Misleading and Deceptive? A Look into Educational and Promotional Messages Comparing the Nature of Biologics and Biosimilars

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ABSTRACT

This Article assesses the legal issues arising from claims that companies commercializing original biological medicines (biologics) have disseminated messages to mislead the public into believing biosimilars are less safe and effective than their reference biologics. Pfizer raised those concerns to the Food and Drug Administration (FDA) and asked the agency to establish standards for communication comparing the nature and properties of biologics and biosimilars. Other players followed suit, arguing the Federal Trade Commission (FTC) should also intervene. In 2020, FDA issued draft guidance on the matter, only partially fulfilling Pfizer's request, while FTC threatened enforcement action. Specifically, this Article analyzes FDA and FTC's regulatory and enforcement limitations preventing the agencies from fully addressing the demands from those concerned that biosimilars have been improperly discredited. The conclusion provides insights on how FDA-led educational initiatives and a different antitrust focus may help with the biosimilars uptake in the United States.

I. INTRODUCTION

This Article explores the regulatory and enforcement limitations preventing the Food and Drug Administration (FDA) and the Federal Trade Commission (FTC) from fully addressing the concerns that original biologics[1] manufacturers have sought to discredit biosimilars[2] by disseminating messages designed to mislead the public into believing that biosimilars are less safe and effective than their reference biologics.

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[1] The term "biologics" refers to a class of biological products licensed by the Food and Drug Administration (FDA) under section 351(a) of the Public Health Service Act (PHSA). Biological product applications are submitted under section 351(k) of the PHSA (42 U.S.C. § 262(i)(4)). Biological medicines derive from living organisms and differ from traditional synthetic drugs. *See infra* Section II(B).

[2] Biosimilar is the follow-on medicine that simulates the reference biologic product, but is not an exact copy; hence, the term "biosimilar." The term "biosimilar" refers to products that FDA has determined

Biosimilars debuted in the United States in 2009 but were only gradually made available to patients.[3] As competition picked up, players increased their efforts to educate healthcare professionals and patients on the complexities of biosimilarity and interchangeability. While education is needed, messages and claims in this space have often been a source of contention among competitors. Such disputes led Pfizer to request FDA to define the boundaries of truthful and not misleading communication on biosimilarity to root out an alleged campaign of misinformation and help with biosimilars' uptake.[4] Other players followed suit, arguing FTC should also take action against biologics manufacturers to stop the alleged misinformation campaign.[5] In response, FDA issued draft guidance only partially addressing Pfizer's request; the draft guidelines issued are limited to aspects of product promotion.[6] FTC threatened enforcement action to stop what it perceived to be anti-competitive practices, but the push has not gained traction thus far.[7]

This Article analyzes the two agencies' regulatory and enforcement limitations, proceeding as follows:

Section II(A) details Pfizer's Citizen Petition, the alleged misleading messages, and the agencies' reactions to the issue. From there, two specific questions are proposed: 1) can FDA set parameters for truthful and not misleading communication on the "nature and properties" of biosimilars, without product reference, to encourage the prescription and use of biosimilars, as Pfizer had requested?; and 2) what statements on the nature and properties of biosimilars are likely to be considered misleading and trigger enforcement action from FTC?

Sections II(B) through II(E) provide the background needed to address those two questions: concepts applicable to biologics, biosimilars, and interchangeables; the existing scientific discussion related to biosimilars; the current U.S. biosimilars marketplace; and the regulatory framework covering biologics and biosimilars.

Section III answers the first question, concluding that FDA cannot set parameters for truthful and not misleading communication on the nature and properties of biosimilars when such communication does not involve drug promotion. The Federal Food, Drug, and Cosmetic Act (FDCA) prohibits misbranding by dissemination of labeling or advertising that is "false or misleading in any particular,"[8] where labeling and advertising relate to communication referencing a specific food, drug, device,

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to be biosimilar to the reference biologic. Public Health Service Act, 42 U.S.C. §§ 262(i)(2), 262(k)(2); *see infra* Section II(B).

3 *See infra* Section II(E).

4 Pfizer, Inc., Citizen Petition, Docket No. FDA-2018-P-3281 (Aug. 22, 2018).

5 *E.g.*, Novartis Services, Inc., Comment Letter on Citizen Petition by Pfizer, Inc. (Nov. 7, 2018), https://www.regulations.gov/comment/FDA-2018-P-3281-0006 [https://perma.cc/8MTR-2ZCC] [hereinafter Novartis Comment Letter].

6 U.S. FOOD & DRUG ADMIN., PROMOTIONAL LABELING AND ADVERTISING CONSIDERATIONS FOR PRESCRIPTION BIOLOGICAL REFERENCE AND BIOSIMILAR PRODUCTS QUESTIONS AND ANSWERS: GUIDANCE FOR INDUSTRY, DRAFT GUIDANCE (Feb. 2020) [Hereinafter FDA, GUIDANCE ON PROMOTIONAL LABELING AND ADVERTISING], https://www.fda.gov/regulatory-information/search-fda-guidance-documents/promotional-labeling-and-advertising-considerations-prescription-biological-reference-and-biosimilar [https://perma.cc/7MF3-EA67].

7 *See infra* Section II.

8 21 U.S.C. § 352.

tobacco product, or cosmetic.[9] As such, FDA sets parameters for truthful and not misleading communication regarding a regulated product, but not anything else. A biologics manufacturer's speech solely addressing its thinking around biosimilarity and interchangeability, without more, is not subject to the FDCA's misbranding provision. The FDCA text, structure, and overall statutory scheme do not reveal a broad delegation of power to FDA to create new restrictions on speech, making it unlikely that courts would uphold regulation as Pfizer requested. Finally, "encouraging the prescription and use of biosimilars" is likely not a public policy FDA is authorized to pursue while regulating the misbranding provision. Nothing indicates that Congress intended the FDCA to be a sweeping delegation of power to regulate speech beyond the specific authority given to FDA.[10]

Section IV analyzes which statements on the nature and properties of biosimilars are likely to be considered misleading within the meaning of the Federal Trade Commission Act of 1914 (FTC Act). Out of the four examples Pfizer brought forward, FTC would likely examine three and consider them advertisements subject to FTC control. At least one advertisement arguably omits material disclaimers, making it misleading. Lastly, Section IV analyzes FTC's apparent chief assertion: stating that a biosimilar is not interchangeable may mislead most reasonable consumers because they "might interpret that to mean that an approved biosimilar could not be prescribed in lieu of the reference product."[11] FTC's argument would likely not hold up in court. With appropriate disclaimers, biologics manufacturers have a reasonable basis to support truthful claims that 1) a biosimilar is not identical to a biologic; 2) until July of 2021, no biosimilar had demonstrated that there would not be a difference in clinical effect if multiple switches occurred;[12] and 3) that patients with more delicate treatment balance are encouraged to speak with their treating physicians before switching to a biosimilar.

Finally, Section V presents a broad conclusion about the limitations FDA and FTC face and what the two agencies can accomplish.

II. LEGAL ISSUES AND BACKGROUND

In February of 2020, FDA released a draft guidance entitled "Promotional Labeling and Advertising Considerations for Prescription Biological Reference and Biosimilar

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[9] 21 U.S.C. § 331(b).

[10] Ultimately, FDA found a different and more appropriate avenue to encourage the prescription and adoption of biosimilars. In 2021, Congress provided authority for FDA to create and disseminate educational content pertaining to biologics and biosimilars. *See* Advancing Education on Biosimilars Act of 2021, Pub. L. No. 117-8, 135 Stat. 254; *see* discussion *infra* Section V.

[11] FTC has publicly defended the theory, but not tried yet, that a message stating that a biosimilar is not interchangeable may mislead most reasonable consumers because consumers "might interpret that to mean that an approved biosimilar could not be prescribed in lieu of the reference product." Richard Cleland, Assistant Dir. for Advertising Practices, Fed. Trade Comm'n at FDA/FTC Workshop on a Competitive Marketplace for Biosimilars at 91 (Mar. 9, 2020), https://www.fda.gov/media/136791/download [https://perma.cc/MA3Z-NLUE].

[12] In July of 2021, FDA approved the first interchangeable biosimilar, no longer making this claim truthful. *See* Press Release, U.S. Food & Drug Admin., FDA Approves First Interchangeable Biosimilar Insulin Product for Treatment of Diabetes (July 28, 2021), https://www.fda.gov/news-events/press-announcements/fda-approves-first-interchangeable-biosimilar-insulin-product-treatment-diabetes [https://perma.cc/NTW2-YNJY].

Products Questions and Answers Guidance for Industry" to provide manufacturers[13] of biological medical products with the agency's understanding of what messages and claims (i.e., speech) related to biosimilars would likely be considered false or misleading.[14] Concomitantly, FDA and FTC released a joint press release informing that both agencies had created a joint task force to support biosimilars and to address potential "anti-competitive practices, such as making false or misleading statements comparing biological reference products and biosimilars."[15]

In March of 2020, both agencies conducted a workshop to discuss the state of the market and unfair trade concerns.[16] FDA adopted a relatively non-contentious tone, reinforcing the need for clarity in the biosimilars' marketplace.[17] FDA Commissioner Stephen Hahn highlighted in his opening remarks that FDA has "seen the publication of materials that seem designed to create uncertainty about biosimilars and discourage patients and healthcare providers from using them."[18] The Commissioner highlighted that, to counter that concern, FDA has created an education campaign on biosimilars and issued the draft guidance document referenced above.[19] However, FTC was more emphatic, indicating an intent to investigate such practices as unfair competition. Ms. Tara Koslov, FTC's Chief of Staff, stated that "competition only works when consumers have reliable and truthful information" and that "in some instances statements from reference-biologic manufacturers . . . may mislead patients and physicians into believing the biosimilar is not as safe or as effective as the reference biologic. Such deception might violate both consumer protection laws and antitrust laws."[20] As to consumer protection laws, Ms. Koslov stated that "advertising that creates an impression of clinically meaningful differences between a reference biologic and its biosimilar is likely false or misleading, and therefore would constitute an unfair or deceptive practice."[21] As to antitrust laws, Ms. Koslov stated that "maintaining or growing share by deceiving patients and physicians about competitors' offerings is not competition on the merits. It also erects artificial barriers to entry and creates costs for biosimilar manufacturers who have to counter the deception. Such deception, therefore, likely would constitute an unfair method of competition."[22]

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[13] *See* 21 C.F.R. § 600.3(t) (defining manufacturer as "legal person or entity engaged in the manufacture of a product subject to license under the [Federal Food, Drug, and Cosmetic] act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards").

[14] FDA, GUIDANCE ON PROMOTIONAL LABELING AND ADVERTISING, *supra* note 6.

[15] Press Release, U.S. Food & Drug Admin., FDA and FTC Announce New Efforts to Further Deter Anti-Competitive Business Practices, Support Competitive Market for Biological Products to Help Americans (Feb. 3, 2020), https://www.fda.gov/news-events/press-announcements/fda-and-ftc-announce-new-efforts-further-deter-anti-competitive-business-practices-support [https://perma.cc/B4EN-NY6T].

[16] FDA/FTC WORKSHOP ON A COMPETITIVE MARKETPLACE FOR BIOSIMILARS, FED. TRADE COMM'N, https://www.ftc.gov/system/files/documents/public_events/1568297/fda-ftc_biosimilars_workshop_transcript_3-9-20.pdf [https://perma.cc/5XFW-U7Q6].

[17] *Id.* at 14.

[18] *Id.* at 20.

[19] *Id.* at 21.

[20] *Id.* at 29.

[21] *Id.*

[22] *Id.* at 29–30.

FDA and FTC have made several moves to further a favorable marketplace for biosimilars, consistent with the strategy laid out in the Biosimilars Action Plan of 2018.[23] However, FDA's draft guidance document on false and misleading communication around biosimilars, the creation of the joint task force, and FTC's strong comments have a particular trigger: a Citizen Petition that Pfizer, Inc., a biosimilar license holder,[24] submitted to FDA and that put the agency in motion in 2018.[25]

A. Pfizer's Citizen Petition to FDA and the Resulting Outcomes

On August 22, 2018, Pfizer submitted a Citizen Petition to FDA requesting the agency "issue guidance to ensure truthful and non-misleading communications by sponsors concerning the safety and effectiveness of biosimilars, including interchangeable biologics, relative to reference product."[26]

In its petition, Pfizer grounds its request primarily on the basis that "just as there is a need for policies that support innovation, there is also a need for policies that ensure that patients and physicians have truthful and non-misleading information that encourages appropriate uptake of biosimilars so that biosimilars can reach their full potential for patients."[27] The company highlights FDA's efforts to "improve understanding of biosimilars among patients, clinicians, and payors," but that existing "communications by [biologics manufacturers] concerning the safety and effectiveness of biosimilars, including interchangeable biologics, relative to reference products undermine efforts to enhance stakeholder confidence in biosimilars by creating doubt and confusion about the safety and effectiveness of these products."[28] Accordingly, Pfizer argues that such situation should serve "as an impetus for the expeditious issuance of guidance . . . on communications concerning the safety and effectiveness of biosimilar . . . products."[29]

Pfizer also points out that biologics meet the definition of drug under the FDCA, and as such are subject to the "misbranding prohibition" and that "certain communications may misbrand biologic products if they are false or misleading"[30]:

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[23] U.S. FOOD & DRUG ADMIN., BIOSIMILARS ACTION PLAN: BALANCING INNOVATION AND COMPETITION (identifying FDA's commitments and tactics to encourage "innovation and competition among biologics and [biosimilars]"), https://www.fda.gov/media/114574/download [https://perma.cc/Y77Z-URAW].

[24] Pfizer, Inc. holds licenses of biologics and biosimilars approved in the United States, including filgrastim-aafi and epoetin alfa-epbx.

[25] Pfizer, Inc., Citizen Petition, *supra* note 4.

[26] *Id.* at 1.

[27] *Id.* Pfizer further describes the policies that have fostered the development and adoption of biosimilars, including the abbreviated pathway for the licensure of biosimilars, the numerous FDA guidance documents providing regulatory clarity for development of biosimilars, and the dissemination of FDA-issued educational material. The petition also makes a parallel with the biosimilars experience in Europe. Pfizer also highlights past comments from former FDA Commissioner Scott Gottlieb that the branded drug industry seemed to be "replaying many of the same tactics" now with the introduction of biosimilars as was the case in the early introduction of generics. *Id.* at 4.

[28] *Id.* at 4–5.

[29] *Id.* at 5.

[30] *Id.* at 6.

> [A] drug shall be misbranded if its "labeling is false or misleading in any particular"; therefore, communications by [biologics manufacturers] that represent or suggest that biosimilars, including interchangeable biologics, are or may not be safe or effective misbrand the reference product under the [FDCA]. Additionally, a promotional communication that makes an unsubstantiated comparison representing or suggesting that a drug is safer or more effective than another drug is considered false or misleading. Thus, communications by a reference product sponsor that imply that its reference product is more effective or safer than the biosimilar are false and misleading . . . . Any such false and misleading statements would misbrand the reference product and cause its distribution to be prohibited under the [FDCA] (internal citations omitted).[31]

The request details four examples of competitors' messages and proposes how FDA should treat them. Tables 1 and 2 below summarize those examples.

[31] *Id.* at 6–7.

Table 1 summarizes three messages that do not appear to reference a specific biologic or biosimilar product. That is, the messages appear only to convey scientific and regulatory concepts pertaining to biosimilarity:

Table 1: General messaging available on websites or social media, providing explanations and opinions on biosimilarity, naming-conventions, and interchangeability. No product mentioned.

	MESSAGE EXCERPTS AT ISSUE:	PFIZER'S PROPOSITION:
(1)	Biosimilar is highly similar + but not identical[32]	Cure omission: prominently disclose "that there are no clinically meaningful differences between the biosimilar and the reference product"[33]
(2)	Biosimilar is highly similar + there's still a chance that patients may react differently[34]	Deem misleading: suggests products cannot be safely switched[35]
(3)	Switch can carry risks "given that no two biologic medicines are identical, and thus can behave differently in the body"[36] + "is not a good idea to switch if your medicine is working for you"[37]	Deem false or misleading: suggests biosimilar cannot be prescribed to treatment-naïve and treatment-experienced patients[38]

[32] *Id.* at 7.

[33] *Id.* at 10.

[34] *Id.* at 7.

[35] *Id.* at 8–9.

[36] *Id.* at 8.

[37] *Id.* at 8.

[38] *Id.* at 11.

Table 2 summarizes the last example, a message contained in a patient brochure that also presents product-specific information. Separating messages connected or not with product-specific references will be helpful to determine whether potentially false or misleading communication can amount to a violation of the FDCA provisions. The specific allegations and proposals are also described in more detail afterward.

Table 2: Product-specific, directed to patient messaging

	MESSAGE EXCERPTS AT ISSUE:	PFIZER'S PROPOSITION:
(4)	"You may be asked to switch to a biosimilar that works in a similar way to REMICADE"[39] + not approved as interchangeable + "switching or alternating back and forth between the interchangeable biologic and REMICADE® would not cause any changes in safety or how well the treatment works – no infliximab biosimilar has yet proven this"[40]	Deem misleading, as to suggest products cannot be safely switched[41]

In more detail, messages that Pfizer alleged violate the FDCA are:

(1) Genentech's Internet page: "Examine Biosimilars" - "FDA requires a biosimilar to be highly similar, but not identical to the [reference product]"[42]

- Alleged violation: Omits that an approved biosimilar must have no clinically meaningful differences from the reference product

(2) Tweet from Amgen Biosimilars[43]: "Biologics or biosimilars? It's not just apples to apples. While #biosimilars may be highly similar to their #biologic reference

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[39] *Id.* at 8.

