blood." Scott Gottlieb, FDA Commissioner, Opening Remarks for Part 15 Public Meeting on Generic Drug Competition (July 18, 2017), https://www.fda.gov/NewsEvents/Speeches/ucm567323.htm (emphasis added).

[15] *See, e.g.*, Hussaarts et al., *supra* note 14 (Tab 6); D. Crommelin et al., *The Similarity Question for Biologicals and Non-Biological Complex Drugs*., 76 Eur. J. of Pharm. Sci., 10-17 (2015) (Tab 7).

[16] 21 C.F.R. § 314.3.

[17] NBCDs are defined as drugs for which the active substance is not a homomolecular structure but, like biological products, consist of different closely-related and often nanoparticulate structures that cannot be isolated nor can be fully quantitated, characterized, and/or described by physicochemical means. *See* Lygature, Non-Biological Complex Drugs (NBCD) Working Group, https://www.lygature.org/non-biological-complex-drugs-working-group (last visited Dec. 12, 2019) (Tab 8).

[18] Letter from House of Representatives, Committee on Energy and Commerce to Hon. Gene L. Dodaro, Comptroller General of the U.S. (Dec. 10, 2015) (Tab 9). The letter takes into account a related bill, H.R. 1576, 114th Cong. (2015).

pursuant to the ANDA pathway, including *inter alia* the risks of an adverse immune response from the follow-on product.[19]

FDA has been operating outside the bounds of the statute in its efforts to date to approve follow-on versions of certain harder-to-copy complex drugs via the ANDA pathway. FDA's shifting explanation of its approval standards in this context reflect these challenges. As discussed in greater detail below, such approvals have been based on *ad hoc* standards, and may require studies that are not in fact permitted under the FDCA's ANDA pathway. Indeed, FDA currently relies on approximations of pharmaceutical equivalence and "weight of the evidence" approaches to safety and efficacy. In some cases, FDA has requested clinical studies post-approval as confirmatory studies (*e.g.*, sodium ferric gluconate complex[20]). Ultimately, FDA's ill-defined and extra-statutory approach has been challenging and costly for the Agency and sponsors alike.[21]

B. The 505(b)(2) Approval Pathway is Appropriate for Follow On Harder-to-Copy Complex Drugs and Can Support Therapeutic Equivalence Ratings

Recently, FDA announced that it would issue guidance to clarify its long-held position that drugs approved pursuant Section 505(b)(2) of the FDCA could *also* be deemed to be therapeutically equivalent to their RLD. FDA has previously made clear that a therapeutically equivalent follow-on drug may be approved either via Section 505(b)(2) or 505(j) of the FDCA. Approval of a follow-on drug pursuant to Section 505(b)(2) is permitted to consider clinical data; approval of a drug pursuant to an ANDA is not. The 505(b)(2) pathway is therefore appropriate when clinical data is necessary to ensure that follow-on versions of harder-to-copy complex drugs approved by FDA have the same clinical effect and safety profile as the RLD.

On January 30, 2019, former FDA Commissioner Scott Gottlieb made the following statement:

> [W]e intend to issue draft guidance for industry, describing how the FDA evaluates therapeutic equivalence (TE) and assigns therapeutic equivalence codes, which are published in the Orange Book. We believe this guidance will increase transparency around the FDA's policies and procedures related to evaluation and assignment of TE codes to support applicants submitting requests for therapeutic equivalence and help advance pathways for

---

[19] U. S. GOV'T ACCOUNTABILITY OFFICE, GAO-18-80, FDA SHOULD MAKE PUBLIC ITS PLANS TO ISSUE AND REVISE GUIDANCE ON NONBIOLOGICAL COMPLEX DRUGS (Dec. 2017) ("GAO Report"), https://www.gao.gov/assets/690/689047.pdf (Tab 10).

[20] M. Kane et al., *Evaluation of Iron Species in Healthy Subjects Treated with General and Reference Sodium Ferric Gluconate*, GRANTOME (Feb. 28, 2019) http://grantome.com/grant/NIH/U01-FD005266-03S2 (Tab 11). In 2013, separate from the Sources Sought Notice, FDA made an award to the Albany College of Pharmacy and Health Sciences to develop an iron-release test for generic IV iron products. University of Albany Press Release, *Faculty Member Receives $500,000 NIH Grant* (Oct. 15, 2013), https://www.acphs.edu/press/faculty-member-receives-500000-nih-grant (accessed Jul. 20, 2015) (Tab 12).

[21] Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research to J. Michael Nicholas, Ph.D., Vice President, Global Specialty Medicines, Teva Pharmaceuticals (Apr. 16, 2015), https://www.regulations.gov/document?D=FDA-2015-P-1050-0012 (Tab 13).

> achieving pharmacy-level substitution of therapeutically equivalent drug products, including products approved under the 505(b)(2) pathway.
>
> We believe this will be particularly beneficial for those seeking to develop generic products for harder-to-copy complex drugs that often face greater scientific and regulatory challenges and thus often have less competition. For some of these drugs, the 505(b)(2) pathway may provide a more efficient development path and the agency is developing policy for how manufacturers can acquire a therapeutic equivalence rating to allow for full substitutability for products developed by this route.[22]

FDA's stated aim is to expand the availability of therapeutically equivalent drug products, and thereby continue to impact drug prices. Vifor welcomes FDA's effort to clarify therapeutic equivalence evaluations for products approved via FDCA Section 505(b)(2). Vifor agrees that approval of follow-on harder-to-copy complex drugs is appropriate under the FDCA Section 505(b)(2) pathway. Vifor urges FDA to make clear in its upcoming guidance that a follow-on complex drug approved pursuant to 505(b)(2) of the Act may be considered to be therapeutically equivalent to its RLD, when the two drugs meet the existing criteria, namely the follow-on product has: (1) the same active ingredient; (2) the same route of administration, dosage form, and strength; (3) the same clinical effect and safety profile; and (4) been shown to be bioequivalent.

Adopting the existing criteria for harder-to-copy complex drugs requires FDA to acknowledge that the "same active ingredient" element cannot be demonstrated by non-clinical means. As discussed further below, harder-to-copy complex drugs have a non-homomolecular structure, have unknown modes of action and/or cannot be fully characterized. Analytical studies can only approximate sameness, and any conclusion that the drugs are the same must be confirmed through clinical studies. For follow-on harder-to-copy complex drugs, therefore, a determination of therapeutic equivalence will need to rely heavily on a clinical demonstration that the follow-on product has the "same clinical effect and safety profile" as the RLD. Such an approach would ensure that any substitutable harder-to-copy drug safeguards patient safety if it is substituted at the pharmacy level.

As discussed in further detail below, the historical development of therapeutic equivalence makes clear that a demonstration of the same clinical effect and safety profile is in fact the crux of any such determination. Clinical studies are particularly critical because harder-to-copy complex drugs can pose significant safety risks. For example, many such products containing nanoparticles, including complex iron formulations, can lead to hypersensitivity reactions, immunosuppression and immunostimulation.[23] Numerous studies have shown that minor changes in manufacturing result in products with significantly different

---

[22] FDA, Statement from FDA Commissioner Scott Gottlieb, M.D., on the Agency's Efforts to Enhance the Utility of the Orange Book to Foster Drug Competition (Jan. 30, 2019), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-efforts-enhance-utility-orange-book-foster-drug (emphasis added).