[40] *Id.* at 8.

[41] *Id.* at 8–9.

[42] *Id.* at 7 (citing source "Genentech, Examine Biosimilars - Biosimilars vs. Generics, available at https://www.examinebiosimilars.com/biosimilars-vs-generics.html, accessed June 12, 2018," and stating "The video posted on the website eventually explains at 1:04 that a biosimilar is '[a] biological product that is highly similar to its reference product—notwithstanding minor differences in clinically inactive components' and 'biosimilars cannot have any clinically meaningful differences in: safety, purity, and potency.' Conveying this information one-third of the way through the video, but not in the lead or takeaways paragraphs on the website is arguably misleading.").

[43] Amgen commercializes biologics and biosimilar products and apparently would be disparaging products it commercializes as well.

products, there's still a chance that patients may react differently. See what you're missing without the suffix: http://bit.ly/2G2zGTa."[44]

- Alleged violation: Contravenes statutory standard of biosimilarity

(3) Amgen's YouTube video: "Intended to explain the importance of naming conventions and identifiers for biosimilars, stating, ' . . . a switch. This carries risks, given that no two biologic medicines are identical, and thus can behave differently in the body. Switching drugs is not a good idea if your medicine is working for you'"[45]

- Alleged violation: Even though "the statement was made in the broader context of avoiding an inadvertent switch at the pharmacy-level," the implication is that switching is risky[46]

(4) Janssen Biotech, Inc.—printed patient brochure:

(a) "Finely Tuned – Your Treatment, Your Choice" - "you may be asked to switch to a biosimilar that works *in a similar way* to REMICADE"[47]

- Alleged violations: Confuses the distinction between reference product and biosimilar, as both are highly similar and use the same mechanism of action, and omits that an approved biosimilar must have no clinically meaningful differences from the reference product[48]

(b) "[t]he infliximab biosimilar is not approved as interchangeable with REMICADE" and "switching or alternating back and forth between the interchangeable biologic and REMICADE® would not cause any changes in safety or how well the treatment works – no infliximab biosimilar has yet proven this"[49]

- Alleged violation: Attempts to mislead patients "into believing that they cannot safely be switched from REMICADE to INFLECTRA by their physician" and "that a non-interchangeable product will not have the same results"[50]

In its petition, Pfizer also provided hypothetical examples of communication, proposed whether they should be deemed truthful and not misleading, and requested FDA to issue guidance covering those aspects.[51] Hypotheticals were of two types: 1)

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[44] Pfizer, Inc., Citizen Petition, *supra* note 4 (citing "Amgen Biosimilars, Apr. 13, 2018 at 5:03 PM, available at https://twitter.com/AmgenBiosim/status/984884845686992896, accessed June 12, 2018.," which is no longer available).

[45] *Id.* at 8 (citing "Amgen, The Arrival of Biosimilars – What's in a name, 2:30–3:08, available at https://www.youtube.com/watch?v=EHDG2NT3KGg&feature=youtu.be, accessed June 12, 2018," which is no longer available).

[46] *Id.* at 8.

[47] *Id.* at 8 (citing source "Janssen Biotech, Inc., Finely Tuned Patient Brochure, Dec. 2017, available at http://images.inform.janssen.com/Web/JanssenNAProd/%7B373a365e-a6e8-4d85-91c1- 4968bc1f1f63%7D_064590-161214_772213_BIO_FinelyTuned_v2_interactive.pdf," which is no longer available).

[48] *Id.* at 8.

[49] *Id.*

[50] *Id.* at 8.

[51] *Id.*

biosimilars' manufacturers ability to use biosimilarity data not on the label; and 2) what biologics' manufacturers would have to disclose when describing aspects of biosimilarity or interchangeability.[52] As to the second type, Pfizer proposed:

- If a reference product sponsor elects to make representations that a biosimilar is "highly similar" to but not "identical" to its reference product, then to avoid giving the false impression that the biosimilar is therefore not as safe or effective as the reference product, the reference product sponsor should also prominently disclose in the same communication that there are no clinically meaningful differences between the biosimilar and the reference product.[53]
- That reference product sponsor representations or suggestions that biosimilar products are inferior to interchangeable biologics in terms of quality or similarity to the reference product would be misleading and therefore in violation of the FDCA.[54]
- To make clear that any communication by a reference product sponsor that suggests that biosimilar products cannot be prescribed to both treatment-naïve and treatment-experienced patients is misleading and therefore inappropriate.[55]
- Janssen Biotech, a biologics' manufacturer, counterargued,[56] claiming, among other things, that Pfizer mixes up the concepts of biologics and interchangeables in its favor and that, rather than issuing new guidance, FDA should enforce the biosimilarity framework described in the statute that regulates it.[57] Janssen also responded with examples, which are summarized below.

Summary of messages that Janssen alleged violate the FDCA:

Pfizer – INFLECTRA® website:

"'Basics of Biologics and Biosimilars', highlights how INFLECTRA has met the biosimilarity standard and presents data on structural and functional similarities with REMICADE® in great detail"

- Alleged violations: Blurs the line between biosimilarity and interchangeability because it omits the interchangeability standard and that INFLECTRA® is not interchangeable and is not expected to have the same clinical result in any given patient. "Net impression of this

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[52] *Id.* at 10–11.

[53] *Id.*

[54] *Id.*

[55] *Id.* at 11.

[56] Janssen Pharmaceutical Companies of Johnson & Johnson, Comment Letter on Citizen Petition by Pfizer, Inc. (Feb. 1, 2019), https://www.regulations.gov/comment/FDA-2018-P-3281-0009 [https://perma.cc/RR3Z-9DV2].

[57] *See* Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, § 7001, 124 Stat. 804, 686 (2010).

presentation is that the biosimilar and REMICADE can be used interchangeably."[58]

Janssen further argued:

- Testimonies from prescriber groups and patients during the Biosimilar Action Plan Part 15 Hearing that took place earlier in 2018 had highlighted that "maintaining high standards for interchangeability and biosimilarity is key to their confidence in biosimilars."[59]

- "Pfizer minimizes the complexity of biologic treatments and the difficulty and duration of patients' journeys to find a treatment that works for them."[60]

- "When patients are told they must switch to a biosimilar product that has not been determined to be interchangeable with their established treatment, patients and their prescribers may prefer not to switch products due to patients' previous medical history and treatments. . . . patient and prescriber should have a choice of medicines . . . ."[61]

- Prior to Janssen's campaign, a market research study indicated patients disfavored non-medical switching (by a pharmacist) to a biosimilar.[62]

- The uptake of biosimilars in the US has been slower than in the European Union because of the differences in characteristics of healthcare models in European countries compared to the U.S.[63]

- All stakeholders in the healthcare system should engage in education around biosimilars, including Janssen and FDA.[64]

- Other parties submitted comments on Pfizer's petition with various points of view.[65] Novartis, which manufacturers biologics and biosimilars, submitted strongly worded considerations.[66] Novartis believes that "a continued series of campaigns to distort, misinform

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58 Janssen Pharmaceutical Companies of Johnson & Johnson, *supra* note 56.

59 *Id.*

60 *Id.*

61 *Id.*

62 *Id.*

63 *Id.*

64 *Id.*

65 *See* U.S. Food & Drug Admin., Comments to *Request that the FDA Issue Guidance to Ensure Truthful and Non-Misleading Communications by Sponsors Concerning the Safety and Effectiveness of Biosimilars*, REGULATIONS, https://www.regulations.gov/docket/FDA-2018-P-3281/comments [https://perma.cc/8SK4-TAWQ].

66 Novartis Comment Letter, *supra* note 5.

> and thereby disrupt the public" exists, a claim which market research allegedly supports.[67] Novartis argues: "By introducing misinformation about biosimilars into the public domain, these campaigns interfere with the special relationship healthcare providers and patients have where important, potentially life-saving decisions are made. Further, these campaigns question the legal and regulatory framework under which biosimilars are developed and reviewed in the U.S., which directly affects FDA's public health mission."[68]

Novartis also proposes several actions, including that FDA partner with FTC "to identify and address these campaigns; issue correspondence directing these organizations to stop their misinformation . . . " and enhance education "to contest the ongoing misinformation campaigns designed to instill fear . . . ."[69]

In 2019, FDA replied to Pfizer informing that it needed time to consider the complex issues raised.[70] Ultimately, in February of 2020, FDA issued the draft guidance "Promotional Labeling and Advertising Considerations for Prescription Biological Reference and Biosimilar Products Questions and Answers Guidance for Industry."[71]

The draft guidance describes FDA's thinking on promotional materials of biologic and biosimilar products.[72] FDA illustrates how companies should identify their products and "what to consider" when presenting information from licensure studies, comparing products, or making other promotional claims.[73] FDA also reiterates that a biosimilar does not need to be identical to the reference biologic to be licensed.[74] Accordingly, as much as promotional materials should avoid suggesting that a biosimilar is less safe or effective than the reference product, promotional materials should also avoid implying that "a finding of biosimilarity means that FDA determined that the [reference and biosimilar products] are identical to one another."[75] However, the draft guidance does not provide standards for communication discussing the nature and properties of biosimilars without product promotion, as Pfizer apparently had

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[67] *Id.*

[68] *Id.*

[69] *Id.*

[70] U.S. Food & Drug Admin., Letter to Pfizer Essential Health (Feb. 15, 2019), https://www.regulations.gov/docket/FDA-2018-P-3281/document [https://perma.cc/3K8C-3SNF].

[71] FDA, GUIDANCE ON PROMOTIONAL LABELING AND ADVERTISING, *supra* note 6.

[72] *Id.* at 1–2 ("This guidance addresses questions firms may have when developing FDA-regulated promotional labeling and advertisements (promotional materials) for prescription reference products licensed under 351(a) of the [PHSA] (42 U.S.C. 262(a)) and prescription biosimilar products licensed under section 351(k) of the PHS Act (42 U.S.C. 262(k)). The guidance discusses considerations for presenting data and information about reference or biosimilar products in these promotional materials in a truthful and non-misleading way.") (footnotes omitted).

[73] *Id.* at 3–8.

[74] *Id.* at 7.

[75] *Id.* at 8. FDA declined to cover the unique aspects of interchangeability in the draft guidance. *Id.* at 4–5.

hoped.[76] For example, FDA did not lay out necessary disclaimers for materials explaining concepts of biosimilarity and stating that a biosimilar is not identical to the reference product.[77]

Because a considerable gap exists between Pfizer's request and the resulting FDA draft guidance, this Article addresses a first legal issue: **Can FDA set parameters for truthful and not misleading communication on "the nature and properties" of biosimilars, without product reference, to encourage the prescription and use of biosimilars?**

In parallel to the issuance of the new guidance, FDA and FTC announced their collaboration in assessing the concerns raised and conducted the FDA–FTC workshop a month later.[78]

FTC indicated an intent to take enforcement action independent from any FDA response.[79] FTC appears to side with Novartis by suggesting that deceptive practices exist irrespective of an FDCA violation.[80] FTC claimed that its enforcement scope extends to commercial speech where, for example, an economic interest motivates the communication.[81] It would include communication that does not refer to a drug by name but that "contained a message promoting the demand for a product or service" or indirectly disparaged competitors' products.[82] The messages on biosimilarity that innovators typically disseminate allegedly "mislead patient and physicians into believing the biosimilar is not as safe or as effective as the reference biologic[,]" or that "clinically meaningful differences between a reference biologic and its biosimilar" exist, resulting in "artificial barriers to entry" and "costs for biosimilar manufacturers who have to counter the deception."[83] FTC also verbalized that communication stating that a biosimilar is not "interchangeable" may mislead most reasonable consumers because they "might interpret that to mean that an approved biosimilar could not be

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[76] As discussed above, Pfizer had described in its Citizen Petition four pieces of communication that are allegedly misleading. Three appear to convey concepts on biosimilarity without referring to any given product.

[77] Pfizer, Inc., Citizen Petition, *supra* note 4, at 10. Pfizer had requested FDA to issue guidance setting forth the types of communications about reference products and biosimilars that would be false or misleading, including not only product comparisons, but also any suggestions that biosimilars in general are less safe or effective: "FDA should explain that if a reference product sponsor elects to make representations that a biosimilar is 'highly similar' to but not 'identical' to its reference product, then to avoid giving the false impression that the biosimilar is therefore not as safe or effective as the reference product, the reference product sponsor should also prominently disclose in the same communication that there are no clinically meaningful differences between the biosimilar and the reference product." *Id.* at 10.

[78] Food and Drug Administration/Federal Trade Commission Workshop on a Competitive Marketplace for Biosimilars; Public Workshop; Request for Comments, 85 Fed. Reg. 6,203 (Feb. 4, 2020).

[79] Tara Koslov, Chief of Staff, FTC, has argued that statements from reference biologic manufacturers misleading "patients and physicians into believing the biosimilar is not as safe or as effective as the reference biologic" "violate both consumer protection laws and antitrust laws." Opening Remarks at FDA/FTC Workshop on a Competitive Marketplace for Biosimilars at 29–31 (Mar. 9, 2020), https://www.fda.gov/media/136791/download [https://perma.cc/MA3Z-NLUE].

[80] *Compare id.*, *with* Novartis Comment Letter, *supra* note 5, at 3.

[81] Richard Cleland, Assistant Dir. for Advertising Practices, Fed. Trade Comm'n at FDA/FTC Workshop on a Competitive Marketplace for Biosimilars at 91-93 (Mar. 9, 2020), https://www.fda.gov/media/136791/download [https://perma.cc/MA3Z-NLUE].

[82] *Id.* at 93.

[83] Koslov, *supra* note 79, at 29–30.

prescribed in lieu of the reference product."[84] These assertions raise the last question this Article addresses: **What statements on the "nature and properties" of biosimilars are likely to be considered misleading and trigger enforcement action from FTC?**[85]

The contentions described above expose the immense tension among biotech giants in the $200 billion U.S. biologics market[86] and the pressure for the federal government and agencies to intervene, be it for the benefit of patients, the healthcare system, or shareholders' pockets.

B. Biologics, Biosimilars, and Interchangeables

"Biologics" refers to biological products, a class of medical products deriving from living organisms, and its medical application dates back more than a century.[87] Innovation in this space gained substantial traction in the past decades after scientists decoded the human genome and sequenced the human DNA. Scientists at university benches began to discover molecular pathways involved in disease pathogenesis and how biology could potentially intervene in the course of a disease.[88] As "proof of principle" surfaced, financing began to pour in. A new boom in bioengineering development came about, making it possible to harness cellular and biomolecular processes to replicate our own genetic makeup in the form of recombinant DNA proteins, monoclonal antibodies, and vaccines.[89] The result: a still-growing number of therapies to treat—and vaccines to prevent—debilitating and life-threatening immunologic and cellular disorders, such as rheumatoid arthritis and cancer, and virus-contracted diseases such as HIV, shingles, hepatitis, and COVID-19. Molecular biology and biotechnology continue to evolve, moving bench research to clinical trials at a fast pace and are enabled by government incentives for innovation and growing public and private investment in the sector.[90]

The biotechnology revolution has addressed critical unmet medical needs, and the benefits to patients are real. A recent study assessed the contributors to life expectancy changes in the United States and found that pharmaceuticals were the second-leading contributors to improvements in life expectancy from 1990 to 2015.[91] Biologics accounted for the majority of the gain in multiple disease areas, including contributing

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[84] Cleland, *supra* note 81, at 96–97.

[85] This Article focuses on analyzing whether FDA or FTC could render the messages on biosimilarity misleading, as any of the market participants have proposed. FTC appears to also raise antitrust issues that are outside the scope of this Article.

[86] IQVIA INST. FOR HUM. DATA SCI., BIOSIMILARS IN THE UNITED STATES 2020–2024 2 (2020), https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/iqvia-institute-biosimilars-in-the-united-states.pdf [https://perma.cc/7VZA-G29V].

[87] *See Science and the Regulation of Biological Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/about-fda/histories-product-regulation/science-and-regulation-biological-products [https://perma.cc/A5L9-RESX] (last updated Mar. 28, 2018).

[88] Ronald Evens & Kenneth Kaitin, *The Evolution of Biotechnology and Its Impact on Health Care*, 34 HEALTH AFFS. 210, 210–19 (2015).

[89] *Id. See also What is Biotechnology?*, BIOTECHNOLOGY INNOVATION ORG., https://www.bio.org/what-biotechnology [https://perma.cc/XAU9-ZQEN].

[90] *See* Evens & Kaitin, *supra* note 88, at 218.

[91] Jason D. Buxbaum, Michael E. Chernew, A. Mark Fendrick & David M. Cutler, *Contributions of Public Health, Pharmaceuticals, and Other Medical Care to US Life Expectancy Changes, 1990–2015*, 39 HEALTH AFFS. 1546, 1546 (2020).

to a 76% improvement in the mortality rate for patients with HIV due to the introduction of new pharmaceuticals in general.[92]

Compared to synthetic drugs (also known as small molecules), biologics are large and complex molecules with clear contrasts. Small molecules are synthesized from well-defined chemical processes, and their generic versions are identical.[93] On the other hand, biologics derive from cell development using different biomolecular approaches, such as recombinant DNA proteins or mono-clonal antibodies,[94] and present a much heavier molecular weight than synthetic drugs. Table 3 below illustrates the differences between chemical drugs and biologics. For example, while the over-the-counter drug aspirin contains nine carbon atoms, the biological product infliximab contains over 6,000.[95]

Table 3: Molecular Formula Comparative

Drug (nonproprietary name)	**Molecular Formula**
Chemical drugs	
aspirin	$C_9H_8O_4$
Tylenol (acetaminophen)	$C_8H_9NO_2$
Sovaldi (sofosbuvir)	$C_{22}H_{29}FN_3O_9P$
Small biologic drugs	
Lantus (insulin glargine)	$C_{267}H_{404}N_{72}O_{78}S_6$
Epogen (epoetin alfa)	$C_{809}H_{1301}N_{229}O_{240}S_5$
Neupogen, Zarxio (filgrastim)	$C_{845}H_{1339}N_{223}O_{243}S_9$
growth hormone (somatropin)	$C_{990}H_{1528}N_{262}O_{300}S_7$
Large biologic drugs	
Enbrel, Erelzi (etanercept)	$C_{2224}H_{3472}N_{618}O_{701}S_{36}$
Remicade, Inflectra (infliximab)	$C_{6428}H_{9912}N_{1694}O_{1987}S_{46}$

Source: Congressional Research Service[96]

92 *Id.*

93 *What Are Generic Drugs?*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/generic-drugs/what-are-generic-drugs [https://perma.cc/X4YA-2RN4] (last updated Aug. 24, 2017).

94 *Biosimilar and Interchangeable Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products [https://perma.cc/7B88-DY72] (last updated Oct. 23, 2017).

95 AGATA DABROWSKA, CONG. RSCH. SERV., R44620, BIOLOGICS & BIOSIMILARS: BACKGROUND AND KEY ISSUES 1 (2019).

96 *Id.*

Biosimilars are the follow-on products that simulate the reference biologic product but are not the same as the generic version of a synthetic drug.[97] Generics are bioequivalent to their reference drugs.[98] By contrast, biologics have "complex molecular characteristics"[99] that cannot be made identical or fully equivalent, hence the name biosimilars.[100] "Even batches of the same biologic product may be dissimilar,"[101] which is why the manufacturing facility must also meet specific quality standards designed to ensure the product continues to be safe, pure, and potent.[102]

FDA licenses a biosimilar through an abbreviated approval pathway when sufficient analytical, animal, and clinical evidence demonstrates it is highly similar (differently from bioequivalent for generics) to the reference product and that it is safe, pure, and potent in at least one condition for which the reference biologic product is approved.[103] FDA may consider the proposed biosimilar and reference product to be highly similar despite minor differences in clinically inactive components, and other indications may be approved by extrapolation of data from one condition to another when the applicant is able to provide sufficient scientific justification.[104] Such approval involves a showing that "there are no clinically meaningful differences in terms of safety, purity, or potency.[105]

The agency looks at the totality of the data presented and takes a staged approach to determine the need for additional evidence, from analytical studies to preclinical, clinical pharmacologic, and comparative clinical trials.[106] In general, the biosimilar license application relies largely on analytical studies, along with a few clinical studies

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[97] *Biosimilar and Interchangeable Products*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products#biosimilar [https://perma.cc/6CHC-LJB8] (last updated Oct. 23, 2017) ("A manufacturer developing a proposed biosimilar demonstrates that its product is highly similar to the reference product by extensively analyzing (i.e., characterizing) the structure and function of both the reference product and the proposed biosimilar. State-of-the-art technology is used to compare characteristics of the products, such as purity, chemical identity, and bioactivity. The manufacturer uses results from these comparative tests, along with other information, to demonstrate that the biosimilar is highly similar to the reference product. Minor differences between the reference product and the proposed biosimilar product in clinically inactive components are acceptable. . . . But biosimilars are not generics, and there are important differences between biosimilars and generic drugs. For example, the active ingredients of generic drugs are the same as those of brand name drugs.").

[98] *See Therapeutic Equivalence*, *Drugs@FDA Glossary*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=glossary.page [https://perma.cc/4QCG-35VV].

[99] Gary H. Lyman, Edward Balaban, Michael Diaz, Andrea Ferris, Anne Tsao, Emile Voest, Robin Zon, Michael Francisco, Sybil Green, Shimere Sherwood, R. Donald Harvey & Richard L. Schilsky, *American Society of Clinical Oncology Statement: Biosimilars in Oncology*, 36 J. CLINICAL ONCOLOGY 1260, 1260 (2018).

[100] Gary H. Lyman, Robin Zon, R. Donald Harvey & Richard L. Schilsky, *Rationale, Opportunities, and Reality of Biosimilar Medications*, 378 NEW ENG. J. MED. 2038 (2018).

[101] *Id.*

[102] 42 U.S.C. §§ 262(a)(2)(C)(i)(II), 262(k)(2)(A)(i)(V).

[103] 42 U.S.C. § 262(k)(2)(A)(i)(II)(cc).

[104] 42 U.S.C. § 262(K)(2)(A)(i)(I)(cc); U.S. FOOD & DRUG ADMIN., SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT GUIDANCE FOR INDUSTRY 21 (Apr. 2015), https://www.fda.gov/media/82647/download [https://perma.cc/M4SB-8CR7].

[105] 42 U.S.C. § 262(i)(2)(B).

[106] Gary H. Lyman, Robin Zon, R. Donald Harvey & Richard L. Schilsky, *Rationale, Opportunities, and Reality of Biosimilar Medications*, 378 NEW ENG. J. MED. 2036, 2038 (2018).

to assess pharmacokinetics, pharmacodynamics, immunogenicity, safety, and efficacy. Key themes peculiar to the biosimilar approval pathway include extrapolation, three-way bridging (when the comparator biologics are sourced in Europe), and slightly different formulations."[107]

A biosimilar obtains interchangeability status if it meets additional standards of evidence showing: 1) it is "expected to produce the same clinical result as the reference product in any given patient;" and 2) if "administered more than once to an individual, 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."[108]

Demonstrating interchangeability poses a significantly high bar in the United States. To date, only two biosimilars have achieved this status in the United States.[109] FDA considers product-specific complexity and immunogenicity risk in each case to determine the level of evidence to be submitted.[110] Factors that can impact the ability to measure whether the biosimilar produces the same clinical result as the reference product in any given patient include: 1) the complexity of the structure and functionality of the biologic product;[111] 2) biologics acting in multiple cell receptors or have "less-defined biological pathways;"[112] and 3) increased immunogenicity risk.[113] Regulatory barriers are likely to persist in the future. While advances in analytical methodologies might help developers demonstrate interchangeability more

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[107] Anna Hung, Quyen Vu & Lisa Mostovoy, *A Systematic Review of U.S. Biosimilar Approvals: What Evidence Does the FDA Require and How Are Manufacturers Responding?*, 23 J. MANAGED CARE & SPECIALTY PHARMACY, 1234, 1234 (2017).

[108] 42 U.S.C. § 262(k)(4).

[109] In July of 2021, FDA approved the first interchangeable biosimilar. Press Release, U.S. Food & Drug Admin., FDA Approves First Interchangeable Biosimilar Insulin Product for Treatment of Diabetes (July 28, 2021), https://www.fda.gov/news-events/press-announcements/fda-approves-first-interchangeable-biosimilar-insulin-product-treatment-diabetes [https://perma.cc/NTW2-YNJY]. In October of 2021, FDA approved a second interchangeable biosimilar. Press Release, U.S. Food & Drug Admin., FDA Approves Cyltezo, the First Interchangeable Biosimilar to Humira (Oct. 18, 2021), https://www.fda.gov/news-events/press-announcements/fda-approves-cyltezo-first-interchangeable-biosimilar-humira [https://perma.cc/3MFX-7MMN].

[110] U.S. FOOD & DRUG ADMIN., CONSIDERATIONS IN DEMONSTRATING INTERCHANGEABILITY WITH A REFERENCE PRODUCT GUIDANCE FOR INDUSTRY 6–8 (May 2019) [hereinafter INTERCHANGEABILITY GUIDANCE], https://www.fda.gov/media/124907/download [https://perma.cc/AGB3-FMEF].

[111] *Id.* at 6. The heavier and more complex molecules are, the harder they are to analyze. For example, the molecular weight of insulin includes over 200 carbon and 400 hydrogen atoms, whereas the molecular weight of infliximab includes over 6,000 carbon and almost 10,000 hydrogen atoms.

[112] *Id. See generally Biological Pathways Fact Sheet*, NAT'L HUM. GENOME RSCH. INST., https://www.genome.gov/about-genomics/fact-sheets/Biological-Pathways-Fact-Sheet [https://perma.cc/6GR2-584H] (last updated Aug. 15, 2020) ("A biological pathway is a series of actions among molecules in a cell that leads to a certain product or a change in the cell. It can trigger the assembly of new molecules, such as a fat or protein, turn genes on and off, or spur a cell to move.").

[113] INTERCHANGEABILITY GUIDANCE, *supra* note 110, at 7 (explaining that clinical experience with the reference product may document "a history of inducing detrimental immune responses" showing increased immunogenicity). *See also, e.g.*, *Remicade® Prescribing Information*, JANSSEN 8, http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/REMICADE-pi.pdf [https://perma.cc/XSR5-UBDW] (last updated Oct. 2021) (reporting that the presence of antibodies in adult patients studied receiving REMICADE® (Infliximab) varied from 10% to 51% depending on the dose and certain patient characteristics).

efficiently at the bench, expensive and time-consuming studies comparing patients switching between the biologic and the biosimilar may still be required.[114]

C. The Scientific Discussion on Biosimilars

Europe and other countries have been approving and using biosimilars longer than the United States. The international experience has been largely successful both economically and clinically.[115] Most countries in Europe, many in Asia and the Americas, exercise some degree of centralized purchase of medicines, or at least in determining which ones will be reimbursed, making it easier for countries to negotiate competitive prices and push for mandatory adoption of biosimilars. Still, the biosimilars' newness coupled with the impossibility of bioequivalence and lower degree of clinical evidence required for biosimilars' approval has generated great discussion in the scientific community and concerns to many.[116]

In 2007, the 110th U.S. Congress assessed the impact of the proposed biosimilars legislation and determined the level of discretion FDA would have to determine when a clinical trial would be required to demonstrate biosimilarity and interchangeability on a case-by-case basis.[117] Janet Woodcock, MD, FDA Deputy Commissioner, Chief Medical Officer, reinforced the existing clinical concerns:

> [F]rom many [biosimilars], in particular the more complex [ones], there is a significant potential for repeated switches between products to have a negative impact on the safety and/or effectiveness. Therefore, the ability to make determinations of substitutability for [biosimilars] may be limited . . . with [biologics], even one product, an innovator product, will vary slightly from batch to batch because they are very complex. So we don't know if you were taking one and if you were switching to another and you switch back and so forth if this might set up an immune response that wouldn't occur if you had just stayed on the same product all along. And that could be very dangerous in some circumstances.[118]

Jay P Siegel, MD, Group President, Biotechnology, Immunology, and Oncology, Research & Development, Johnson & Johnson explained that variability between a biologic and biosimilar can be very different than batch-to-batch variability for the biologic:

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[114] *See* Tony Hagen, *The Difference Between an Interchangeable Biosimilar and One That Isn't*, CTR. FOR BIOSIMILARS (May 5, 2021), https://www.centerforbiosimilars.com/view/the-difference-between-an-interchangeable-biosimilar-and-one-that-isn-t [https://perma.cc/9NMM-HT39].

[115] Lyman et al., *supra* note 100, at 2041; *see also* Liese Barbier, Hans C. Ebbers, Paul Declerck, Steven Simoens, Arnold G. Vulto & Isabelle Huys, *The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review*, 108 CLINICAL PHARMACOLOGY & THERAPEUTICS 734, 734 (2020).

[116] *See* Liese Barbier, Hans C. Ebbers, Paul Declerck, Steven Simoens, Arnold G. Vulto & Isabelle Huys, *The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review*, 108 CLINICAL PHARMACOLOGY & THERAPEUTICS 734 (2020); *see also Mixed Messages? Complexities of Biosimilar Use in the USA*, 1 LANCET RHEUMATOLOGY e133 (2019).

[117] *Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the Subcomm. on Health of the Comm. on Energy and Commerce*, 110th Cong. (2007).

[118] *Id.*

> [A]ccess to [cell line] information is very important: an innovator changing its own process can "compare not only final product but also various components and intermediates that are produced during various stages of the new and old manufacturing process." This may allow for "detect[ion] [of] the presence of new variants or contaminants that, after purification and/or formulation, may be reduced or masked such that they are still present but undetectable in final product."[119]

Even today, a decade after the passage of biosimilars legislation, the lack of consensus on patient switching persists, even though strong support for biosimilars uptake exists.[120] Some argue that biologics variability from one lot to another is not much different from the variability present in switching between biologics and biosimilars due to the high standard of regulatory review.[121] Others argue that the switching between biologics and biosimilars without medical supervision would introduce "potential health consequences."[122] In general, findings support the conclusion that clinicians in both the United States and Europe "approach biosimilar medicines with caution, citing limited biosimilar knowledge, low prescribing comfort, and safety and efficacy concerns as main deterrents for biosimilar use."[123]

D. The Opportunity with Biosimilars

In 2019, the United States spent $211 billion in biologic medicines alone (invoice-price level), which represented 43% of the total spending in medicines that year and a growth rate of 14.6% (CAGR) over the past five years (more than twice the growth in expenditure with small molecules).[124]

Biosimilars bring great potential to reduce biologics prices by increasing competition, and estimates vary on the amount. Before FDA granted the first biosimilars licenses, $44 billion in savings (U.S.) from 2014 to 2024 seemed reasonable.[125] However, substantial barriers to entry gate biosimilars' full potential for savings. These include the complexity of the U.S. healthcare market, exclusivity rights, patent maneuvers, litigation settlements resulting in so-called "pay-for-delay" agreements, limited ability to source the reference product for biosimilarity studies, testing and regulatory costs, and, of course, healthcare professional and patient resistance to biosimilars because of the lack of clinical evidence deriving from clinical trials and experience. All of that led to a slow uptake in biosimilars use. In addition to

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[119] Krista Hessler Carver, Jeffrey Elikan & Erika Lietzan, *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671, 729 (2010).

[120] *See* Barbier et al., *supra* note 115.

[121] Ammara Mushtaq & Farooq Kazi, *Switching to Biosimilars: Boon or Bust?*, 5 LANCET GASTROENTEROLOGY & HEPATOLOGY 341 (2020).

[122] *Id.*

[123] Emily Leonard, Michael Wascovich, Sonia Oskouei, Paula Gurz & Delesha Carpenter, *Factors Affecting Health Care Provider Knowledge and Acceptance of Biosimilar Medicines: A Systematic Review*, 25 J. MANAGED CARE & SPECIALTY PHARMACY 102 (2019).

[124] IQVIA INST. FOR HUM. DATA SCI., *supra* note 86.

[125] ANDREW W. MULCAHY, ZACHARY PREDMORE & SOEREN MATTKE, THE COST SAVINGS POTENTIAL OF BIOSIMILAR DRUGS IN THE UNITED STATES (2014), https://www.rand.org/pubs/perspectives/PE127.html [https://perma.cc/6FKJ-CSCW].

barriers, development and manufacturing complexities place a premium on biosimilars, which are commercialized at a higher price when compared to generics.[126]

In 2008 and 2009, FTC conducted a public consultation process to assess the biologics markets, barriers to entry, and likely outcomes of competition with biosimilars.[127] An extensive report from June 2009 summarized findings.[128] Though FTC focused on arguing against a twelve-to-fourteen-year exclusivity period, the report brings other insights relevant to the questions we address in this Article. Key highlights are:

- "Current technology does not yet allow for the creation of an exact replica of a pioneer biologic drug product . . . technology is not yet robust enough to determine whether [a biosimilar] is "interchangeable" with the pioneer product such that a patient would be able to switch between the two products without the risk of an adverse effect. In light of these complexities, current legislative proposals permit FDA approval of [a biosimilar] that is sufficiently similar to, but not an exact replica of, the pioneer biologic product."[129]
- Competition between biologics and biosimilars would likely resemble brand-to-brand competition: "Pioneer manufacturers, potential [biosimilars] manufacturers, and payors were virtually unanimous in their predictions that competition from [biosimilars] is likely to resemble brand-to-brand competition, rather than brand-to-generic drug competition."[130]
- "Given these high entry costs, . . . entrants are likely to be large companies with substantial resources, and it is likely that only two to three [biosimilar] entrants will seek approval to compete with a particular pioneer biologic drug."[131]
- Challenges would likely exist in "gaining market share due to concerns about safety and efficacy differences between a pioneer biologic drug and the competing [biosimilar]. Physicians and their patients who have been taking a pioneer biologic drug may be reluctant to switch to [a biosimilar] due to a risk that the patients will react differently."[132]

Albeit an unexciting forecast at that time, new estimates emerged in 2020, predicting a much broader biosimilars uptake and adoption resulting from a pipeline of new follow-on biologics that will likely help transform the market and improve

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[126] Generic drugs are considered bioequivalent to their reference products, are substantially easier to manufacture than biologics, and do not require the level of testing and analysis that biologics do.

[127] FED. TRADE COMM'N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION (2009).

[128] *Id.*

[129] *Id.* at ii.