[23] *See*, *e.g.*, FDA Draft Guidance, Drug Products, Including Biological Products, that Contain Nanomaterials, *supra* note 5, at 24; Shah and Dobrovolskaia, *supra* note 5 (Tab 1); Dobrovolskaia et al., *supra* note 5 (Tab 2); Ilinskaya et al., *supra* note 5 (Tab 3); Smith et al., *supra* note 5 (Tab 4).

clinical efficacy and safety profiles, with resulting adverse effects in patients.[24] This simply is unacceptable. Patient safety is paramount. Any potentially substitutable product should only be approved once there is clinical data to demonstrate the same clinical effect and safety profile in patients.

Ultimately, relying on the 505(b)(2) pathway to make therapeutic equivalence determinations would greatly facilitate FDA's DCAP goal of increasing competition and lowering the prices of prescription drugs. It is important, however, that FDA squarely address the challenges in approving follow-on harder-to-copy drugs. As a part of its guidance, FDA should state that any therapeutic equivalence determination for a follow-on harder-to-copy drug must rely in part on clinical studies.

[24] See, e.g., J. Rottembourg et al., Do Two Intravenous Iron Sucrose Preparations Have the Same Efficacy?, 26 NEPHROL. DIAL TRANSPLANT 3262-67 (2011) (Tab 14); M. L. Agüera et al., Efficiency of Original versus Generic Intravenous Iron Formulations in Patients on Haemodialysis, 10 PLOS ONE 1 (2015) (Tab 15); and E. Sil Lee et al., Comparison of Adverse Event Profile of Intravenous Iron Sucrose and Iron Sucrose Similar in Postpartum and Gynecologic Operative Patients, 29 CURR MED RES OPIN. 141, 146 (2013) (Tab 16).

II. The ANDA Pathway Is Not Appropriate for Harder-to-Copy Complex Drugs and Instead FDA Should Clarify that Applications Should Be Submitted Pursuant to FDCA Section 505(b)(2)

A. The FDCA Provides for Two Abbreviated Pathways Depending on Whether Clinical Data is Necessary to Ensure Safety and Efficacy

The Hatch-Waxman Amendments[25] to the FDCA that were enacted in 1984 introduced two pathways for approval of follow-on drug drugs: Sections 505(j) and 505(b)(2). Section 505(j) (the ANDA pathway) was explicitly designed for approval of generic versions of small molecule drugs.[26] Unlike the requirements for approval of a New Drug Application ("NDA") under Section 505(b) of the FDCA, the ANDA pathway does not require a demonstration of the safety and effectiveness of a follow-on drug.[27] Instead, the safety and effectiveness of such a drug is presumed based upon the 505(j) applicant's demonstration that the proposed generic meets standards of pharmaceutical equivalence and bioequivalence.[28] The assessment of pharmaceutical equivalence and bioequivalence is intended to ensure that a generic drug has "the same risks and benefits of brand-name drugs."[29] No clinical studies are required or, in fact, permitted under the ANDA pathway.[30]

In addition to the ANDA pathway under Section 505(j), the Hatch-Waxman Amendments created Section 505(b)(2) of the FDCA, an abbreviated approval pathway appropriate for non-duplicate follow-on drugs.[31] Section 505(b)(2) requires a demonstration that the follow-on drug meets the same standards of safety and efficacy as a full NDA under Section 505(b)(1). However, the 505(b)(2) pathway permits an applicant to satisfy the standards for approval of a full NDA by relying in part on clinical data 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," in addition to clinical data of the type necessary to support a full NDA (*i.e.*, "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use"). Typically, a 505(b)(2) applicant will submit at least some data from clinical studies to address differences between the proposed follow-on drug and the RLD to support a finding that, despite the differences, the

---

[25] Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417 (1984) (Tab 17).

[26] For example, the committee report of the House Energy and Commerce Committee in 1984 emphasized the value of approving generic versions of specific drugs—Valium, Motrin, Inderal, Dyazide, and Lasix—all of which are small molecule drugs. *See* H. R. Report No. 98-857, pt. 1, at 4 (1984) (Tab 18). There was no indication in this report that the Committee contemplated the approval of generic versions of complex drugs.

[27] Section 505(j) of the FDCA. *See also* 21 C.F.R. §§ 314.50(d)(2), (3), (5).

[28] *See* Sections 505(j)(2)(A) and (7) of the FDCA and 21 C.F.R. § 314.3(b). *See also* 21 C.F.R. § 314.94(a)(5)(i) (an ANDA must contain "information to show that the active ingredient is the same as that of the reference... listed drug.").

[29] FDA, Generic Drugs: Questions & Answers (June 1, 2018), http://www.fda.gov/drugs/resourcesforyou/consumers/questionsanswers/ucm100100.htm.

[30] Sections 505(j)(2)(A)(vi) (an ANDA is not required to contain full reports of safety-and-effectiveness investigations) and 505(j)(2)(A)(viii) of the FDCA ("The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)").

[31] 21 C.F.R. § 314.101(d)(9) ("FDA may refuse to file an NDA ...if... The NDA is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act").

applicant's 505(b)(2) drug is safe and effective. A 505(b)(2) application is also appropriate where sameness cannot be established for a given follow-on product.[32]

Importantly, FDA recognized in a proposed rule in 1989 that in some cases the ANDA pathway is not appropriate:

> If preclinical or clinical data are needed to support safety, or if clinical data are needed to support the effectiveness of the requested change, then an ANDA is not appropriate for the proposed drug product.[33]

In a recent guidance, FDA reiterated that "[i]n some instances, current limitations of scientific understanding and technology may preclude approval of an ANDA with the data permitted for submission in an ANDA, including, for example, with respect to establishing active ingredient sameness for a given product."[34]

According to FDA, "a 505(b)(2) application will be appropriately submitted for a drug product where safety and effectiveness of the change must, at least in part, be established by investigations."[35] In a 1999 draft guidance on the 505(b)(2) pathway, FDA states that the types of drugs appropriate for 505(b)(2) approval are, among other things, those having a new chemical or molecular entity or changes from the RLD that "require the review of clinical data."[36] In addition, the 505(b)(2) pathway is appropriate where "clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug."[37] The guidance also recognizes that certain complex drugs may raise distinct safety issues for approval that make the drugs unsuitable for the ANDA pathway.[38]

B. The Challenges of Attempting to Approve Harder-to-Copy Complex Drugs Via the ANDA Pathway are Widely Recognized by FDA and Other Stakeholders

The FDCA ANDA pathway does not permit the consideration of data from clinical studies. Thus, efforts to approve follow-on versions of harder-to-copy complex drugs under this pathway are challenging and may obscure important differences that have clinical and safety impacts. This problem is particularly acute for complex drugs in which the active ingredient is

---

[32] *See* 21 C.F.R. § 314.54(a). *See also* FDA Guidance for Industry, Determining Whether to Submit an ANDA or a 505(b)(2) Application, at 4-5 (May 2019) , https://www.fda.gov/media/124848/download. ("To the extent that the listed drug and the drug proposed in the 505(b)(2) application differ (e.g., a product with a different dosage form or a product that is intentionally more bioavailable than the listed drug), the 505(b)(2) application must include sufficient data to support those differences.")