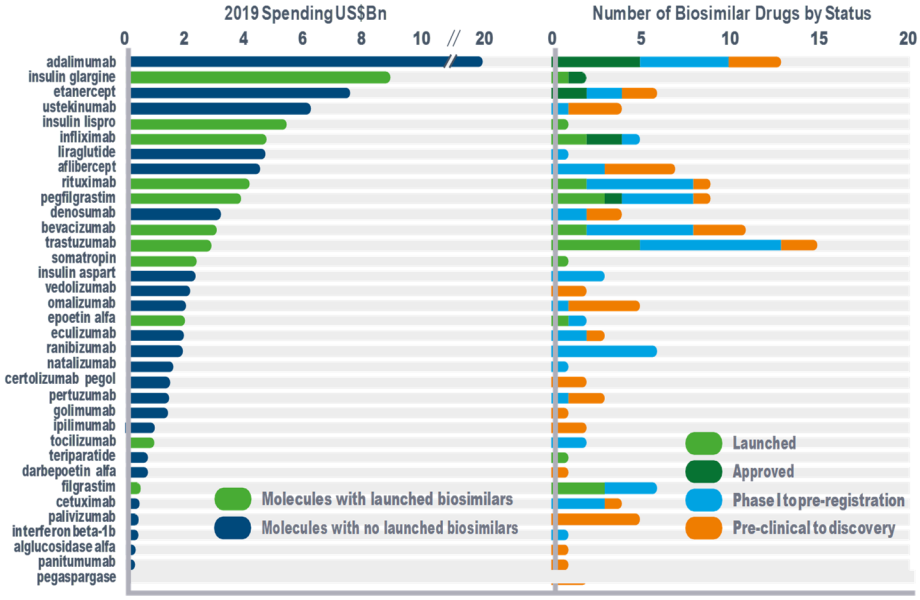
[130] *Id.* at iii.

[131] *Id.* at iii–iv.

[132] *Id.*

savings.[133] Updated estimates indicate potential savings exceeding $100 billion in aggregate over the next five years.[134] Figure 1 below illustrates well how biosimilars have been penetrating the market for molecules with the highest level of spending, which will continue to drive greater savings[135]:

Figure 1: 2019 Total Molecule Spending and Approved, Launched, and Pipeline Biosimilar Products for the Molecule[136]



Biosimilars' discounts range substantially but represent "roughly 30%" in lower price.[137] The market penetration also varies greatly, but recently launched biosimilars have been substantially more successful than previous ones, tracking towards nearly 60% of market share after two years of launch.[138] Market data suggests that the adoption of biosimilars in the United States depends on physician preference and, more importantly, hospital network and pharmacy benefit managers' financial incentives and preferences.[139]

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[133] IQVIA INST. FOR HUM. DATA SCI., *supra* note 86, at 2.

[134] *Id.*

[135] Note that many biosimilars' manufacturers receive FDA approval but are not launched, usually due to patent litigation.

[136] *See* IQVIA INST. FOR HUM. DATA SCI., *supra* note 86, at 5 (illustration reproduced with approval from the source).

[137] *Id.*

[138] *Id.* at 10.

[139] *Id.* at 12 ("Patient access to and uptake of biosimilars may vary based on incentives of various stakeholders. In the case of pharmacy-reimbursed drugs[,] . . . pharmacy benefit managers (PBMs) are the key stakeholder in the negotiation of formularies and/or rebates, and may prefer either biosimilar or

E. Statutory Framework

1. FDA

Although FDA impacts healthcare broadly, it regulates products:[140] food, drug, device, tobacco products, and cosmetics under the FDCA[141] and biological products under the Public Health Service Act (PHSA).[142] The agency regulates over one-third of products commercialized in the United States.[143] FDA belongs within the Public Health Service in the Department of Health and Human Services (HHS).[144] The agency's Commissioner answers to the Secretary of HHS, and both ultimately answer to the President.[145] Congress oversees FDA through the Senate Committee on Health Education, Labor and Pensions[146] and the House Committee on Energy and Commerce.[147] Congress conducts periodic hearings and has amended both the FDCA and PHSA several times.[148] Yet, the FDCA's structure has been maintained since 1938, including through important changes that broadened FDA's regulatory and oversight authorities. The focus on safety has been evident[149] from 1906[150] to date.

originators for financial reasons."). As an example, the uptake of biosimilar "insulin glargine and insulin lispro have differed greatly with the former reaching a 23% share of molecule volume and the latter 10%" among patients with private insurance. *Id.* Conversely, these two biosimilars have achieved a 68% uptake in Managed Medicaid by the end of 2019. *Id.* The biosimilar glargine "launched in December 2016 . . . was not included on the Medicare Part D formularies until January 2018, reflecting the difficulty of penetrating some insurance pay types." *Id.*

140 Scholars consider the Food and Drugs Act of 1906 the "first comprehensive U.S. legislation relating to foods and drugs," designed as an "'enforcement statute.'" A PRACTICAL GUIDE TO FDA'S FOOD AND DRUG LAW AND REGULATION 24 (Kenneth R. Piña & Wayne L. Pines eds., 6th ed. 2017).

141 Federal Food, Drug, and Cosmetic Act, 21 U.S.C.A. §§ 301–399i (Westlaw through Pub. L. No. 117–52). The FDCA provides authority to regulate to the Secretary of Health and Human Services and FDA as its designee.

142 42 U.S.C. § 262.

143 S. REP. NO. 105–43, at 2, 5 (1997).

144 *See HHS Agencies and Offices*, U.S. DEP'T HEALTH & HUM. SERVS., https://www.hhs.gov/about/agencies/hhs-agencies-and-offices/index.html#:~:text=The%20Food%20and%20Drug%20Administration that%20emit%20radiation%20are%20safe [https://perma.cc/P9JT-YMCJ].

145 Biologics and drug regulation date back for over a century. The Biologics Control Act in 1902 came to life in response to the medicinal use of contaminated serum extracted from horse blood that led to the death of children. Regulation then was decentralized and embedded in different sections within the PHSA.

146 *Issues*, U.S. SENATE COMM. ON HEALTH, EDUC., LABOR & PENSIONS, https://www.help.senate.gov/about/issues [https://perma.cc/358X-M5ZC].

147 *Health*, HOUSE COMM. ON ENERGY & COMMERCE, https://energycommerce.house.gov/subcommittees/health-117th-congress [https://perma.cc/88J8-2GLG].

148 *E.g.*, *Examining FDA's Generic Drug and Biosimilar User Fee Programs: Hearing Before the Subcomm. on Health of the H. Comm. on Energy & Commerce*, 115th Cong. (2017), https://energycommerce.house.gov/committee-activity/hearings/hearing-on-examining-fda-s-generic-drug-and-biosimilar-user-fee-programs [https://perma.cc/HTT3-CN34].

149 *See* S. REP. NO. 105–43, at 15–16 ("From the 1906 Food and Drugs Act through the 1990 Safe Medical Devices Act, food and drug law has emphasized that the duty of the FDA is to protect the public against unsafe or ineffective products.").

150 A PRACTICAL GUIDE TO FDA'S FOOD AND DRUG LAW AND REGULATION, *supra* note 139, at 19 ("The [FDA] is the oldest federal regulatory agency, beginning in 1848 as the Agricultural Division of the Patent Office, subsequently becoming part of the U.S. Department of Agriculture; the Federal Security Agency; the Department of Health, Education and Welfare; and now the Department of Health and Human

Congress has provided increased authority to FDA over the years to protect the public from harmful products, while ensuring important new drugs that can improve public health come to the market.[151] Initially, safety was the goal of drug pre-market review, but Congress eventually required FDA to ensure approval of drugs, reviewing them for efficacy as well as aiming at keeping ineffective or useless products off the market.[152] "FDA's role has expanded from one of removing adulterated or misbranded products from the market to one of preapproving the testing and marketing of products."[153] In 1989, the Secretary of HHS had chartered the Advisory Committee tasked with the responsibility of assessing concerns about FDA's ability "to perform its job" and providing recommendations to Congress.[154] One of the Committee's findings underlies FDA's mission statement as enacted: "the agency should be guided by the principle that expeditious approval of useful and safe new products enhances the health of the American people. Approving such products can be as important as preventing the marketing of harmful or ineffective products."[155]

While the intent was clear, only with the promulgation of the Food and Drug Administration Modernization Act of 1997 (FDAMA)[156] did Congress finally set forth a formal mission statement for the agency,[157] which focuses on

> (1) protecting the public health by ensuring that the products it regulates meet the appropriate FDA regulatory standards, (2) promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a manner which does not unduly impede innovation or product availability, and, (3) participating with other countries to reduce regulatory burdens, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements with other countries.[158]

Services."). Also, the Food and Drugs Act of 1906 gave origin to FDA as regulatory consumer protection agency. *See id.* at 24.

151 S. REP. NO. 105–43, at 2 (brief history of the FDCA provided within the Senate Report recommending approval of the Food and Drug Administration Modernization and Accountability Act of 1997—bill S. 830, 105th Congress—to amend the FDCA and the PHSA "to improve the regulation of food, drugs, and biological products").

152 *Id.* at 6.

153 S. REP. NO. 105–43, at 6.

154 *Id.* at 8.

155 *Id.*

156 Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105–115, 111 Stat. 2296 (1997).

157 42 U.S.C. § 393.

158 Food and Drug Administration Modernization Act of 1997, at 2–3. With FDAMA, Congress sought to build upon earlier administrative reforms and findings of the ongoing Advisory Committee to drive more accountability and focus within FDA and reauthorize the agency to charge user fees in exchange for more efficient drug application reviews. "The legislation accomplishes three major objectives: it builds upon recent administrative reforms that both streamline FDA's procedures and strengthen the agency's ability to accomplish its mandate in an era of limited Federal resources; it requires a greater degree of accountability from the agency in how it pursues its mandate; and it provides for the reauthorization of PDUFA." S. REP. NO. 105–43, at 2.

Congress also intended the FDAMA to be a clear direction to FDA to position itself as a collaborative agency that focuses its resources on the pursuit of one single mission, curtailing power-grab temptations that may occur in an agency of FDA's size and relevance: "If we are to confront these challenges and realized the opportunities on today's and tomorrow's horizons, we cannot afford an overly complex, bureaucratic, time-consuming, and expensive regulatory system. **Nor can we afford an adversarial relationship between FDA and the industries it regulates or an agency pursuing so many agendas that it lacks a clear-cut mission and sphere of responsibility**."[159]

Significantly, the FDCA and the PHSA provide no authority for FDA to drive public policies or regulation to reduce drug costs, except in two circumstances: 1) to help create a competitive market through the expeditious and efficient review and approval or licensing of competing new drugs and biologics, generics, and biosimilars, which we discuss further below; and 2) more recently, Congress enacted the Advancing Education on Biosimilars Act of 2021, requiring FDA to advance education and awareness among healthcare professionals regarding biologics and biosimilars.[160]

2. Drugs, Biologics, Generics, and Biosimilars

The FDCA defines "drug" broadly to include virtually any medical article considered a drug in use before the act and any new compounds intended for use in the diagnosis, prevention, cure, or medical treatment of diseases.[161] Thus, biological products are considered drugs and also subject to the FDCA regulatory scheme, except for application of product review pathways (e.g., Biologics License Application for biologics). Congress intended drugs to cover biologics, despite the confusing use of the terminology in the PHSA.[162]

The abbreviated pathway for approval of generics came through the Drug Price Competition and Patent Term Restoration Act of 1984[163] (known as the Hatch-

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[159] S. REP. NO. 105–43, at 10 (emphasis added).

[160] *See* Advancing Education on Biosimilars Act of 2021, Pub. L. No. 117–8, 135 Stat. 254 (2021). Senator Bill Cassidy, M.D. (R-LA), the bill's co-sponsor, stated the bill would "help improve confidence in the safety and effectiveness of these FDA-approved products. Improved confidence in biosimilars could lead to increased use, which in turn could increase health care savings." *Senate Passes Two Pieces of Cassidy Legislation to Lower Prescription Costs*, BILL CASSIDY, M.D. (Mar. 11, 2021), https://www.cassidy.senate.gov/newsroom/press-releases/senate-passes-two-pieces-of-cassidy-legislation-to-lower-prescription-costs [https://perma.cc/9T4V-THH5].

[161] "The term 'drug' means (A) articles recognized in the official United States Pharmacopœia, official Homœopathic Pharmacopœia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)." 21 U.S.C. § 321(g)(1).

[162] "[B]ecause biological products are also drugs, more recent regulatory concepts that were applied to new drugs, (e.g., compliance with drug GMP regulations) were incorporated into the older system for biological products." S. REP. NO. 105–43, at 39. Even though biologics and drugs retain separate statutory sources, Congress has progressively sought to streamline their regulatory frameworks to ensure consistency in regulation of new drugs and biological products. Amendments brought with FDAMA made the Biologic License Application more similar to the New Drug Application. FDAMA requires FDA to continue to minimize the differences in review and approval between them, except for generic products, which count with specific authority for Abbreviated New Drug Applications under FDCA section 505(j).

[163] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98–417, 98 Stat. 1585 (1984).

Waxman Act[164]), which amended the FDCA. The shortened approval process allows the generic copy to obtain market approval by showing bioequivalence to the reference drug, piggybacking on the existing safety and efficacy studies,[165] substantially reducing research costs and time to approval. Congress collaborated with innovator and generic manufacturer groups more actively[166] to pass the Hatch-Waxman Act after failed attempts to simply introduce an abbreviated generics approval pathway alone.[167]

The struggle with competing priorities surfaced again when Congress had to deal with biosimilars. In the turn of the 21st Century, biosimilars started to gain regulatory life internationally, including in Europe (2004). By the end of 2008, the European Medicines Agency had approved three biosimilars.[168] Multiple congressional hearings brought to light the immense challenges wanting resolution. From balancing incentives to innovation with competition to speed with safety, Congress felt the pressure building. Finally, after strong collaboration with FDA, the scientific community, and representatives from both the innovation and generics industries, Congress succeeded in passing the Biologics Price Competition and Innovation Act of 2009 (BPCIA). The new statute amended the PHSA to add an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed biologic.[169]

III. CAN FDA SET PARAMETERS FOR TRUTHFUL AND NOT MISLEADING COMMUNICATION ON "THE NATURE AND PROPERTIES" OF BIOSIMILARS, WITHOUT PRODUCT REFERENCE, TO ENCOURAGE THE PRESCRIPTION AND USE OF BIOSIMILARS?

This Article addresses the question at hand by assessing three legal issues.

First, would a guidance document be the appropriate regulatory instrument to set parameters for truthful and not misleading communication on the nature and properties

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[164] Informally named after its two principal sponsors, Representative Henry Waxman (D-CA) and Senator Orrin Hatch (R-UT).

[165] 21 U.S.C. § 355(j)(2)(A).

[166] "The two parts of the bill were intended to provide a careful balance between promoting competition among pioneers or brand-name and generic drugs, and encouraging research and innovation." Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872 (proposed July 10, 1989) (to be codified at 21 C.F.R. pts. 10, 310, 314 & 320).

[167] The act restored patent time and a period of exclusivity for manufacturers of the branded products, which must invest in expensive research and development and undergo a lengthier approval process, but also provided the new shortened and straightforward pathway for generic approval. The time involved in researching, developing, and approving a new drug under FDA in practice reduces materially the action patent term that can be explored commercially. Restoring some of that term helped compensate for an easier and expedited approval process for generics, which in turn led to substantial cost savings for the healthcare system.

[168] LINDA HORTON, THE EUROPEAN EXPERIENCE WITH FOLLOW-ON BIOLOGICS LEGISLATION AT FTC ROUNDTABLE: EMERGING HEALTHCARE COMPETITION AND CONSUMER ISSUES, at 19 (Nov. 21, 2008).

[169] 42 U.S.C. § 262(k). The Act balances "competing policies of facilitating the introduction of low-cost . . . [biosimilars] . . . in the market and providing incentives for pioneering research and development of new biologics." *Genentech, Inc. v. Immunex Rhode Island Corp.*, 395 F. Supp. 3d 357, 360 (D. Del. 2019).

of biosimilars?[170] If so, would this hypothetical new FDA guidance document, fulfilling Pfizer's request, create legal rights and responsibilities for regulated agents and be reviewable in court?

Secondly, is there any statutory provision authorizing FDA to set parameters for truthful and not misleading communication on the nature and properties of biosimilars?

Lastly, can FDA interpret the FDCA's misbranding provision expansively to apply to manufacturers' communication that does not reference a biologic or biosimilar product? Could FDA make that interpretation to encourage the prescription and use of biosimilars as Pfizer proposes?[171]

A. Applicable Law

1. Enforceability and Judicial Review of FDA Guidance Documents

The FDCA authorizes FDA to promulgate regulation for the "efficient enforcement" of the statute.[172] In turn, provisions in FDA-issued regulation may be equally enforced as laws or intended as guidance to the market on the agency's thinking and interpretation of the law.[173] FDA issues rules, orders, and guidance documents by ultimately publishing them in the Federal Register.[174] FDA guidance documents "do not create or confer any rights for or on any person."[175] The agency has also issued good guidance practices, which adds the disclaimer that guidance documents do not establish legally enforceable responsibilities and do not bind the public.[176] Although guidance documents are not binding on the Secretary of HHS, agency employees "cannot deviate from such guidances without appropriate justification and supervisory concurrence."[177] The agency can issue hundreds of draft guidance documents in a year,[178] including those interpreting the FDCA and FDA rules on misbranding.[179] Referring to a similar course of action involving the Environmental Protection Agency, one court noted:

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[170] Pfizer requested FDA to "issue guidance setting forth the types of sponsor communications about [biologics] and biosimilars . . . that would be inappropriate because they would be false or misleading . . .." Pfizer, Inc., Citizen Petition, *supra* note 4.

[171] To fulfill Pfizer's apparent request. *Id.*

[172] 21 U.S.C. §§ 371(a), (h).

[173] FDA Administrative Practices and Procedures, 21 C.F.R. § 10.90.

[174] *Id.*

[175] 21 U.S.C. § 371(h).

[176] FDA Administrative Practices and Procedures, 21 C.F.R. § 10.115(d).

[177] 21 U.S.C. § 371(h).

[178] U.S. FOOD & DRUG ADMIN., FACT SHEET: FDA GOOD GUIDANCE PRACTICES (Dec. 04, 2017), https://www.fda.gov/about-fda/transparency-initiative/fact-sheet-fda-good-guidance-practices [https://perma.cc/P4UL-K8X5].

[179] *E.g.*, U.S. FOOD & DRUG ADMIN., MEDICAL PRODUCT COMMUNICATIONS THAT ARE CONSISTENT WITH THE FDA-REQUIRED LABELING—QUESTIONS AND ANSWERS, GUIDANCE FOR INDUSTRY 3 (June 2018), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/medical-product-communications-are-consistent-fda-required-labeling-questions-and-answers [https://perma.cc/V5BM-

> The phenomenon we see in this case is familiar. Congress passes a broadly worded statute. The agency follows with regulations containing broad language, open-ended phrases, ambiguous standards and the like. Then as years pass, the agency issues circulars or guidance or memoranda, explaining, interpreting, defining and often expanding the commands in the regulations. One guidance document may yield another and then another and so on. Several words in a regulation may spawn hundreds of pages of text as the agency offers more and more detail regarding what its regulations demand of regulated entities.[180]

The Administrative Procedure Act of 1946 (APA) establishes procedures by which federal agencies propose and issue regulation[181] and the standards by which courts may review agency action.[182] Affected parties may demand judicial review of an "[a]gency action made reviewable by statute and final agency action for which there is no other adequate remedy in a court."[183] Agency action includes "rule, order, license, sanction, relief, or the equivalent or denial thereof, or failure to act."[184] "Rule" takes a broad definition and includes an agency's "***statement of general*** or ***particular applicability and future effect designed*** to implement, ***interpret***, or prescribe law or policy . . . " (emphasis added).[185]

As held in *Bennett*,[186] an agency action is final when two conditions are satisfied: 1) "the action must mark the consummation of the agency's decisionmaking process" as opposed to "a merely tentative or interlocutory" determination; and 2) "the action must be one by which rights or obligations have been determined, or from which legal consequences will flow."[187] Courts assess the action's "finality" in a "pragmatic" and flexible way.[188]

Bennett's first prong is met when the challenged action represents a final decision that has been submitted to the necessary approvals, marking "the consummation of the agency's decision making process."[189] An order from a board pending approval of the board president is not final because the president had the power to disapprove the

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UQW2]. The guidance document "provides general (but not comprehensive) recommendations intended to aid firms in complying with requirements in the FD&C Act and FDA's implementing regulations . . .." *Id.*

[180] Appalachian Power Co. v. EPA, 208 F.3d 1015, 1020 (D.C. Cir. 2000).

[181] 5 U.S.C.A. §§ 551–552 This does not apply to military or foreign affairs functions and matters relating to agency management or personnel, public property, loans, grants, benefits, or contracts. 5 U.S.C. § 553.

[182] 5 U.S.C.A. § 706. *See also* 5 U.S.C. § 551 ("'[A]gency action' includes the whole or a part of an agency rule, order, license, sanction, relief, or the equivalent or denial thereof, or failure to act.").

[183] 5 U.S.C.A. § 704.

[184] 5 U.S.C.A. § 551(13).

[185] 5 U.S.C.A. § 551(4).

[186] Bennett v. Spear, 520 U.S. 154 (1997).

[187] *Id.* at 177–78 (where the Court rejected the government's contention that EPA's biological opinion was not final action because it did not conclusively determine the action the agency would take in the future).

[188] Abbott Labs. v. Gardner, 387 U.S. 136, 149 (1967).

[189] *Bennett*, 520 U.S. at 178 (citing Chi. & S. Air Lines, Inc. v. Waterman S.S. Corp., 333 U.S. 103, 113 (1948), where demand for judicial review made against certain orders of the Civil Aeronautics Board was not viable because the order was merely a recommendation to the Board President, who concededly had the ultimate control in deciding the matter).

order.[190] Regulation FDA promulgated following the creation steps, formally and definitively, meets the first prong.[191] That FDA has never enforced the regulation is irrelevant.[192] The Court, in dicta, has explained that the first prong is equally met when the challenged action refers to agency opinion that could still be revised within five years upon new information.[193]

An agency action meets the second prong in *Bennett* when the action creates legal consequences, even when encapsulated in agency recommendations.[194] In *Bennett*, the plaintiff-petitioners sought to challenge a Fish and Wildlife Service's Biological Opinion, which concluded that a land reclamation program would threaten two endangered species but recommended feasible options allowing some harm to be caused to the endangered species.[195] The agency had argued that Biological Opinions "theoretically" are advisory and not compulsory.[196] However, the Court reasoned that if the third party managing the land reclamation program were to accept the recommendations, and they are regularly accepted,[197] the protected species could suffer harm.[198] As such, the Court found that the Biological Opinion met the second prong because it had significant and direct legal consequences.[199]

In *U.S. Army Corps of Engineers*, the court found that a final jurisdictional determination (JD) had legal consequences because it warned plaintiff-respondents that they would risk significant criminal and civil penalties if they proceeded with an intended activity, even though the JD itself could not be the basis for an administrative or criminal proceeding.[200] The plaintiff-respondents had sought to challenge a final jurisdictional determination (JD) from the U.S. Army Corps of Engineers regarding the presence of "waters of the United States" on their parcel.[201] The JD was

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[190] *Chi. & S. Air Lines, Inc.*, 333 U.S. at 113.

[191] *Abbott Labs.*, 387 U.S. at 151. The challenged rule at the time was ultimately superseded by the Clean Air Amendments of 1970, Pub.L. No. 91–604, 84 Stat. 1676 (codified as amended at 42 U.S.C.A. § 7607 (1997 & 2010 Supp.)), as recognized in Califano v. Sanders, 430 U.S. 99, 105 (1977) and Lubrizol Corp. v. Train, 547 F.2d 310 (6th Cir. 1976).

[192] *Id.*

[193] U.S. Army Corps of Eng'rs v. Hawkes Co., 578 U.S. 590, 598 (2016) (where an approved jurisdictional determination (JD) the U.S. Army Corps of Engineers issued was judicially reviewable under the APA because the JD was a final agency action, even though the U.S. Corps of Engineers could revise the JD within five years based on new information).

[194] *Bennett*, 520 U.S. at 178.

[195] *Id.* at 157–60.

[196] *Id.* at 169, 177.

[197] *Id.* at 169 ("What this concession omits to say, moreover, is that the action agency must not only articulate its reasons for disagreement (which ordinarily requires species and habitat investigations that are not within the action agency's expertise), but that it runs a substantial risk if its (inexpert) reasons turn out to be wrong.").

[198] *Id.*

[199] *Id.* ("A Biological Opinion of the sort rendered here alters the legal regime to which the action agency is subject.").

[200] U.S. Army Corps of Eng'rs v. Hawkes Co., 578 U.S. 590, 600 (2016) ("[W]hile no administrative or criminal proceeding can be brought for failure to conform to the approved JD itself, that final agency determination not only deprives respondents of a five-year safe harbor from liability under the Act, but warns that if they discharge pollutants onto their property without obtaining a permit from the Corps, they do so at the risk of significant criminal and civil penalties.").

[201] *Id.* at 590.

unfavorable to the plaintiff and binding on the Environmental Protection Agency (EPA) for five years.[202] The government had argued the JD was not final action because the plaintiffs had alternative remedies that precluded judicial review: they could still seek an EPA permit and challenge that determination or discharge in the waters and wait to challenge any enforcement action.[203] The Court disagreed, reasoning that affected parties did not have to go through an "arduous, expensive, and long" process or take the risk of enforcement action.[204]

In *Frozen Food Express*, the Court found that an agency's order interpreting a statute to exempt certain carriers from supervision, but not others, was immediately reviewable, even though the order had no authority except to give notice of how the agency interpreted the relevant statute, and would have effect only if and when a particular action was brought against a particular carrier.[205] There, the Court explained that the order "warns every carrier, who does not have authority from the Commission to transport those commodities, that it does so at the risk of incurring criminal penalties."[206]

In *Appalachian Power Company*, the Court of Appeals for the District of Columbia held that a guidance document was final action because it reflected "a settled agency position which has legal consequences" for regulated actors, despite the lack of formal rulemaking and boilerplate language in the document indicating otherwise.[207] Petitioners challenged parts of an EPA guidance document that sought to clarify EPA rules and statutory requirements.[208] Federal pollution emission standards demand compliance with complex testing requirements not sufficiently explained in EPA rules.[209] The challenged guidance document contained additional explanations that were understood to expand beyond the existing rules,[210] and had not been a "product of notice and comment rulemaking," in accordance with the Clean Air Act, and publication in the Federal Register.[211] First, the EPA argued the document was not binding because it had not been formalized as rule and represented a "policy statement, rather than an interpretative rule . . . ."[212] The court disagreed, reasoning that: 1) agency pronouncements not formalized as rules can be binding if the agency acts as if the document is controlling;[213] and 2) the EPA had agreed with petitioners that such

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[202] *Id.* at 600.

[203] *Id.* at 600.

[204] *Id.*

[205] Frozen Food Express v. United States, 351 U.S. 40, 46 (1956).

[206] *Id.* at 44.

[207] Appalachian Power Co. v. EPA, 208 F.3d 1015, 1023 (D.C. Cir. 2000).

[208] *Id.* at 1021.

[209] *Id.* at 1020.

[210] *Id.*

[211] *Id.* at 1021.

[212] *Id.* at 1021–23.

[213] *Id.* at 1021 ("If an agency acts as if a document issued at headquarters is controlling in the field, if it treats the document in the same manner as it treats a legislative rule, if it bases enforcement actions on the policies or interpretations formulated in the document, if it leads private parties or State permitting authorities to believe that it will declare permits invalid unless they comply with the terms of the document, then the agency's document is for all practical purposes 'binding.' *See* Robert A. Anthony, *Interpretative*

agency's position was centered on the legal issue in dispute, "a position it plan[ed] to follow" and EPA agents "bound to apply."[214] Secondly, the EPA argued the guidance had no legal consequences, pointing to a disclaimer in the document reading: "The policies set forth in this paper are intended solely as guidance, do not represent final Agency action, and cannot be relied upon to create any rights enforceable by any party."[215] The court also disagreed, pointing out in an arguably caustic tone that while the guidance may not have created rights, it certainly created obligations: "since 1991 EPA has been placing it at the end of all its guidance documents" and the "policies" consisted of "obligations on the part of the State regulators and those they regulate."[216]

The district courts in D.C. have considered FDA guidance and Secretary of HHS's interpretative rules final and subject to judicial scrutiny.[217] In *Philip Morris*, the court assessed that various factors can determine whether a guidance document is "sufficiently final to warrant pre-enforcement review," and concluded that "an agency's interpretation of its governing statute, with the expectation that regulated parties will conform to and rely on this interpretation, is final agency action fit for judicial review."[218] In *Pharmaceutical Research*, the court found that an HHS's Interpretative Rule constituted final agency action subject to judicial review, reasoning that guidance documents can have practical binding effect.[219] In another case, a D.C. district court has rendered the 1997 Final Guidance on Industry-Supported Scientific and Educational Activities,[220] along with specific FDAMA provisions, unconstitutional.[221] Plaintiff had sought an order enjoining FDA from "enforcing policies restricting certain forms of manufacturer promotion of off-label uses for FDA-approved drugs and devices . . . expressed through Guidance Documents . . . ."[222] The court rejected FDA's stance that "guidance documents are merely an outcome of the overall statutory scheme," thus not violative of First Amendment rights, and found

Rules, Policy Statements, Guidances, Manuals, and the Like—Should Federal Agencies Use Them to Bind the Public?, 41 DUKE L.J. 1311, 1328–29 (1992), and cases there cited.").

[214] *Id.*

[215] *Id.* at 1023.

[216] *Id.*

[217] The HHS Interpretative Rule challenged in *Abbott* was ultimately superseded by statute (as stated in Califano v. Sanders, 430 U.S. 99, 105 (1977) and Lubrizol Corp. v. Train, 547 F.2d 310, 315 (6th Cir. 1976)), but the prescribed rule is still in force.

[218] Philip Morris USA, Inc. v. FDA, 202 F. Supp. 3d 31, 46–47 (D.D.C. 2016) (reasoning that "boilerplate language" FDA adopts to disclaim in guidance that such document "does not establish legally enforceable responsibilities . . . cannot dictate whether the [Guidance] is a final agency action fit for review") (referencing Appalachian Power Co. v. EPA, 208 F.3d 1015, 1021 (2000) ("'Interpretative rules' and 'policy statements' may be rules within the meaning of the APA and the Clean Air Act, although neither type of 'rule' has to be promulgated through notice and comment rulemaking.")).

[219] Pharm. Research & Mfrs. of Am. v. Dep't Health & Hum. Servs., 138 F. Supp. 3d 31, 44 (D.D.C. 2015) (concluding that "the Interpretive Rule very clearly requires pharmaceutical manufacturers and covered entities alike to change their behavior in a not insignificant way").

[220] *See* Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074 (1997); *See also* Wash. Legal Found. v. Friedman, 36 F. Supp. 2d 16, 18 (D.D.C. 1999).

[221] Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000).

[222] *Friedman*, 13 F. Supp. at 54.

that guidance documents are subject to First Amendment scrutiny."[223] At appeal,[224] the case was ultimately dismissed, as the key constitutional issue was no longer in controversy, seemingly due to plaintiff counsel's fatal miscalculation during the hearing.[225] FDA sustained that guidance documents merely described safe harbors and that manufacturers were free to go against them.[226] Plaintiff's counsel was hard-pressed on FDA's new "safe harbor" argument and agreed "it no longer [had] a constitutional objection," but insisted the court should decide and affirm the district court decision because the plaintiff still feared FDA could decide to prosecute drug manufacturers in the future based on the agency's guidance document.[227] The court declined to provide judgment on the merit, dismissing the appeal and vacating the district court's order.[228]

2. Statutory Language Authorizing FDA to Enforce the "Truthful and Not Misleading" Standard

FDA holds police power in enforcing the FDCA and PHSA. The former prohibits "[t]he adulteration or misbranding of any food, drug, device, tobacco product, or cosmetic in interstate commerce."[229] The misbranding provision serves as the essential enforcement tool that authorizes FDA to limit speech (product labeling and advertising).[230]

A drug is misbranded if its labeling "is false or misleading in any particular" or if its label or labeling fails to meet the various requirements set forth in the statute.[231] This includes failure to provide adequate directions of use and warnings and disclose certain statements of fact in its label, labeling, and "advertisements" and "other descriptive printed matter" . . . "with respect to that drug."[232] A drug can be misbranded also if its labeling or advertising fails to reveal material facts in the light of the representations being made and the consequences which may result from the use of the drug.[233] FDA has implemented the misbranding provision by further detailing drug

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[223] *Id.* at 62.

[224] *Henney*, 202 F.3d at 335.

[225] *Id.* at 335 ("The stage therefore appeared set for us to consider a difficult constitutional question of considerable practical importance. However, as a result of the government's clarification at oral argument, the dispute between the parties has disappeared before our eyes.").

[226] *Id.* at 335 (stating that FDA would have the right to consider the conduct not recommended in guidance document as "intended use" of the drug—off-label promotion—and subject to enforcement under FDCA's misbranding provision).

[227] *Id.* at 336.

[228] *Id.*

[229] 21 U.S.C.A. § 331 (b).

[230] Congress had long before the FDCA made drug misbranding illegal. "The Federal Food and Drugs Act of 1906, the first national statute enacted by Congress to regulate the American food and drug supply, gave the Agency the authority to police the market and remove adulterated or misbranded foods and drugs." S. REP. 105-43, at 6 (1997). Congress and state legislation have also established certain requirements for disclosure of healthcare and drug costs, including through the Social Security Act of 1935 and the Physician Payments Sunshine Act of 2010, but FDA is not responsible for enforcement of those requirements.

[231] 21 U.S.C.A. § 352.

[232] *Id.*

[233] 21 U.S.C. § 321(n) ("If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into

labeling and advertisement requirements.[234] For example, prescription drug advertisements must include "information in brief summary relating to side effects, contraindications, and effectiveness," among other things.[235] A drug is also misbranded if its labeling contains false or misleading comparative representations "with respect to another drug."[236]

The term "labeling" includes the product label and any other "written, printed, or graphic matter (1) upon any article[237] or any of its containers or wrappers, or (2) accompanying such article."[238] Courts have interpreted the concepts of "advertisement" and written matter "accompanying such article" expansively. In *Kordel*, the Court found that misbranded labeling encompassed advertisement itself and literature designed to aid in the sale of a drug, including booklets distributed separately.[239] While applying *Kordel*, courts have found that misbranded labeling under the FDCA covers oral, written, printed, or graphic advertising.[240] Lectures transcribed by a government agent are proper evidence of misbranding.[241] Noteworthy, the split court in *Kordel* highlighted a more textualist approach in dissent. Justices Black, Frankfurter, Murphy, and Jackson asserted that false and misleading promotion should be attributed only to items accompanying the drug ("If Congress left a hiatus, Congress should fill it if it so desires.").[242] Still, the majority's expansive reading of the term "labeling" prevailed, and courts have interpreted the FDCA's misbranding provision to apply to any promotional messaging pertained to a regulated product.[243]

FDA distinguishes promotional messaging (product labeling and advertising) from scientific or general communication unrelated to a regulated product.[244] For example, medical education that does not refer to a drug or that is conducted independently, without influence from a manufacturer, is not labeling and advertising:[245] "company-

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account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual.").