[33] 54 Fed. Reg. 28,872, 28,880 (July 10, 1989). Inexplicably, in its recent final guidance, "Determining Whether to Submit an ANDA or a 505(b)(2) Application" (May 2019), *supra* note 32, FDA deletes this language which was cited in the draft version of the guidance. Instead, FDA paraphrases this regulatory language to refer only to clinical studies and cites to its approval of generic enoxaparin, as an example of the types of studies that can be included in an ANDA. *See* GAO Report at 7 (Tab 10).

[34] FDA Guidance for Industry, Determining Whether to Submit an ANDA or a 505(b)(2) Application, at 8 (May 2019).

[35] 54 Fed. Reg. at 28,891.

[36] *See* FDA, Draft Guidance for Industry, Applications Covered by Section 505(b)(2) (Oct. 1999), https://www.fda.gov/media/72419/download.

[37] *Id.*

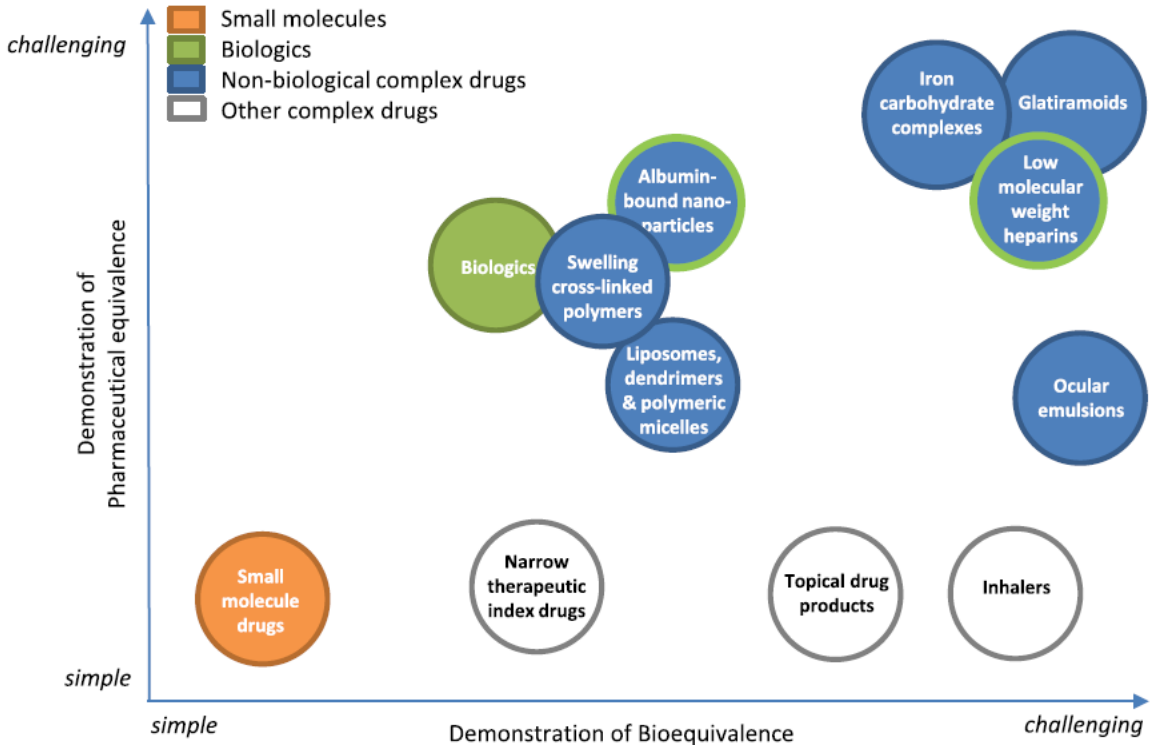
[38] *Id*. at 5.

not a homomolecular structure as found in small molecule drugs, but rather—like biological products—consists of different closely-related and often nanoparticulate structures that cannot be isolated and fully quantitated, characterized, and/or described by physicochemical analytical means.[39] For such drugs, the entire complex is the active pharmaceutical ingredient. Further, the composition, quality, and *in vivo* performance of these drugs are highly dependent on the manufacturing process and formulation and must be highly monitored to ensure appropriate therapeutic effect.

FDA has acknowledged challenges associated with assessing the safety and effectiveness of a related category, namely drugs containing nanomaterials. In a 2017 draft guidance, FDA recognized, among other things, that "characterization of the material structure and its function," the "mechanism by which the physicochemical properties of the material impact its biological effects," and "manufacturing changes" are issues that should be addressed with respect to follow-on drugs containing nanomaterials,[40] and that these issues may have effects on safety and effectiveness.[41] [42]

It is also widely acknowledged in the scientific literature that it is difficult—if not impossible—to determine pharmaceutical equivalence for certain follow-on drugs that have complex active ingredients and/or formulations.[43] These challenges are illustrated in the figure below, which appeared in a 2017 publication in the Annals of the New York Academy of Sciences entitled, "Equivalence of complex drug products: advances in and challenges for current regulatory frameworks."[44] The New York Academy of Sciences publication was co-authored by industry scientists, academic researchers, and regulators, including from FDA.

[39] This definition of NBCD has been developed by the international NBCD Working Group. *See* Lygature, Non-Biological Complex Drugs (NBCD) Working Group, *supra* note 17 (Tab 8).
[40] FDA Draft Guidance, *Drug Products, Including Biological Products, that Contain Nanomaterials*, *supra* note 5, at 6.
[41] "In some instances, nanomaterials may take on different chemical, physical, or biological properties than their larger-scale counterparts that may impact quality, safety, or efficacy.... Compared to other products, further understanding may be needed regarding the interactions of nanomaterials with biological systems. These interactions include, but are not limited to, the impact of intrinsic (e.g., disease, age, sex) and extrinsic factors (e.g., co-administered drugs) on exposure and response, the role of enzymes and transporters in their disposition, and their immunogenic potential." *Id.* at 5.
[42] *See also*, FDA, List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic (June 24, 2019), https://www.fda.gov/media/128236/download. Therein, the Agency distinguishes between those drugs for which a submission under Section 505(j) of the FDCA is appropriate and those having "regulatory or scientific complexities" for which "submission and/or approval of an ANDA via the 505(j) pathway may not be appropriate; section 505(b)(2) of the FDCA may be an appropriate abbreviated pathway for these products." FDA acknowledged a significant error in the composition of Part I of the version of the List published on June 24, 2019, namely that the Agency erroneously included iron sucrose, a harder-to-copy complex drug, in Part I. FDA corrected this error in its December 2019 update of the list. FDA Communication on File. See, FDA, List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic (Dec. 13, 2019), https://www.fda.gov/media/133524/download.
[43] *See, e.g.,* Hussaarts et al., *supra* note 14 (Tab 6). *See also* H. Schellekens et al., *How to Regulate Nonbiological Complex Drugs (NBCD) and Their Follow-on Versions: Points to Consider*, 16 AAPS J. 15 (2014) (Tab 19).
[44] Hussaarts, et al., *supra* note 14 (Tab 6).