234 *See generally* 21 C.F.R. pts. 202–03.

235 21 C.F.R. § 202.1.

236 21 C.F.R. § 331(tt)(2)–(3) (emphasis added).

237 "Article" should be understood as a "drug" under the FDCA.

238 21 U.S.C.A. § 321(m).

239 Kordel v. United States, 335 U.S. 345, 350–51 (1948) (reasoning that the wording currently under article 321(m)(2) was not limited to "upon" any drug or its containers or wrappers); *see also* United States v. Articles of Drug Consisting of Following: 5,906 Boxes, 745 F.2d 105, 114 (1st Cir. 1984).

240 Nature Food Ctrs., Inc. v. United States, 310 F.2d 67, 70 (1st Cir. 1962).

241 *Id.*

242 *Id.* at 351–53.

243 *See also* United States v. 23, More or Less, Articles, 192 F.2d 308 (finding that phonograph records labeled as being "sleep inducing" conveyed the impression that the record was an adequate substitute for medication for insomnia and was false and misleading, thus, misbranded, within meaning of the FDCA).

244 *E.g.*, Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,093 (Dec. 3, 1997), https://www.govinfo.gov/content/pkg/FR-1997-12-03/pdf/97-31741.pdf.

245 In 1997, FDA issued a guidance document with the purpose of establishing the agency's intent not to treat independent medical education as product promotion, but it also provided broader comments related to communication that is non-product related.

supported educational activity or part thereof that does not relate to the company's products or a competing product, or suggest a use for the company's products, would not be considered a promotional activity, thus not subject to the FDCA's labeling and advertising provisions."[246]

FDA further explained:

> The agency traditionally has recognized the important public policy reasons not to regulate all industry-supported activities as advertising or labeling. To permit industry support for the full exchange of views in scientific and educational discussions, including discussions of unapproved uses, FDA has distinguished between those activities supported by companies that are nonpromotional and otherwise independent from substantive influence of the supporting company and those that are not.[247]

FDA also has distinguished disease awareness communications from labeling and advertising.[248] A draft guidance document defined "disease awareness communications" as those "disseminated to consumers or health care practitioners that discuss a particular disease or health condition, **but do not mention any specific drug or device or make any representation or suggestion concerning a particular drug or device**. Help-seeking communications are disease awareness communications directed at consumers" (emphasis added).[249] FDA withdrew that draft guidance document in 2015 as part of a declared effort to improve transparency and efficiency of the guidance document process.[250] However, the agency also made it implicit that the draft guidance had no basis under the FDCA:

> Unlike drug and device promotional labeling and prescription drug and restricted device advertising, **disease awareness communications are not subject to the requirements of the [FDCA]** and FDA regulations. FDA recognizes the importance of distinguishing between communications that are under FDA jurisdiction and those that are not [emphasis added].[251]

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[246] Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. at 64,096.

[247] *Id.* at 64,095.

[248] In 2004, FDA issued draft guidance covering disease awareness communications by or on behalf of the drug manufacturers. *See generally* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY "HELP-SEEKING" AND OTHER DISEASE AWARENESS COMMUNICATIONS BY OR ON BEHALF OF DRUG AND DEVICE FIRMS – DRAFT GUIDANCE (Jan. 2004) (later withdrawn), https://www.hlregulation.com/files/2015/05/2004-draft-guidance-on-disease-awareness-activities.pdf [https://perma.cc/3B8B-MNDT] [hereinafter FDA, "HELP-SEEKING" GUIDANCE FOR INDUSTRY].

[249] *Id.* at 1.

[250] Withdrawal of Draft Guidance Documents Published Before December 31, 2013, 80 Fed. Reg. 26,059 (May 6, 2015), https://www.govinfo.gov/content/pkg/FR-2015-05-06/pdf/2015-10477.pdf [https://perma.cc/GD2X-8UEE].

[251] *Id.*

Finally, triggered by Pfizer's request, FDA draft guidance "Promotional Labeling and Advertising Considerations for Prescription Biological Reference and Biosimilar Products" makes the point clear: the draft guidance applies to "FDA-regulated promotional labeling and advertisements (promotional materials)" only.[252]

3. Legal Test to Determine Whether FDA Could Apply the "Truthful and Not Misleading" Standard to Communication on "The Nature and Properties" of Biosimilars, to Drive a Public Policy of Encouraging the Prescription and Use of Biosimilars

Courts apply the well-established two-part test in *Chevron*[253] to determine whether Congress has authorized the agency to issue the regulation at issue.[254] Under *Chevron*'s first prong, the Court reasoned that if Congress has spoken directly about the issue at hand and its words are clear, the agency can regulate the matter and courts must give effect to that unambiguous intent.[255] The second prong applies when the statute is silent or ambiguous with respect to a specific issue.[256] In this case, courts will give effect to the regulation if the agency's interpretation "is based on a permissible construction of the statute."[257]

To meet *Chevron*'s first prong, the statute must hardly leave any doubt as to Congress' intent. It requires a direct alignment between the regulatory act and the meaning of the statute. To decide whether Congress has addressed the precise question at issue, the reviewing court applies "'the traditional tools of statutory construction.'"[258] It analyzes "the text, structure, and the overall statutory scheme, as well as the problem Congress sought to solve."[259] In *Chevron*, the Court found that neither the statute nor the legislative history had provided valuable clues as to the

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[252] FDA, GUIDANCE ON PROMOTIONAL LABELING AND ADVERTISING, *supra* note 6.

[253] Chevron, U.S.A., Inc. v. NRDC, Inc., 467 U.S. 837, 840 (1984). In the landmark *Chevron* case, the Supreme Court assessed whether an Environmental Protections Agency (EPA)'s regulation designed to implement a permit program under the Clean Air Act Amendments of 1977 (Pub. L. 95-95, 91 Stat. 685) was "based on a reasonable construction of the statutory term 'stationary source.'" *Chevron*, 467 U.S. at 840. EPA's regulation changed during the Reagan Administration, introducing more relaxed controls, then interpreting the term "stationary source" to include what the agency called a "bubble policy" that allowed for one permit to cover all pollution-emitting devices within one plant, as opposed to each device individually. In practice, that allowed plants to make changes and increase emissions without having to seek new permits for the same plant. The EPA sought to reverse a decision from the U.S. Court of Appeals for the District of Columbia Circuit that had set aside EPA's regulation at issue, arguing the agency's interpretation of the statutory term was reasonable.

[254] *Id.*

[255] *Id. See also* Am. Hosp. Ass'n v. Azar, 468 F. Supp. 3d 372 (D.D.C. 2020) ("[T]he Court must apply the ordinary tools of statutory construction to determine 'whether Congress has directly spoken to the precise question at issue. If the intent of Congress is clear, that is the end of the matter . . . .'" (quoting Merck & Co. v. U.S. Dep't of Health & Hum. Servs., 385 F. Supp. 3d 81, 88 (D.D.C. 2019))).

[256] *Chevron*, 467 U.S. at 467.

[257] *Id.* In contrast, another slightly different legal test would apply had the issue examined been whether FDA had interpreted its rules and guidances (not the statute) consistently. *Kisor* would control. Kisor v. Wilkie, 139 U.S. 2400 (2019) (explaining Auer v. Robbins, 519 U.S. 452 (1997), and establishing that courts should defer to an agency's interpretation of its own regulations, where the applicable regulation is truly ambiguous, but where a regulation has only one reasonable meaning, courts should apply it).

[258] Fin. Planning Ass'n v. Sec. & Exch. Comm'n, 482 F.3d 481, 487, 375 U.S. App. D.C. 389 (D.C. Cir. 2007) (quoting *Chevron*, 467 U.S. at 843 n.9).

[259] *Id. See also* Prevor v. FDA, 67 F. Supp. 3d 125, 133 (D.D.C. 2014).

definition of the terms then at issue to determine whether EPA had used an unambiguous legislative intent.[260] The Court reasoned that the statute at issue reflected the legislative struggle between interests seeking to establish regulatory schemes to reduce pollution but not retard industrial development and progressed to assess the second prong.[261] *Chevron*'s first prong was met in *Prevor*, where a court found that FDA had "contravened the plain meaning of the law" by giving "unduly expansive meanings to certain language in the [FDCA]" to reach a conclusion that the plaintiff's product was a drug, not a medical device.[262] The court in *Prevor* reasoned that FDA had contradicted a "congressional directive" because "Congress sought to limit the number of combination products to be regulated as drugs, including only those which relied on chemical action to achieve their primary intended purposes."[263]

To meet the second test prong, where Congress has been silent or ambiguous regarding the matter at issue, the agency's interpretation must be "based on a permissible construction of the statute."[264] Where a statute is ambiguous and "Congress has explicitly left a gap for the agency to fill," the court must determine "whether the agency's answer is based on a permissible construction of the statute."[265] "Such legislative regulations are given controlling weight unless they are arbitrary, capricious, or manifestly contrary to the statute."[266] As generally happens, enabling legislation is general and broad. In a way, statutes pencil a landscape in a canvas and task agencies to color the picture through its own regulation.[267] However, the canvas is not "boundless,"[268] and the agency cannot use its color palette without cohesion. Courts have rejected overly broad construction of statutes:

> An agency action usually is arbitrary or capricious if the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so

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[260] *Chevron*, 467 U.S. at 845 ("Congress did not have a specific intention on the applicability of the bubble concept in these cases."); *see also id.* at 862 ("We find that the legislative history as a whole is silent on the precise issue before us. It is, however, consistent with the view that the EPA should have broad discretion in implementing the policies of the 1977 Amendments.").

[261] *Id.* at 847 (also stating that "it does . . . plainly disclose that in the permit program Congress sought to accommodate the conflict between the economic interest in permitting capital improvements to continue and the environmental interest in improving air quality." *Id.* at 851.)

[262] Prevor v. FDA, 67 F. Supp. 3d 125, 128 (D.D.C. 2014).

[263] *Id.* at 137 ("The Agency's expertise cannot re-write the law."). FDA appealed the district court's decision but later requested dismissal of the appeal. Prevor v. FDA, No. 14-5274, 2014 U.S. App. LEXIS 24682 (D.C. Cir. Dec. 17, 2014).

[264] *Chevron*, 467 U.S. at 840.

[265] *Id.* at 843.

[266] *Id.* at 844. *See also* Am. Hosp. Ass'n v. Azar, 468 F. Supp. 3d 372, 380 (D.D.C. 2020).

[267] Morton v. Ruiz, 415 U.S. 199, 231 (1974) ("The power of an administrative agency to administer a congressionally created and funded program necessarily requires the formulation of policy and the making of rules to fill any gap left, implicitly or explicitly, by Congress.").

[268] Merck & Co. v. U.S. Dep't of Health & Hum. Servs., 962 F.3d 531, 537 (D.C. Cir. 2020) (finding that the Department of Health and Human Services' Centers for Medicare and Medicaid Services lacked statutory basis and "acted unreasonably in construing its regulatory authority" when it promulgated rule broadly requiring manufacturers to disclose the wholesale acquisition cost of many prescription drugs and biologics in TV ads).

> implausible that it could not be ascribed to a difference in view or the product of agency expertise.[269]

Also, "courts should not lightly presume congressional intent to implicitly delegate decisions of major economic or political significance to agencies."[270] Interpretation of a statute that would "seem to give it unbridled power to promulgate any regulation" would not meet *Chevron*'s second prong.[271] In *Merck*, the court reasoned that regulation forcing drug manufacturers to disclose Average Wholesale Price in TV advertisement, "under arguable effect of driving down drug prices," suggested "a staggering delegation of power, far removed from ordinary administration."[272] Defendant-appellant, HHS, had argued the rule was "not of major significance because compliance costs would be low," but the court reasoned the issue was not with cost of compliance but with the fact that the regulation implicated "a substantial constitutional question concerning the government's authority to regulate the public speech of companies just because some percentage of the audience is involved in a governmental program from which the businesses indirectly derive financial benefit."[273]

B. Application of the Law

Pfizer petitioned FDA to issue broad guidance to clarify the appropriate conditions under which biologics manufacturers may disseminate information on "the nature and properties" of biosimilars, irrespective of whether the communication would refer to a specific product.[274] Pfizer argued that as much as FDA has set parameters for truthful and not misleading promotion of drugs, it should also set them for truthful and not misleading communication discussing scientific and regulatory propositions, such as the safety and effectiveness of biosimilars in general.[275] Pfizer suggests that any communication on biosimilarity disseminated by a biologics manufacturer can be misleading in violation of the FDCA's misbranding provision.[276] Three of the four communication examples Pfizer provided did not refer to any product; instead, they appeared to be general discussions on the science and regulation of biosimilars. Thus, Pfizer's request aims to extend the truthful and not misleading standard under the FDCA to any manufacturer's communication on the nature and properties of biosimilars, thereby creating regulatory pressure to suppress the dissemination of messages disfavoring biosimilars.

FDA has not embraced such a broad proposition. The existing draft guidance on promotional labeling and advertising on biologics and biosimilars points to the

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[269] Prevor v. FDA, 67 F. Supp. 3d 125, 134 (D.D.C. 2014) (citing Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983)).

[270] FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 160 (2000) (declaring FDA did not have statutory authority to regulate tobacco products; superseded by subsequent amendment to the FDCA); *see also* Utility Air Regulatory Grp. v. EPA, 573 U.S. 302, 324 (2014) ("When an agency claims to discover in a long-extant statute an unheralded power to regulate 'a significant portion of the American economy,' we typically greet its announcement with a measure of skepticism.").

[271] *Merck*, 962 F.3d at 540. *See also* Loving v. IRS, 408 U.S. App. D.C. 281, 742 F.3d 1013 (2014).

[272] *Merck*, 962 F.3d at 540.

[273] *Id.* at 535–40.

[274] Pfizer, Inc., Citizen Petition, *supra* note 4, at 1. *See* discussion *supra* Section II(A).

[275] *Id.*

[276] *Id.*

FDCA's authority clearly indicating it applies to "FDA-regulated promotional labeling and advertisements (promotional materials)" only.[277] Examples of misleading communication are limited to potentially false or misleading product claims without adequate substantiation or disclaimers.[278] The three legal issues proposed in this section are answered to reach this broad conclusion.

First, an FDA guidance document cannot be the appropriate instrument to set parameters for truthful and not misleading communication on the nature and properties of biosimilars. FDA guidance must be limited to explaining how existing FDA rules apply (for the efficient enforcement of the FDCA provisions and FDA rules implemented through the appropriate rulemaking process).[279] In the absence of statutory provision or rule on point to rely on, the guidance document itself would constitute rulemaking (rule includes statements of general applicability and future effect designed to interpret law or policy).[280] Here, neither the FDCA nor FDA rules on misbranding ever apply to communication on the nature and properties of a class of products. Instead, the provision exclusively applies to product labeling and advertising,[281] generally considered product label and promotion (labeling and advertising).[282] Messages on the nature and properties of biosimilars without product mentioning are not promotion, and its regulation would be a departure from FDA's interpretation of the law (FDA has long regulated product promotion and declined to regulate other types of communication).[283] "The agency traditionally has recognized the important public policy reasons not to regulate all industry-supported activities as advertising or labeling."[284]

Legal challenges are sure to follow should FDA adopt Pfizer's proposition and promulgate a guidance document articulating that the FDCA misbranding provision applies to communication on the nature and properties of biosimilars. Such interpretation, even if materialized in a guidance document disclaimed as nonbinding and not legally enforceable, would not be insulated from legal review. Such interpretation would meet *Bennett*'s two prongs and constitute final agency action.[285] Here, a guidance document duly approved by FDA officers and published in the Federal Register would likely mark the consummation of the agency's decision-making process and from which legal consequences would flow.[286]

Bennett's first prong: As in *Abbott*, the guidance document would represent the final and settled understanding approved by FDA officers (assuming that such guidance

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[277] FDA, GUIDANCE ON PROMOTIONAL LABELING AND ADVERTISING, *supra* note 6.

[278] *Id.*

[279] 21 C.F.R. § 10.90 (2021).

[280] 5 U.S.C. § 551(4).

[281] 21 U.S.C. § 352; 21 C.F.R. Parts 202 and 203 (2021).

[282] Kordel v. United States, 335 U.S. 345, 347 (1948).

[283] Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,074, 64,096 (Dec. 3, 1997) ("A company-supported educational activity or part thereof that does not relate to the company's products or a competing product, or suggest a use for the company's products, would not be considered a promotional activity," and thus not subject to the FDCA's labeling and advertising provisions.).

[284] *Id.* at 64,095.

[285] 5 U.S.C. § 704.

[286] Meeting *Bennett*'s two conditions for finality. Bennett v. Spear, 520 U.S. 154, 177–78 (1997).

would have been approved and published).[287] Such a guidance document distinguishes from situations where the agency action is a mere recommendation to an officer with absolute power to decide differently.[288] In fact, FDA agents could "not deviate from such guidances without appropriate justification and supervisory concurrence."[289] Also, even though the guidance document could still be revised after consultation or at any time, its consummation aspect would still exist.[290] In *U.S. Army Corps of Engineers*, a final jurisdictional determination (JD) was considered final action because it had gone through all the necessary steps for its issuance.[291] The fact that the agency could still change the conclusions expressed in the JD, based on new information, did not negate its consummation aspect.[292] Here, FDA can still change its position expressed in a guidance document based on new information arising from public consultation or otherwise. However, this possibility would not negate the consummation of FDA's thinking expressed in the document. As in *Appalachian*, also, the guidance would reflect "a settled agency position."[293]

Bennett's second prong: Such FDA guidance would also meet *Bennett*'s second prong because it would establish new agency interpretation, making the guidance a rule under the APA.[294] Legal consequences can flow from new agency interpretation of the law even when encapsulated in a guidance document.[295] In *Bennett*, the agency-respondent had argued that the action was not final because it was a mere recommendation for affected parties to follow or not.[296] However, in practice, states and regulated parties would hardly ever consider not following those recommendations due to the threat of hefty fines and criminal liability.[297] Equally here, biologics manufacturers would have to carefully calculate the risks of not complying with an FDA guidance document due to the threat of enforcement action that could result in civil and criminal penalties. The parallel is also true between the facts in *U.S. Army Corps of Engineers* and the hypothetical facts here. In both cases, a JD and a guidance document themselves could not be the basis for administrative or criminal proceedings but represented a clear threat of enforcement action (the affected parties do not have to risk enforcement action to make the agency action reviewable).[298]

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[287] Abbott Lab'ys v. Gardner, 387 U.S. 136, 151 (1967), *superseded by statute*, Clean Air Amendments of 1970, Pub. L. No. 91–604, 84 Stat. 1676 (codified as amended at 42 U.S.C.A. § 7607 (1997 & 2010 Supp.)), as recognized in Califano v. Sanders, 430 U.S. 99, 105 (1977) and Lubrizol Corp. v. Train, 547 F.2d 310 (6th Cir. 1976)).

[288] Chi. & S. Air Lines, Inc. v. Waterman S.S. Co., 333 U.S. 103, 113 (1948).

[289] 21 U.S.C. § 371(h).

[290] U.S. Army Corps of Eng'rs v. Hawkes Co., 136 S. Ct. 1807, 1814.

[291] *Id.*

[292] *Id.*

[293] Appalachian Power Co. v. EPA, 208 F.3d 1015, 1023 (D.C. Cir. 2000).

[294] 5 U.S.C. § 551(4).

[295] Bennett v. Spear, 520 U.S. 154, 178 (1997).

[296] *Id.* at 169, 177.

[297] *Id.* at 169.

[298] U.S. Army Corps of Eng'rs v. Hawkes Co., 136 S. Ct. 1807, 1815 ("[W]hile no administrative or criminal proceeding can be brought for failure to conform to the approved JD itself, that final agency determination not only deprives respondents of a five-year safe harbor from liability under the Act, but

Frozen Food Express also provides support to establish *Bennett*'s second prong in this case. There, the agency action was immediately reviewable because it put some carriers on notice that they would be subject to supervision and could face criminal penalties.[299] Here, Janssen, Genetech, Amgem, and potentially other manufacturers would immediately be on notice that their prior messaging would expose them to civil and criminal liability.

Finally, the appeals and district courts in the District of Columbia have examined the finality of the agency's guidance documents more closely and held that they are final when they represent a settled agency position on the law.[300] In *Appalachian Power Company*, an EPA guidance document was held final action because it expanded on existing rules creating legal consequences for regulated actors.[301] The lack of formality on the issuance of the guidance and boilerplate language in the document indicating the recommendations there described were not binding did not negate the actual legal consequences flowing from the document.[302] In *Philip Morris*, the district court held that HHS's interpretative rules created an expectation that regulated parties would conform with it; thus, it was final action.[303] Here, a hypothetical FDA guidance regulating communication on biosimilarity would be reviewable, despite the traditional boilerplate language found in guidance documents (as in *Appalachian*). This analysis gains even more weight when assessing the conditions of finality flexibly and pragmatically.[304]

Meeting *Bennett*'s two conditions, an FDA guidance document applying the FDCA misbranding provision would warrant immediate pre-enforcement judicial review.

Next, this Article provides a negative and more straightforward answer to the second question: whether any statutory provision authorizes FDA to set parameters for truthful and not misleading communication on the nature and properties of biosimilars. The FDCA narrowly defines the truthful and not misleading standard to apply it with one primary purpose: protect the health of consumers[305] (FDA's mission includes "protecting the public health by ensuring that the products it regulates meet the appropriate FDA regulatory standards."[306]). Although closely contained in its scope,

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warns that if they discharge pollutants onto their property without obtaining a permit from the Corps, they do so at the risk of significant criminal and civil penalties.").

[299] Frozen Food Express v. United States, 351 U.S. 40 (1956) (first citing Abbott Lab'ys v. Gardner, 387 U.S. 136, 150 (1967) and then *U.S. Army Corps of Eng'rs*, 136 S. Ct. at 1815).

[300] Appalachian Power Co. v. EPA, 208 F.3d 1015, 1023 (D.C. Cir. 2000).

[301] *Id.*

[302] *Id.*

[303] Philip Morris USA, Inc. v. FDA, 202 F. Supp. 3d 31, 46–47 (D.C. Cir. 2016); *see also* Pharm. Research & Mfrs. of Am. v. U.S. Dep't Health & Hum. Servs., 138 F. Supp. 3d 31, 44 (D.C. Cir. 2015).

[304] *Abbott Lab'ys*, 387 U.S. at 149.

[305] 21 U.S.C. § 352. *See also* S. REP. 105-43, at 15–16 (1997) ("From the 1906 Food and Drugs Act through the 1990 Safe Medical Devices Act, food and drug law has emphasized that the duty of the FDA is to protect the public against unsafe or ineffective products.").

[306] S. REP. 105-43, at 2–3 (1997). With FDAMA, Congress sought to build upon earlier administrative reforms and findings of the ongoing Advisory Committee to drive more accountability and focus within FDA and reauthorize the agency to charge user fees in exchange for more efficient drug application reviews. *See id.* at 2 ("The legislation accomplishes three major objectives: it builds upon recent administrative reforms that both streamline FDA's procedures and strengthen the agency's ability to accomplish its mandate in an era of limited Federal resources; it requires a greater degree of accountability from the agency in how it pursues its mandate; and it provides for the reauthorization of PDUFA.").

failure to meet the truthful and not misleading standard can lead to severe liability, with civil and criminal penalties.[307] Accordingly, the standard applies only to product labeling and advertising, which, when false or misleading, misbrands the product at issue.[308] The FDCA's misbranding provision applies to any product promotional communication.[309] However, it does not apply beyond that:

> company-supported educational activity or part thereof that does not relate to the company's products or a competing product, or suggest a use for the company's products, would not be considered a promotional activity, thus not subject to the FDCA's labeling and advertising provisions.[310]

Also:

> The agency traditionally has recognized the important public policy reasons not to regulate all industry-supported activities as advertising or labeling. To permit industry support for the full exchange of views in scientific and educational discussions, including discussions of unapproved uses, FDA has distinguished between those activities supported by companies that are nonpromotional and otherwise independent from substantive influence of the supporting company and those that are not. . . . [311]

It is no accident FDA has reiterated in different instances that the agency recognizes the important public policy reasons not to regulate all industry-supported activities as advertising or labeling.[312] The misbranding provision is narrowly defined to apply exclusively to product-specific communication, because no statutory provision authorizes FDA to set parameters for truthful and not misleading communication on the nature and properties of biosimilars.

Finally, this section answers the last question: FDA cannot interpret the FDCA's misbranding provision expansively to apply to manufacturers' communication that does not reference a biologic or biosimilar product, with or without the intent to encourage the prescription and use of biosimilars. Even if mounting evidence would exist to show that manufacturers are disseminating inaccurate or misleading information on the science and regulation of biosimilars, FDA could not issue final guidance granting Pfizer's demand because doing so would require the FDCA misbranding provision to be construed to apply beyond product-specific promotion.

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[307] 21 U.S.C. § 333 (see misdemeanor culpability without scienter requirement, felony, and additional civil penalties for direct-to-consumer advertisement that is false or misleading).

[308] 21 U.S.C. § 352. *See also* S. REP. 105-43, at 15–16 (1997) ("From the 1906 Food and Drugs Act through the 1990 Safe Medical Devices Act, food and drug law has emphasized that the duty of the FDA is to protect the public against unsafe or ineffective products.").

[309] Kordel v. United States, 335 U.S. 345, 350–35; *see also* Nature Food Ctrs., Inc. v. United States, 310 F.2d 67, 70 (1962).

[310] Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64,093, 64,096 (Dec. 3, 1997).

[311] *Id.* at 64,095.

[312] *See id.* at 64,096; FDA, "HELP-SEEKING" GUIDANCE FOR INDUSTRY, *supra* note 248.

Under *Chevron*'s first prong, the FDCA would have to unambiguously authorize FDA to regulate manufacturers' dissemination of opinions on scientific and regulatory discussions and messaging unrelated to their products. However, the FDCA text, structure, and the overall statutory scheme neither reveal equivalent authority nor provide broad delegation of power to FDA to create new restrictions on speech (which FDA has already recognized in past draft guidances to the market).[313] As such, under *Chevron*'s first prong, it is very unlikely that courts would uphold any regulation embracing Pfizer's proposition. On the contrary, an attempt to apply the existing misbranding provision to non-product communication would likely be considered a failure to follow clear statutory language and traditional FDA understanding that only labeling and advertising, as product-specific communication, can misbrand a drug.

Moreover, Congress has used strong words to define FDA's focus and scope: "we cannot afford" an FDA that maintains an "adversarial relationship" with "industries it regulates" or that pursues "so many agendas that it lacks a clear-cut mission and sphere of responsibility."[314] As such, courts will likely find that FDA would contradict a "congressional directive" by seeking to expand its regulatory scope to support the uptake and encourage prescription of biosimilars.

To move from *Chevron*'s first to second prong, a court would have to determine that the FDCA's misbranding provision is silent or sufficiently ambiguous as to allow for more than one reasonable interpretation or construction to apply the truthful and not misleading standard to communication on the "nature and properties" of biosimilars. If the statute would allow for wiggle room, courts could give FDA deference, so long as the construction is not arbitrary, capricious, or manifestly contrary to the statute. However, that is not the case here. Not only the misbranding provision, but also the entire statutory scheme, center around regulated products, including labeling and advertising of such products; that is, FDA regulates products, not companies in isolation or their speech.[315] As courts reject overly broad construction of statutes, they will likely also consider arbitrary or capricious FDA's reliance on FDA's interest to regulate speech pertaining to aspects of biosimilarity in absence of drug promotion because of a desire to foster prescription of biosimilars. As in *Merck*, that would amount to a staggering delegation of authority to regulate speech that Congress did not intend and that would implicate substantial constitutional questions.

Therefore, the misbranding prohibition likely cannot be reasonably construed to prohibit communication on aspects of biosimilarity in absence of a product comparison, even if a manufacturer conducted or directed the communication. To interpret otherwise could lead to the conclusion that the FDCA intended to prohibit manufacturers from sharing opinions and views on scientific topics broadly and inconsistently with its misbranding provision. It would also indicate that manufacturers of biologic products alone were prohibited from sharing their views, while other stakeholders would not.

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313 Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. at 64,096 (Dec. 3, 1997).

314 S. REP. 105-43, at 10 (1997) (emphasis added).

315 Misbranding occurs if: 1) a drug's label, labeling, or advertising fails to fulfil the warning or disclosure requirements set forth in the statute; 2) a drug's communication fails to review material facts in light of the representations being made about the drug and the consequences which may result from the use of the drug; or 3) if representations being made that are false or misleading relate to another drug (i.e., comparative claims between reference biologics and biosimilars).

Finally, "encouraging the prescription and use of biosimilars" is likely not a public policy FDA is authorized to pursue while regulating the misbranding provision under the FDCA. Nothing indicates that Congress intended the FDCA and PHSA to be sweeping delegations of power to regulate and expand beyond FDA's specific authority and outside its mission. Instead, Congress intended FDA to focus on "protecting the public health," "promptly and efficiently reviewing clinical research," and reducing "regulatory burdens" through collaboration and harmonization of regulatory requirements with other health agencies."[316]

IV. WHAT STATEMENTS ON THE "NATURE AND PROPERTIES" OF BIOSIMILARS ARE LIKELY TO BE CONSIDERED MISLEADING AND TRIGGER ENFORCEMENT ACTION FROM FTC?

A. Applicable Law

The Federal Trade Commission Act of 1914 (FTC Act) prohibits "deceptive acts or practices in or affecting commerce,"[317] including false advertisement that is likely to induce, "directly or indirectly, the purchase in or having an effect upon commerce" of drugs and other products.[318]

The FTC Act and the FDCA define the term "drugs" equally, leading to an overlap of responsibilities for assessing the truth or falsity of drug advertisement.[319] In practice, both agencies have sought to solve the issue through a joint agreement and understanding. FDA has maintained primary responsibility for policing prescription drug advertisements. In turn, FTC exercises primary responsibility for overseeing nonprescription drug (i.e., an over-the-counter drug) advertisements.[320] However, an apparent gap emerges from this solution when the communication disseminated by manufacturers solely relates to the nature and properties of biosimilarity, conveying scientific and regulatory concepts that implicate a class of prescription drugs but not referring to one drug in specific. FDA would not have jurisdiction to review such communication under the FDCA,[321] and FTC does not exercise jurisdiction over prescription drug advertisement.

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[316] S. REP. 105-43, 10 (1997) (emphasis added). Ultimately, FDA found a different and more appropriate avenue to encourage prescription and use of biosimilars. In 2021, Congress provided authority for FDA to create and disseminate educational content pertaining to biologics and biosimilars. Advancing Education on Biosimilars Act of 2021, 117 Pub. L. No. 8, 135 Stat. 254.

[317] 15 U.S.C. § 45(a)(1).

[318] 15 U.S.C. § 52 ("False advertisement likely to induce the purchase in or have an effect upon commerce of drugs is unlawful and deemed a deceptive act or practice in or affecting commerce.").

[319] *See* 15 U.S.C. § 55(c); 21 U.S.C. § 321(g)(1).

[320] FDA exercises primary responsibility for preventing misbranding of prescription drug advertising while FTC exercises primary responsibility for assessing the truth or falsity of nonprescription drug advertisement. Memorandum of Understanding Between the Federal Trade Commission and the Food and Drug Administration, P914502 (May 1971), https://www.ftc.gov/policy/cooperation-agreements/memorandum-understanding-between-federal-trade-commission-food-drug [https://perma.cc/547Y-B8YK] [hereinafter FTC–FDA MOU].

[321] *See supra* Section III(A)(2).

To establish jurisdiction, FTC must also demonstrate that the communication conveying scientific and regulatory concepts is advertisement and constitutes commercial speech. Even though the FTC Act does not define the term advertisement, the Act prohibits "false advertisement" intended to induce, or that is "likely to induce, directly or indirectly, the purchase" of drugs.[322] As such, the messaging in the advertisement must be likely to induce customer behavior in furtherance of a commercial interest. "The more limited protection accorded commercial speech permits FTC to act when necessary to challenge false or deceptive advertising."[323] When the government imposes limitations on speech disseminated for one purpose (i.e., advertisement) but not others (i.e., opinions by disinterested persons), the restrictions are content-based and subject to intermediate scrutiny.[324]

On the other hand, noncommercial speech is generally immune from government control.[325] Not all advertisements are commercial speech and subject to restrictions under the FTC Act.[326]

The facts in the case determine whether the advertisement can be classified as commercial speech.[327] Here, FTC carries the burden of proof.[328] Courts have not established a precise test to determine when an advertisement would be commercial speech. In *Bolger*, the Court found that each of the following factors, by itself, did not render the advertisement commercial speech: 1) pamphlets distributed as paid advertisements;[329] 2) reference to a specific product; and 3) existence of an economic motivation for the advertisement's sponsor to disseminate it. However, the Court

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[322] 15 U.S.C. § 52(a).

[323] In the Matter of R.J. Reynolds Tobacco Company, Inc., 111 F.T.C. 539, 1988 FTC LEXIS 9, at *8 (1988). *See also* Thompson Medical Co. v. FTC, 791 F.2d 189 (D.C. Cir. 1986), *cert. denied*, 107 S. Ct. 1289 (1987); Sears, Roebuck & Co. v. FTC, 676 F.2d 385 (9th Cir. 1982); Warner-Lambert Co. v. FTC, 562 F.2d 749 (D.C. Cir. 1977), *cert. denied*, 435 U.S. 950 (1978); Beneficial Corp. v. FTC, 542 F.2d 611 (3d Cir. 1976), *cert. denied*, 430 U.S. 983 (1977).

[324] *See* Sorrell v. IMS Health Inc., 564 U.S. 552, 557 (2011). In *Sorrell*, the Court held that a Vermont statute prohibiting pharmacies from selling prescriber data and pharmaceutical companies from using such data for marketing purposes was unconstitutional because it was content-based; that is, the statute disfavored the speech for marketing purposes by pharmaceutical companies, but not for other uses and by other speakers. *Id.* at 564. Even though pharmaceutical companies would use the data in commercial speech, the Court held that heightened (intermediate) judicial scrutiny applies in assessing state action limiting speech "because of disagreement with the message it conveys." *Id.* at 566. The government must show at least that the limitation on commercial speech "directly advances a substantial governmental interest and that the measure is drawn to achieve that interest." *Id.* at 572. *See also* Bolger v. Youngs Drug Prods. Corp., 463 U.S. 60, 65 (1983) (comparing noncommercial and commercial speech regulation. "Regulation of commercial speech based on content is less problematic. In light of the greater potential for deception or confusion in the context of certain advertising, content-based restrictions on commercial speech may be permissible.").