As explained in the publication:

> Drug products are positioned [in the illustration] on the basis of the challenge to assess pharmaceutical equivalence (PE) and bioequivalence (BE) of two drug products (i.e., the reference product and its follow-on version). Conventional low-molecular-weight drugs that can be fully characterized are shown in orange; demonstration of PE and BE is relatively simple. Biologics are shown in green; demonstration of PE and BE is more difficult depending on the complexity of the biologic. Complex drugs are shown in blue (NBCDs) or white (other complex drugs). For the majority of NBCDs, both PE and BE are difficult to demonstrate, owing to the inability to synthesize homomolecular material, an unknown mode of action, and/or the difficulty to fully characterize the products. Albumin-bound nanoparticles and low-molecular-weight heparins are blue with a green outline (classification of these drugs varies across the globe).[45]

The complex drugs shown in white in the table above are those with complex routes of delivery, dosage forms, or complex drug-device combinations where bioequivalence may be difficult to establish. As noted, demonstration of pharmaceutical equivalence for these drugs may be simple, while a demonstration of bioequivalence may require sophisticated analytical

[45] *Id*. (emphasis added).

techniques. Such analytical techniques may be developed so as to make these types of complex drugs appropriate for the 505(j) pathway.

In contrast, demonstrating both pharmaceutical equivalence and bioequivalence is difficult—if not impossible—for NBCDs, which are shown in blue as shown in the illustration. A "generic" version of an NBCD will not be the same as the RLD due to the inability to synthesize homomolecular material, an unknown mode of action, and/or the difficulty to fully characterize the drugs. Clinical studies comparing the two versions are generally necessary to address potential issues of safety and effectiveness.

The GAO Report reflects a comprehensive review of the scientific literature, FDA's perspective, and stakeholders' (brand and generic) views. Therein, GAO affirms there are significant challenges to establishing the therapeutic equivalence of follow-on NBCDs under the current legal framework. In this sense, the GAO Report echoes the view set forth by Former Commissioner Gottlieb at an FDA meeting that "[i]n many cases, the traditional requirements used to demonstrate sameness may not be appropriate when it comes to complex drugs that can't be easily measured in the blood, or where the drug's therapeutic affect is delivered locally to a particular organ, rather than systemically, through the blood."[46]

The GAO Report makes clear that there are additional challenges in ensuring that follow-on NBCDs will have the same clinical effect and safety profile as their RLDs. Toward this end, the Report states:

> 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 these processes between the brand and generic sponsors may result in significant differences in the drugs' clinical effects.... [In addition] 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.[47]

The GAO Report's observations are consistent with studies showing the negative impacts of switching patients in other jurisdictions from a complex RLD to a follow-on version that was approved without clinical studies. For example, one study evaluated the effects of switching iron treatment in 75 consecutive stable, haemodialysis-dependent chronic kidney disease French patients from the complex iron sucrose drug Venofer®, to a different follow-on iron sucrose drug that had been deemed to meet standards of therapeutic equivalence by French regulators.[48] The haemoglobin levels in the patients who were switched to the follow-on drug decreased rapidly, and anemia medication had to be increased to return to targeted haemoglobin levels. In addition, there was a decrease in corresponding transferrin

[46] Scott Gottlieb, FDA Commissioner, Opening Remarks for Part 15 Public Meeting on Generic Drug Competition, *supra* note 14 (emphasis added).
[47] GAO Report at 15 (Tab 10). FDA and most of the participating stakeholders agreed that the manufacturing process and the immunogenicity risk are challenges.
[48] Rottembourg et al., *supra* note 24 (Tab 14).

saturation (TSAT) and serum ferritin values in these patients.[49] Other follow-on iron sucrose drugs have been associated with an elevated risk of adverse events, even where the follow-on drugs had been evaluated and approved as therapeutically equivalent to the RLD.[50] Studies such as these, which were conducted in the EU where generic versions had been approved, are a concerning indicator of what can happen when clinical study requirements for approving follow-on versions of harder-to-copy complex drugs are not implemented. In addition, these observations are even more relevant in light of recent revelations about the quality of drugs produced by generic manufacturers.[51]

C. FDA Efforts to Approve Follow-On Versions of Harder-to-Copy Complex Drugs Via the ANDA Pathway are Ad Hoc and are Outside the Plain Language of the FDCA

FDA has acknowledged the difficulty of approving follow-on versions of harder-to-copy drugs. However, the Agency has also taken the conflicting position that it has the analytical tools to assess all follow-on complex drugs under the ANDA pathway, and further, that no additional clinical studies are required to ensure therapeutic equivalence for such drugs. In practice, FDA's approach to approving follow-on versions of harder-to-copy complex drugs under the ANDA pathway has been anything but straightforward. Moreover, FDA often operates beyond the plain language of the FDCA, which states that no clinical studies are required or, in fact, permitted under that pathway.[52]

As part of its effort to approve follow-on versions of harder-to-copy complex drugs via the ANDA pathway, the Agency has articulated a "new paradigm of equivalence" applicable to its assessment of complex drugs that it refers to as its "weight of the evidence" approach.[53] This inchoate approach is reflected in comments from FDA summarized in the GAO Report as well. Toward this end, the GAO Report states, "FDA officials told us that by relying on multiple confirmatory tests, the Agency could mitigate the risk that the proposed generic drug was

---

[49] *Id*. In addition, M. L. Agüera et al., *supra* note 24 (Tab 15), affirms Rottembourg's finding regarding marked differences in effectiveness between an original iron sucrose formulation and an approved Iron Sucrose Similar (ISS). There, anaemia parameters and doses of ESA and iron sucrose were prospectively recorded before and after the switch in 342 patients with a follow up period of 56 weeks. Though the haemoglobin levels were stable in the study patients, the mean dose of IV iron sucrose per patient necessary to achieve appropriate levels decreased by 34.3% after switching from the generic iron sucrose to the original iron sucrose formulation. The mean dose of ESA decreased by 12.5% per patient over the same period after the switch to the original iron sucrose formulation. Meanwhile, significant positive effects were also seen on mean TSAT levels and serum ferritin levels following the switch from the generic to the original iron sucrose formulation. Over the same period, the mean TSAT level increased by 6.8% and sodium ferritin levels rose by 12.4%.

[50] E. Sil Lee et al., *supra* note 24 (Tab 16). It is worth noting that after the publication of these studies, the EU appears to have shifted its approval consideration for follow-on versions of iron sucrose and other NBCDs to make use of the Hybrid 10.3 procedure under Directive 2001/83/EC. *See* K. Klein, et al., *The EU Regulatory Landscape of Non-Biological Complex Drugs (NBCDs) Follow-on Products: Observations and Recommendations*, 133 EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES 228-35 (Tab 20).

[51] *See, e.g.*, Katherine Eban, Bottle of Lies: The Inside Story of the Generic Drug Boom, at Prologue & Ch. 1 (1st. ed., Ecco, 2019) (Tab 21).

[52] Section 505(j)(2)(A)(vi) of the FDCA (an ANDA is not required to contain full reports of safety-and-effectiveness investigations); Section 505(j)(2)(A)(viii) of the FDCA ("The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)").

[53] Robert Lionberger, Director, Office of Research and Standards, Office of Generic Drugs, CDER, Challenges in Bioequivalence for Locally Acting Products (Nov. 12, 2016), https://zerista.s3.amazonaws.com/item_files/1d43/attachments/260430/original/438.pdf (Tab 22).

different from the brand."[54] In addition, in an FDA presentation titled, "Science and Generic Drugs," the Agency again diverts significantly from the statutory dictates on approval of generic drugs. In that presentation, the Agency includes a standard of "clinical relevance" in its evaluation of pharmaceutical equivalence and bioequivalence; introduces the analytical concept that "Equivalence is a Judgment not a Fact"; and thereafter appears to conclude that an ANDA drug should be approved as long as there are "No Significant Differences from the RLD." [55]

Notably, the standard under Section 505(j)(2)(A) of the ANDA pathway is, in fact, whether the follow-on is the "same as" the RLD The standard is not "clinical relevance" or "no significant difference". And, with generic small molecule drugs, sameness is indeed a scientific fact, rather than a "judgment," as FDA seemed to suggest. It is also worth noting that the regulations implementing the ANDA pathway at 21 C.F.R. § 314.92(a)(1) define "same as" to mean "identical." Being identical cannot simply be reduced to having "no significant difference" without impairing the meaning and intent of the regulation. Seemingly, FDA has pushed the statutory boundaries of Section 505(j) of the FDCA to accommodate its approval of generic drugs containing complex active ingredients and/or complex formulations.

Further, FDA's recent final guidance, "Determining Whether to Submit an ANDA or a 505(b)(2) Application," proffers ANDA approval standards that are inconsistent with the actual FDCA statutory parameters. Specifically, in the final guidance, FDA seems to open the door to accepting preclinical studies demonstrating safety and/or efficacy as part of an ANDA submission.[56] Indeed, the draft version of the guidance in 1999 quoted language from the 1989 preamble making clear that an ANDA may not include "preclinical or clinical" data "necessary to evaluate the safety and effectiveness of the changed drug product."[57] However, the recent final guidance—without any explanation—simply deletes this standard. The final guidance thus arguably opens the door to submission of data in an ANDA that the statute specifically excludes.[58]

In fact, FDA has required clinical studies for ANDA approvals in certain cases, clearly outside the plain language of the statute. For example, FDA approved a therapeutically equivalent version of sodium ferric gluconate complex pursuant to the ANDA pathway in 2011, accompanied by an assertion in a citizen petition response that clinical studies were not necessary to explore known differences between the follow-on drug and the RLD.[59] Despite this, two years later, FDA announced that it was *reassessing* whether its approval criteria used to approve the follow-on sodium ferric gluconate drug were sufficient to ensure that the drug would have the same clinical effect and safety profile, as required for a designation of therapeutic equivalence. Since making this announcement, the Agency has undertaken a

---

[54] GAO Report at 17 (emphasis added) (Tab 10).
[55] John R. Peters, Deputy Director, Office of Generic Drugs, CDER, Science and Generic Drugs, at 8-10, https://www.fda.gov/downloads/Drugs/NewsEvents/UCM579161.pdf; *see also* Xiaohui (Jeff) Jiang, Deputy Director Division of Therapeutic Performance Office of Research and Standards Office of Generic Drugs, CDER, Introduction to Complex Products and FDA Considerations, at 25, https://www.fda.gov/downloads/Drugs/NewsEvents/UCM582950.pdf ("How similar is equivalent?").
[53] FDA Guidance for Industry, Determining Whether to Submit an ANDA or a 505(b)(2) Application, at 8 (May 2019).
[57] 54 Fed. Reg. at 28,880.
[58] Section 505(j)(2)(A)(vi) of the FDCA (an ANDA is not required to contain full reports of safety-and-effectiveness investigations).
[59] Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research to David Zuchero et al. (Mar. 31, 2011), https://www.regulations.gov/document?D=FDA-2004-P-0494-0008 (Tab 23).

series of post-approval studies,[60] including funding a comparative clinical study of the type that could be required as part of a 505(b)(2) application. This study is being conducted by the University of Maryland and had a study completion date in April of this year.[61]

Introducing an insufficiently tested compound into medical practice prior to establishing clinical effect and safety—yet implying through choice of pathway that these compounds have demonstrated equivalence—is contrary to the intent of the regulatory framework and the goal of informing accurate healthcare professional practice. It would have been more appropriate for FDA to designate sodium ferric gluconate, as well as other harder-to-copy follow-on complex drugs, as BX in the Orange Book. The Orange Book Preface makes clear that BX is appropriate for "drug products for which the data are insufficient to determine therapeutic equivalence."[62] Accordingly, BX drug products "are presumed to be therapeutically inequivalent until the Agency has determined that there is adequate information to make a full evaluation of therapeutic equivalence."[63] BX is thus a more appropriate category for sodium ferric gluconate, as well as for other harder-to-copy follow-on complex drugs that are not supported by adequate studies to establish therapeutic equivalence.

Ultimately, FDA's ever-changing approach to establishing pharmaceutical equivalence and bioequivalence creates ambiguity for stakeholders. By requiring an *ad hoc* array of studies under the ANDA pathway, FDA has created a process that is costly and labor intensive, requiring the painstaking development of new analytical approaches for each potential new follow-on version. An approach that requires clinical studies to some extent would be more predictable and consistent and would provide sponsors of follow-on versions of harder-to-copy complex drugs a clearer route to ensuring the same clinical effect and safety profile.

D. FDA's Current Approach is Challenging and Costly for the Agency and Stakeholders

The difficulties associated with approving a therapeutically equivalent version of a harder-to-copy complex drug via the ANDA pathway were aptly illustrated by FDA's approval in 2015 of a follow-on version of glatiramer acetate. In that context, FDA and the Section 505(j) applicant, Momenta Pharmaceuticals ("Momenta"), invested significant time and resources first developing what were deemed to be appropriate non-clinical approval criteria, and then in performing testing per those criteria. According to the Agency, it approved the first follow-on version of glatiramer acetate injection after a review period that required FDA and Momenta to develop a "battery of characterizations that, when combined, [could] be applied to comparatively characterize the glatiramer acetate and provide a collection of scientific evidence sufficient to

---

[60] These include a comparative evaluation of U.S. brand and generic sodium ferric gluconate complex in terms of in vitro cellular uptake (M. Wu et al., *Comparative Evaluation of U.S. Brand and Generic Intravenous Sodium Ferric Gluconate Complex in Sucrose Injection: In Vitro Cellular Uptake*, 7 NANOMATERIALS 451 (2017) (Tab 24)); physicochemical characterization (D. Sun et al., *Comparative Evaluation of U.S. Brand and Generic Intravenous Sodium Ferric Gluconate Complex in Sucrose Injection: Physicochemical Characterization*, 8 NANOMATERIALS 25 (2018) (Tab 25)); and biodistribution after intravenous dosing in rats (CR Beekman et al., *Comparative Evaluation of U.S. Brand and Generic Intravenous Sodium Ferric Gluconate Complex in Sucrose Injection: Biodistribution after Intravenous Dosing in Rats*, 8 NANOMATERIALS 10 (2018) (Tab 26)).

[61] *See* IV Iron Safety: Evaluation of Iron Species in Health Subjects, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT02399449 (indicating a study completion date of April 25, 2019) (Tab 27).

[62] FDA, Orange Book Preface (Feb. 5, 2018), https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface.

[63] *Id.*

establish active ingredient sameness."[64] FDA and Momenta reportedly developed at least 45 physicochemical, biological, and immunological methods to minimize the risk that there were significant differences between the brand and the generic version.[65] In Momenta's securities filings, it appears that the cost of external research and development expenses for this follow-on drug was close to $49 million between 2006 (the year of the inception of this development program) and 2015 (the year of first approval of the two generic formulations).[66]

Ultimately, FDA's efforts to approve follow-on versions of harder-to-copy complex drugs through the ANDA pathway is significantly problematic. First, the statutory language of the ANDA pathway precludes FDA from considering clinical studies relevant to safety or efficacy. Generic versions of harder-to-copy complex drugs approved through the ANDA pathway may be deemed to be therapeutically equivalent and substitutable for the RLD even though *known risks* have not been addressed through clinical studies. As such, ANDA approvals of follow-on versions of harder-to-copy drugs pose significant safety risks to patients.

Second, FDA appears to mitigate these risks by simply operating outside the plain language of the statute and allowing for comparative clinical endpoint studies, confirmatory studies and even post-approval studies within the ANDA pathway. Consequently, FDA's efforts to use the ANDA pathway for generic versions of harder-to-copy complex drugs is uncertain, at odds with statutory authority, and costly for sponsors and FDA alike. A better approach is to approve such products via the Section 505(b)(2) pathway, where appropriate clinical studies can be required in a transparent manner and considered in the approval process.

---

[64] Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research to J. Michael Nicholas, Ph.D., Vice President, Global Specialty Medicines, Teva Pharmaceuticals, at 21 (Apr. 16, 2015), https://www.regulations.gov/document?D=FDA-2015-P-1050-0012 (Tab 13).

[65] *Id.* Momenta subsequently described this complex assessment in a journal article published in 2017. *See* B. Weinstock-Guttman et al., *Two decades of glatiramer acetate: From initial discovery to the current development of generics*, 376 J. OF THE NEUROLOGICAL SCIENCES 255–259 (2017), https://www.jns-journal.com/article/S0022-510X(17)30199-5/pdf (Tab 28).

[66] Momenta, Inc., 2015 Annual Report (Form 10-K), at 71 (Feb. 26, 2016), http://ir.momentapharma.com/static-files/4513b1f3-e0c8-4ba8-afbb-a5e2a5d58bc3 (Tab 29).

III. FDA Should Issue Guidance Making Clear that Therapeutic Equivalence Ratings for Follow-On Harder-To-Copy Drugs Require Clinical Studies to Show Same Clinical Efficacy and Safety Profile

Based on the discussion above, it is clear that the 505(b)(2) pathway is the appropriate regulatory mechanism for the consideration and approval of safe and effective follow-on harder-to-copy complex drugs. Importantly, reliance on the 505(b)(2) pathway does not foreclose the possibility of therapeutic equivalent determinations for follow-on harder-to-copy complex drugs. FDA has long taken the position that follow-on drugs approved under either the ANDA or 505(b)(2) pathway are eligible for a determination that they are therapeutically equivalent to the reference, and that such a determination may rely on clinical studies. A drug designated as therapeutically equivalent to a reference drug may be substituted for that drug under applicable state law. The net effect is to increase competition amongst drug manufacturers and to lower the costs of prescription drugs.[67] Thus, approval of follow-on harder-to-copy complex drugs via the 505(b)(2) pathway is consistent with the goals of the DCAP as well as FDA's role in ensuring the safety and efficacy of the drug supply.

FDA has promised to issue guidance to educate stakeholders about the availability of the 505(b)(2) pathway to establish therapeutic equivalence for harder-to-copy complex drugs and to provide a roadmap that will allow sponsors of such drugs to conduct the requisite clinical studies.[68] Good Guidance Practice regulations require the issuance of guidance where, as here, FDA's policies have not been clearly articulated and the issue is related to the evaluation or approval of submissions to the agency.[69] Vifor supports FDA's effort to issue such guidance and agrees that it would promote competition by clarifying the approval pathway and enhancing efficiency in the application submission and review processes.

A. The History of Therapeutic Equivalence Makes Clear that Same Clinical Efficacy and Safety Profile are Critical Considerations

The requirements for therapeutic equivalence are not stated in the FDCA. Rather, therapeutic equivalence ratings and the Orange Book listing of such ratings were developed by FDA in the 1970s as guidance in response to repeated requests from States and consumers for information on when marketed copies of brand name drugs could be safely substituted for that drug. At that time, prior to the introduction of the Hatch-Waxman amendments with its structured approval pathways for follow-on drugs, there were often multiple versions of approved drugs on the market. This resulted in confusion over when and whether these drugs could be expected to have the same therapeutic effect in patients. States developing substitution laws to address drug costs repeatedly asked FDA for guidance on whether drugs should be designated as substitutable in state formularies, and consumers frequently sought guidance on whether such drugs were therapeutically the same. In response, FDA initiated an

---

[67] *See, e.g.*, IMS Institute for Healthcare Informatics, *supra* note 8 (Tab 5).

[68] FDA, Statement from FDA Commissioner Scott Gottlieb, M.D., on the Agency's Efforts to Enhance the Utility of the Orange Book to Foster Drug Competition (Jan. 30, 2019), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-efforts-enhance-utility-orange-book-foster-drug.

[69] GGPs must be followed whenever "regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad audience" and FDA "may not use documents or other means of communication that are excluded from the definition of guidance document to informally communicate new or different regulatory expectations to a broad public audience for the first time." 21 C.F.R. § 10.115(e). The definition of "guidance documents" includes the evaluation or approval of submissions. Id. § 10.115(b)(2).

effort to develop criteria for determining that one version of a small molecule drug would have the same therapeutic effect as another, and therefore was appropriate for substitution.[70]

In the preamble to a 1979 proposed rule on therapeutic equivalence, FDA proposed that its judgments about such equivalence would rely on evidence that the drugs in question were pharmaceutical equivalents, bioequivalent, adequately labeled, and in compliance with current good manufacturing practice (cGMP).[71] This approach reflected expert findings that evidence of pharmaceutical equivalence, or chemical sameness, *alone* was often insufficient to ensure that one small molecule drug would have the same therapeutic effect as another.[72] FDA participated in consensus building around the fact that pharmaceutical equivalence and bioequivalence could together predict the therapeutic equivalence of a small molecule drug to ensure that it has the same clinical effect and safety profile. Based on this finding, FDA stated in its preamble to the proposed rule that, for drugs meeting these factors, clinical trials would generally be considered unnecessary. At the same time, and importantly, the Agency made clear that its approach to therapeutic equivalence would not preclude reliance on clinical studies where there were "reasonable grounds for believing that the two drugs will not be of equivalent safety and effectiveness."[73]

In 1980, FDA published a final rule that announced the availability of "a list of all FDA-approved prescription drug products, together with therapeutic equivalence evaluations of products in the List that are available from more than one source."[74] This publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," became known as the "Orange Book," based on the color of its cover. FDA was clear from the outset that its definition of therapeutic equivalence encompassed both clinical efficacy and safety:

> The term "therapeutically equivalent drug products" simply means that two such drug products can be expected, in the judgment of FDA, to have equivalent therapeutic effect and equivalent potential for adverse effects when used under the conditions set forth in their labeling.[75]

FDA subsequently incorporated the "same clinical effect and safety profile" standard into the definition itself. Thus, the current definition in the Orange Book Preface states:

> Therapeutic equivalents are approved drug products that are pharmaceutical equivalents for which bioequivalence has been

---

[70] FDA, Orange Book Preface (Feb. 5, 2018), https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface. *See also* D. Carpenter and D.A. Tobbell, *Bioequivalence: The Regulatory Career of a Pharmaceutical Concept*, 85 BULL. HIST. MED. 93, 97-110 (2011) (Tab 30).

[71] 44 Fed. Reg. 2,932, 2,937 (Jan. 12, 1979).

[72] Carpenter and Tobbell, *supra* note 70 (Tab 30).

[73] 44 Fed. Reg. at 2,937 (emphasis added).

[74] 45 Fed. Reg. 72,582, 72,608 (Oct. 31, 1980). This final rule administratively created the concept of therapeutic equivalence. It amended 21 C.F.R. § 20.117 by adding a new paragraph (a)(3) that concerns the availability of a list of facts about new drugs, including "an evaluation of the therapeutic equivalence" of approved drugs. That list (the Orange Book, including its preface) was published concurrently with the final rule. Subsequently, the preface has been modified through the publication of annual editions.

[75] 44 Fed. Reg. at 2,932.

> demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[76]

The takeaway is that the "same clinical effect and safety profile" standard is essential to any finding that a follow-on drug is therapeutically equivalent to an RLD.

B. Drugs Approved Under FDCA Section 505(b)(2) May Receive Therapeutic Equivalence Ratings As Long As Demonstrated to Have the Same Clinical Efficacy and Safety Profile

Although therapeutic equivalence is not a statutory concept, the Hatch-Waxman Amendments incorporated elements of FDA's therapeutic equivalence approach into the FDCA Section 505(j) ANDA pathway. Thus, as discussed above, an ANDA approval requires that a proposed generic be pharmaceutically equivalent and bioequivalent to its RLD (as well as having the same labeling and being in compliance with cGMP). An ANDA approved drug is therefore effectively deemed by FDA upon approval to be therapeutically equivalent to its RLD and is listed as such in the Orange Book. In addition, FDA has generally tied the concept of therapeutic equivalence to the ANDA pathway through the pharmaceutical equivalence and bioequivalence standards of the Orange Book Preface[77] and through the definitions of "reference listed drug"[78] and "therapeutic equivalents" in 21 C.F.R. § 314.3(b).[79]

Nevertheless, FDA has also consistently taken the position that follow-on drugs can be therapeutically equivalent when approved pursuant to the 505(b)(2) pathway.[80] However, to date, the Agency has provided relatively little guidance as to how a Section 505(b)(2) approved drug can meet the administrative criteria for therapeutic equivalence. FDA's explanation of the 505(b)(2) pathway to therapeutic equivalence to date has been limited to a 2014 response to a citizen petition filed by Abbott Labs (and later pursued by one of its successors, AbbVie). Therein, FDA explains that a 505(b)(2) drug may receive a designation of therapeutic equivalence when the drug is "essentially" a duplicate of the RLD, but an application "cannot be submitted pursuant to Section 505(j) of the FD&C Act because the type(s) of studies needed to support the differences between the proposed drug and the listed drug are outside the scope of what can be appropriately reviewed through the 505(j) pathway."[81]

Critically, FDA has not addressed therapeutic equivalence for a broader range of 505(b)(2)-approved follow-on drugs, including complex drugs. This gap is particularly acute for follow-on versions of harder-to-copy complex drugs, as highlighted in the former FDA

---

[76] FDA, Orange Book Preface, *supra* note 70 (emphasis added).
[77] *See id*.
[78] A reference listed drug is "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA".
[79] The definition refers to "pharmaceutical equivalents for which bioequivalence has been demonstrated."
[80] FDA, Orange Book Preface, *supra* note 70.
[81] Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research to Dan Himmelfarb, Mayer Brown, et al., at 4 (July 23, 2014), https://www.regulations.gov/document?D=FDA-2011-P-0610-0010; (The FDA response also addressed citizen petitions by the follow-on manufacturers that concerned other issues in Docket No. FDA-2013-P-0371.)

Commissioner's recent statement about the need for 505(b)(2) therapeutic equivalence guidance.[82]

As discussed above, there is conclusive evidence that, for harder-to-copy complex drugs, pharmaceutical equivalence and bioequivalence can be approximated through laboriously developed case-by-case analytic methods. These approximations may be reasonable indicators that such a drug could have the same clinical effect and safety profile. However, without data from clinical studies concerning potential immunogenicity and also the impact of changes from the RLD's manufacturing process, analytical data alone is insufficient to establish that a follow-on version of a harder-to-copy complex drug will have the same clinical effect and safety profile in patients as the RLD. Without clinical studies, such drugs should appropriately be designated as BX rated in the Orange Book, a category that describes drug products for which the data are insufficient to determine therapeutic equivalence.

Vifor asks that FDA' s promised guidance on therapeutic equivalence for FDCA 505(b)(2) products make clear that therapeutic equivalence is available for follow-on harder-to-copy complex drugs only where clinical studies have been conducted to demonstrate that such drug is the same as and will have the same clinical efficacy and safety profile as the RLD. Specifically, FDA should state that a 505(b)(2) complex drug may be determined to be safe and effective, and therapeutically equivalent to its RLD (and is therefore substitutable), only on the basis of clinical studies demonstrating that the follow-on drug meets the standard requirements for therapeutic equivalence, namely that it has: (1) the same active ingredient; (2) the same route of administration, dosage form, and strength; (3) the same clinical effect and safety profile; and (4) been shown to be bioequivalent.

Adopting the existing criteria for harder-to-copy complex drugs requires FDA to acknowledge that the first element, namely "same active ingredient" cannot be demonstrated by non-clinical means alone. As discussed above, many harder-to-copy complex drugs have a non-homomolecular structure, have unknown modes of action and cannot be fully characterized. Analytical studies can only approximate sameness, and any conclusion that the drugs are the same can only be confirmed through clinical studies. For follow-on harder-to-copy complex drugs, therefore, a determination of therapeutic equivalence will need to rely heavily on a clinical demonstration that the follow-on product has the "same clinical effect and safety profile" as the RLD. Such an approach would ensure that any substitutable harder-to-copy drug safeguards patient safety if it is substituted at the pharmacy level.

It is worth noting that this proposed pathway for determining therapeutic equivalence is analogous to the pathway for approval of interchangeable biosimilars under Section 351(k)(4)(A) of the Public Health Service Act ("PHSA"). Akin to a biosimilar, a follow-on harder-to-copy complex drug will not be the same as the RLD. Accordingly, just as it would be for a proposed interchangeable biosimilar, FDA must require clinical studies, submitted pursuant to Section 505(b)(2) of the FDCA, to determine that a follow-on drug will have the same clinical effect and safety profile as the RLD. We discuss the analogy to the interchangeable biosimilar pathway in more detail below.

[82] FDA, Statement from FDA Commissioner Scott Gottlieb, M.D., *supra* note 22.

C. The Interchangeable Biosimilar Pathway Provides a Model for Demonstrating that a Follow-On Harder-to-Copy Complex Drug is Therapeutically Equivalent to the RLD

Congress explicitly recognized the difficulties of establishing sameness—and thus bioequivalence and ultimately the question of equivalent safety and effectiveness—for certain complex molecules when it established the biosimilars approval pathway in Section 351(k) of the PHSA (added by the Biologics Price Competition and Innovation Act ("BPCIA")).[83] Leading up to this development, FDA's Dr. Janet Woodcock testified before the House Energy and Commerce Committee in 2007 that "it is not clear that [the ANDA] pathway, which determines that a drug is the same based on a chemical comparison to the brand-name product, would be appropriate for follow-on protein products."[84]

Pursuant to the BPCIA, the term "biosimilar" or "biosimilarity" refers to a follow-on biological product that is "highly similar to the reference product notwithstanding minor differences in clinically inactive components;" and "there are no clinically meaningful differences" between the follow-on biological product and the reference product in terms of safety, purity and potency of the product.[85] FDA's biosimilars guidance documents make clear that structural and functional characterization form the foundation of the informational requirements necessary to demonstrate biosimilarity.[86] Then, depending on the "residual uncertainty" remaining after consideration of the results of these analytical studies, FDA determines the scope and extent of additional studies necessary to demonstrate biosimilarity—such as animal studies, pharmacokinetic (PK) studies, pharmacodynamic (PD) studies, immunogenicity studies, and comparative clinical trials—in a "stepwise" manner.[87] This approach allows uncertainty regarding the impact of minor differences on safety and effectiveness to be resolved by increasingly higher-order testing performed on a step-by-step basis. The biosimilars approval pathway gives FDA flexibility, including authority to require more or less clinical evidence as the Agency determines appropriate in order to ensure patient safety.

Further, a biosimilar will only be deemed to be "interchangeable" with the reference product if FDA determines the biosimilar product "can be expected to produce the same clinical result as the reference product in any given patient."[88] According to FDA's recent Interchangeability Guidance, there are two key "steps" that inform the scope of additional

---

[83] Patient Protection and Affordable Care Act, Pub. L. No. 111-148, Title VII, Subtitle A (2010), Section 7002 (Tab 31).

[84] H.R Rep. No. 110-40, Statement from Janet Woodcock, M.D., Deputy Commissioner and Chief Medical Officer, Food and Drug Administration on Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States, at 29 (May. 2, 2007), https://www.govinfo.gov/content/pkg/CHRG-110hhrg40500/pdf/CHRG-110hhrg40500.pdf (Tab 32).

[85] Sections 351(i)(2)(A) and (B) of the PHSA.

[86] *See* FDA, Draft Guidance for Industry, Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations, at 8 (May 2019), https://www.fda.gov/media/125484/download.

[87] *See* FDA, Guidance for Industry, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, at 7-8 (Apr. 2015), https://www.fda.gov/media/82647/download.

[88] The statute additionally provides that "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished effectiveness of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. Section 351(k)(4)(B) of the PHSA. *See also* Interchangeability Guidance, *supra* note 6.

studies or post-marketing analyses that may be required. These are (1) comparative analysis of the reference and potential interchangeable product; and (2) analysis of immunogenicity risks raised by the reference product. FDA makes clear that it is willing to rely to some extent on comparative and functional characterization to demonstrate similarity between a reference and follow-on product, but that "products with a documented history of inducing detrimental immune responses may require more data to support a demonstration of interchangeability than products with an extensive documented history that immunogenicity does not impact clinical outcomes."[89] FDA goes on to discuss the types of studies that may be necessary to demonstrate that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch" as required under the statute.[90]

Just as for biosimilars, it is difficult to demonstrate that follow-on versions of harder-to-copy complex drugs are the same as their reference product without clinical studies. For this reason, FDA's well-articulated interchangeability pathway can serve as an appropriate model for determining the therapeutic equivalence of a follow-on harder-to-copy complex drug. Vifor urges FDA to make clear in guidance that clinical studies are necessary to determine that follow-on versions of harder-to approve complex drugs will have the same clinical effect and safety profile as the RLD. Like the Interchangeability Guidance, the new guidance should make clear that FDA will target clinical studies to known areas of concern—such as potential immunogenicity—and design appropriate clinical studies.

FDA's guidance would replace its current practice of trying to "mitigate the risk" of differences between a follow-on and originator harder-to-copy drug[91] or making a "judgment" about equivalence. This approach would ultimately increase transparency for sponsors, reduce risks for patients, and make the approval process more efficient.

[89] Interchangeability Guidance, *supra* note 6, at 7.
[90] *Id.* at 2; Section 351(k)(4)(B) of the PHSA.
[91] *See* GAO Report at 17 (Tab 10).

IV. Conclusion

Vifor supports FDA's DCAP and its efforts to enhance competition and lower prices for drugs. However, Vifor urges FDA to take two important steps to ensure that follow-on harder-to-copy complex drugs are safe and effective for patients.

First, Vifor asks FDA to issue guidance and publicly affirm that the ANDA pathway is not appropriate for consideration or approval of follow-on harder-to-copy complex drugs. FDA and other stakeholders have long recognized that the ANDA pathway does not allow submission of data from clinical studies in support of approval.[92] Harder-to-copy complex drugs are composed of non-homomolecular material, generally have an unknown mode of action of the drug, and/or are difficult to fully characterize. These characteristics mean that it is difficult – if not impossible – to demonstrate pharmaceutical equivalence and bioequivalence to a reference drug. As a result, any follow-on drug approved via the ANDA pathway will *de facto* not be the same as the reference product and therefore may not have the same clinical effect and safety profile. FDA's current reliance on ad hoc standards and practices that contravene the plain language of the statute are simply not acceptable. FDA should instead confirm that Section 505(b)(2) of the statute is the appropriate regulatory pathway for such drugs.

Second, Vifor asks FDA to clarify in its promised guidance that therapeutic equivalence for follow-on harder-to-copy drugs approved via Section 505(b)(2), is available upon a showing that follow-on harder-to-copy drugs meet the current criteria, namely that they have: (1) the same active ingredients; (2) the same route of administration, dosage form, and strength; (3) the same clinical effect and safety profile; and (4) been shown to be bioequivalent. "Same active ingredient," in this context cannot be demonstrated by non-clinical means. Therefore, any determination of therapeutic equivalence will need to rely on clinical studies to demonstrate both that the active ingredient is the same and that the follow-on product has the "same clinical effect and safety profile" as the RLD. An appropriate approach could be modelled on the pathway for approval of interchangeable biosimilars, which would give FDA great flexibility in determining the scope of clinical evidence that is necessary.

Ultimately, these requested actions will facilitate approval of follow-on versions of harder-to-copy complex drugs, protect patient safety, and increase competition, and thereby support the goals of FDA's DCAP.

ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 C.F.R. § 25.31.

ECONOMIC IMPACT

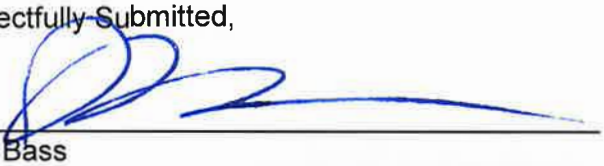
Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

[92] Sections 505(j)(2)(A)(vi) (an ANDA is not required to contain full reports of safety-and-effectiveness investigations) and 505(j)(2)(A)(viii) of the FDCA ("The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii)").

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: March 28, 2012 [Publication date of original Draft Bioequivalence Guidance for Iron Sucrose, 77 Fed. Reg. 18,827 (2012)] and January 30, 2019 [Statement from FDA Commissioner Scott Gottlieb, M.D., on the Agency's Efforts to Enhance the Utility of the Orange Book to Foster Drug Competition (Jan. 30, 2019)(announcing that FDA will publish a draft guidance for industry describing how FDA evaluates therapeutic equivalence and assigns therapeutic equivalence codes, including for products approved under the 505(b)(2) pathway)]. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Vifor Pharma. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully Submitted,



Scott Bass
Emily Marden
Sidley Austin LLP
1501 K Street, N.W.
Washington D.C. 20005
(202) 736-8000
Attorneys for Vifor Pharma