[325] *Bolger*, 463 U.S. at 65 (reasoning that the government cannot restrict noncommercial speech "because of its message, its ideas, its subject matter, or its content" and "content-based restrictions" are viable "only in the most extraordinary circumstances"); *see also* Janus v. AFSCME, Council, 138 S. Ct. 2448, 2464 (2018) ("Free speech . . . is essential to [our] democracy and furthers the search for truth. Whenever the federal government or a state prevents individuals from saying what they think on important matters or compels them to voice ideas with which they disagree, it undermines these ends.").

[326] *R.J. Reynolds Tobacco Company, Inc.*, 1988 FTC LEXIS 9, at *5.

[327] *Id.* at *12.

[328] *Bolger*, 463 U.S. at 70 n.20. ("The party seeking to uphold a restriction on commercial speech carries the burden of justifying it.").

[329] *Id.* at 66.

determined that the presence of all three factors "provided strong support . . . for the conclusion that the informational pamphlets" were commercial speech,[330] "notwithstanding the fact that they contain discussions of important public issues."[331] Similarly, advertisement that links a product to a "current public debate is not thereby noncommercial."[332] Advertisement sponsored by an egg producers' trade association characterizing study conclusions in a way that minimizes cholesterol and heart disease issues in connection with egg consumption was considered commercial speech.[333] The FTC has treated a reference to a product class, cigarettes in general, in advertisement as if it were a reference to the advertiser's own product.[334] In *R.J. Reynolds Tobacco Company*, paid advertisement allegedly falsely and misleadingly described a study as "credible scientific evidence that smoking is not as hazardous," among other things.[335]

Next, FTC must establish that the challenged advertisement is false. An advertisement is false when it is "misleading in a material respect."[336] To determine whether an advertisement is misleading, FTC must assess the message in its entirety, including representations made and suggested, material facts not revealed, and the consequences which may result from the representations and omissions.[337] One court stated that

> A statement may be deceptive even if the constituent words may be literally or technically construed so as to not constitute a misrepresentation. The buying public does not weigh each word in an advertisement or a representation. It is important to ascertain the impression that is likely to be created upon the prospective purchaser.[338]

Consequently, an advertisement is deceptive when "it is likely to mislead consumers, acting reasonably under the circumstances, in a material respect."[339] "A finding of 'tendency and capacity to mislead' is sufficient and that actual deception

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[330] *Id.* "Nor do we mean to suggest that each of the characteristics present in this case must necessarily be present in order for speech to be commercial. For example, we express no opinion as to whether reference to any particular product or service is a necessary element of commercial speech." *Id.* at 66 n.14.

[331] *Id.* at 66.

[332] Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557, 562 n.5, 563 (1980).

[333] Nat'l Comm'n on Egg Nutrition v. FTC, 570 F.2d 157, 158–59 (7th Cir. 1977).

[334] In the Matter of R.J. Reynolds Tobacco Co., Inc., 111 F.T.C. 539, 1988 FTC LEXIS 9, at *15 (1988) (reversing administrative law judge's order that had granted motion to dismiss; other factors also considered in determining that advertisement entitled "Of Cigarettes and Science" was to be considered commercial speech at that stage in the process).

[335] *Id.* at *2.

[336] 15 U.S.C. § 55 ("[I]n determining whether any advertisement is misleading, there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, sound, or any combination thereof, but also the extent to which the advertisement fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the commodity to which the advertisement relates under the conditions prescribed in said advertisement, or under such conditions as are customary or usual.").

[337] *Id.*

[338] Kalwajtys v. FTC, 237 F.2d 654, 656 (7th Cir. 1956) (internal citations omitted).

[339] Kraft, Inc. v. FTC, 970 F.2d 311, 314 (7th Cir. 1992).

need not be shown."[340] To determine whether deceit exists, FTC examines the overall net impression that the advertisement conveys to the public,[341] conducting a three-part inquiry: 1) what representations, omissions, or practices exist; 2) whether such representations, omissions, or practices likely mislead consumers acting reasonably under the circumstances; and 3) whether the misleading representations, omissions, or practices are material.[342] Courts are not necessarily bound by this test, but FTC is, as per precedent FTC established in *Cliffdale Associates, Inc.*[343]

In the first inquiry, FTC looks at the advertisement's express statements and likely implied claims by analyzing the entire document and omissions.[344] Omissions are determined where a claim is made without providing clarifying context or specifying the limitations of such claim, for example.[345] In the second inquiry, FTC establishes whether any representations made in the advertisement are false on their own or misleading because "the advertiser lacked a reasonable basis for asserting that the message was true."[346] Omissions can also create a misleading net impression by failing to disclose material facts.[347] In *Porter*, the court sustained FTC's finding that testimonials rendered advertisement false or misleading because the advertisement failed to disclose that "weight losses of the magnitude claimed, far from being typical, as the advertisements implied, are extremely rare."[348] Finally, to assess materiality, FTC seeks to determine whether the misrepresentation or omission is likely to affect reasonable consumers' conduct towards a product, for example deciding between the purchase of one over another.[349] In sum, an advertisement that presents unsubstantiated claims or fails to disclose material facts in a way that materially induces reasonable consumers' conduct towards a product is deceptive.

B. Application of the Law

FTC can exercise jurisdiction over advertisements that drug manufacturers disseminate to the general public on the nature and properties of biosimilars, where a prescription drug is not referenced.[350] The FDA–FTC joint understanding and agreement establishing FDA as the primary agency responsible for overseeing prescription drug advertisement does not supersede the FTC Act and will not deter FTC from taking action when appropriate.[351] Conversely, where advertisement on

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[340] Vacu-Matic Carburetor Co. v. FTC, 157 F.2d 711, 713 (7th Cir. 1946), *cert. denied*, 331 U.S. 806 (1947) (citing FTC v. Algoma Lumber Co., 291 U.S. 67, 81 (1934).

[341] FTC Policy Statement on Deception (Oct. 14, 1983) (appended to Cliffdale Associates, Inc., 103 F.T.C. 110, 174 (1984)).

[342] Kraft, Inc. v. FTC, 970 F.2d 311, 314 (7th Cir. 1992); *see also* Cliffdale Associates, Inc., 103 F.T.C. 110, 170–71, 174 (1984); FTC v. Pantron I Corp., 33 F.3d 1088, 1095 (9th Cir. 1994).

[343] Agency interpretation of the law is as compelling as arguments before the court.

[344] FTC Policy Statement on Deception (Oct. 14, 1983) (appended to Cliffdale Associates, Inc., 103 F.T.C. 110, 174 (1984)).

[345] *Id.*

[346] *Pantron I Corp.*, 33 F.3d at 1096 (citing Thompson Medical Co., 104 F.T.C. 648, 818–19 (1984).

[347] Porter & Dietsch, Inc. v. FTC, 605 F.2d 294, 303 (7th Cir. 1979).

[348] *Id.*

[349] *Id.*

[350] FTC–FDA MOU, *supra* note 320.

[351] *Id.*

biosimilarity also refers to a specific product, FDA will likely take primary oversight responsibility. Thus, FTC would likely review the following pieces of communication: 1) Genentech's Internet page: Examine Biosimilars; 2) Tweet from Amgen Biosimilars; and 3) Amgen's YouTube video.[352]

Next, FTC should assess whether each of the three pieces of communication is commercial speech in the form of advertisement. Information on each communication is limited to what Pfizer described in its Citizen Petition, making a detailed analysis unviable. In favor of a general finding that all three examples are commercial speech, it is conceivable that they are paid advertisements. All three communications are disseminated by companies with a clear commercial interest in inducing patients to choose biologic products in lieu of biosimilars. Amgen's Tweet more prominently appears to adopt a promotional look and feel. Conversely, in favor of a finding that the advertisements are noncommercial, Genentech's Internet page and Amgen's YouTube video appear to be educational in nature. Factors such as whether the material was prepared and distributed by the scientific or marketing department, the look and feel, and the level of technical details made available would inform the determination. These factors, to some degree, may distinguish clinical and regulatory discussions on biosimilarity from egg and tobacco companies' flawed conclusions on clinical studies, which led to a finding that they were commercial speech. Moreover, Genentech's website may be a passive source of information, different from social media platforms. Whether and how Genentech invested in maximizing search hits will likely also influence the determination. In a more controversial analysis, companies could also argue that, as a matter of law, those contents are not advertisements under the more specialized FDCA misbranding provision and should not be treated as advertisements under the FTC Act. For example, biologics manufacturers disseminate disease awareness information to patients without it being considered advertisement under the FDCA.

Last, FTC will assess whether each advertisement contains material misrepresentations or omissions that likely affect reasonable consumers' choice or conduct towards biosimilars in relation to biologics. If so, the advertisement is false or misleading. The three advertisements are likely to influence reasonable patients' conduct towards biosimilars because they point out, at minimum, that the biosimilar is highly similar but not identical to the reference biologic product. It suggests that switching to a biosimilar may not be right for the reasonable patient. Thus, the materiality element likely is present. The critical question in each instance is whether the advertisement presents misrepresentations or impermissible omissions at all. To determine that, the net impression of the advertisement must be assessed without consideration to desired public healthcare policies. Certainly, misrepresentations or omissions that lead reasonable patients to riskier behavior or more costly choices render the advertisement false or misleading. However, truthful representations cannot be rendered misrepresentations simply because the advertisement is biased towards one therapeutic class and not another that may be cheaper. If truthful information is provided, the question should be whether omissions or phrasing make them half-truths that tend to mislead the consumer acting reasonably.

In giving effect to the FTC Act, the aim must merely be to protect consumers against false or misleading claims that inappropriately affect their choices. Advertisements,

[352] FDA has likely already assessed Janssen Biotech's printed patient brochure referencing Janssen's product REMICADE.

by nature, are designed to drive behavior; otherwise, the expense would make little sense. For example, drug manufacturers often invest in disease and product campaigns to increase disease awareness, improve diagnosis, and drive the selection of a drug which is perhaps more expensive and effective than another. Those campaigns benefit patients and impact the healthcare system by accelerating the adoption of clinical interventions and utilization of more costly therapy. The fact that such campaigns may potentially lead to increased adoption and costs to the healthcare system cannot be relevant to determine whether the campaign impermissibly omitted the fact that the drug is more expensive than another. It is up to the competitor to counter that advertisement with its own campaign if it so wishes. Similarly, biologics and biosimilars' manufacturers engage in awareness campaigns around the "nature and properties" of biosimilarity. While innovators may have a bias towards certain aspects of the information, biosimilars' manufacturers will focus on others. Yet, agents are likely able to successfully disseminate their messages with some variability without deceiving reasonable patients. Whether FTC dislikes one side of the message, because it drives up costs or slows down biosimilars' uptake, cannot be relevant in determining whether the message presents misrepresentations or omits material facts. The BPCIA, which introduced the concept of biosimilarity to the U.S. statutory framework, did not make illegal or less truthful one's legitimate opinion regarding biosimilarity or disclosure of regulatory differences between biosimilars and interchangeables. In this case, the protected right of free speech likely weighs heavier against FTC's drive to foster biosimilars' adoption in the marketplace.

Furthering the rationale that claims to differentiate biosimilars are not misrepresentations on its face, the PHSA clearly distinguishes biosimilars and interchangeable biosimilars.[353] Only interchangeables have shown the same clinical effect on every patient and can automatically substitute the reference biologic without intervention from the treating physician.[354] Effectively, the biosimilar might not work well for a patient, especially in complex chronic diseases where immunogenicity is a constant concern.[355] The fact that only the treating physician can help the patient decide whether to switch to a biosimilar may support the appropriateness of a public awareness campaign that recommends that patients discuss options with their doctors.

Should FTC give reasonable weight to these arguments, analyzing the advertisements' truthfulness or falsity would likely proceed as follows:

Genentech's Internet page "Examine Biosimilar," intended to present information on regulatory requirements for approval of biosimilars and interchangeables, apparently delays one minute into the video to disclose "that a biosimilar is '[a] biological product that is highly similar to its reference product – notwithstanding minor differences in clinically inactive components' and 'biosimilars cannot have any

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353 42 U.S.C. § 262(k).

354 *Id.*

355 U.S. FOOD & DRUG ADMIN., CONSIDERATIONS IN DEMONSTRATING INTERCHANGEABILITY WITH A REFERENCE PRODUCT—GUIDANCE FOR THE INDUSTRY at 7–8 (May 2019) (clinical experience with the reference product may document "a history of inducing detrimental immune responses" showing increased immunogenicity); *see also* REMICADE® (INFLIXIMAB) PRESCRIBING INFORMATION, JANSSEN BIOTECH, INC. 8 (the presence of antibodies in adult patients studied receiving REMICADE® (Infliximab) varied from 10% to 51% depending on the dose and certain patient characteristics), http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/REMICADE-pi.pdf [https://perma.cc/3RRM-36K5].

clinically meaningful differences in: safety, purity, and potency.'"[356] Genentech apparently had a website dedicated to presenting information on biologics manufacturing and used physicians to explain biosimilarity concepts. FTC would likely be unable to show that the content is false or misleading because the net impression would likely still be truthful. The website appears to fully describe the regulatory requirements for biosimilars and interchangeables, including disclosing that there are no clinically meaningful differences between the biosimilar and the reference product.[357] Courts will likely find that reasonable patients who proactively research on the Internet and read the content provided by a biologics manufacturer can fully understand the message, without being deceived, and have educated conversations with their healthcare professionals.

Amgen's YouTube video "[i]ntended to explain the importance of naming conventions and identifiers for biosimilars, stating, '. . . a switch. This carries risks, given that no two biologic medicines are identical, and thus can behave differently in the body. Switching drugs is not a good idea if your medicine is working for you."[358] Pfizer acknowledged the statement was made in the broader context of avoiding an inadvertent switch at the pharmacy-level from a biologic product to a biosimilar.[359] To show that this message contains misrepresentations, FTC would likely have to argue that switching patients between a biologic product and a non-interchangeable biosimilar does not carry risks or that switching drugs is a good idea even if the medicine is working for the patient. Despite the assurances that FDA's review process provides to ensure that a biosimilar is as safe and effective as the reference biologics, only an interchangeable biosimilar would have demonstrated it is capable of producing the same clinical effect on every patient. Amgen hangs on the concept of interchangeability to state that a given patient may have a different effect and on the well-documented concern that treatment switches can trigger immunogenicity responses, especially in complex cases. Thus, Amgen's statements would likely not be considered false and are supported by reasonable evidence. A more difficult question here is whether the message may mislead reasonable patients by omitting that there are no clinically meaningful differences between a reference biologic and its biosimilar. This finding will depend on disclaimers and the video's net impression.[360]

Amgen's Tweet: "Biologics or biosimilars? It's not just apples to apples. While #biosimilars may be highly similar to their #biologic reference products, there's still a chance that patients may react differently. See what you're missing without the suffix: http://bit.ly/2G2zGTa."[361] Amgen would likely show that it has a reasonable basis to support a claim that biosimilars and biologics are not the same, despite being highly similar. However, the Tweet appears to omit that there are no meaningful clinical differences between the biologics and biosimilars. Also, stating that "it's not just

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[356] REQUEST THAT THE FDA ISSUE GUIDANCE TO ENSURE TRUTHFUL AND NON-MISLEADING COMMUNICATIONS BY SPONSORS CONCERNING THE SAFETY AND EFFECTIVENESS OF BIOSIMILARS, INCLUDING INTERCHANGEABLE BIOLOGICS, RELATIVE TO REFERENCE PRODUCT(S), REGULATIONS, https://www.regulations.gov/docket/FDA-2018-P-3281/document [https://perma.cc/2ZMM-FSJP] [hereinafter REQUEST THAT THE FDA ISSUE GUIDANCE].

[357] *Id.*

[358] *Id.*

[359] *Id.* at 8.

[360] The video is no longer available through the source Pfizer provided.

[361] REQUEST THAT THE FDA ISSUE GUIDANCE, *supra* note 356.

apples to apples," without better qualifiers, likely produces a net impression to reasonable patients that biosimilars are less effective or safe, and would likely be deemed misleading.[362]

In summary, FTC would likely seek to classify all three examples of communication as advertisements and commercial speech. Genentech may have a chance to successfully negate a finding that its statements are misleading, and Amgen a narrower one. Nevertheless, manufacturers likely have a reasonable basis to support truthful claims that: 1) a biosimilar is not identical to a biologic; 2) no biosimilar has demonstrated that there will not be a difference in clinical effect if multiple switches occur; and 3) that patients with more delicate treatment balance are encouraged to speak with their treating physicians. Critical here is the presence of disclaimers when needed. FTC should not deem misleading on its face the statement that a biosimilar is not "interchangeable" under the rationale that most reasonable consumers "might interpret that to mean that an approved biosimilar could not be prescribed in place of the reference product."[363] The FDCA differentiates biosimilars from interchangeables and establishes a higher standard of proof for the latter, as discussed.[364] The claim is truthful and should not be deemed misleading simply because it highlights that difference.

V. CONCLUSION

This Article concludes that no legal basis exists for FDA to apply the truthful and not misleading standard under the FDCA to communications on the "nature and properties" of biosimilars, where the communication does not reference a specific drug. The FDCA's misbranding provision does not apply in this case and any regulation or final guidance document should be limited to assessing product claims. The existing FDA draft guidance document on biosimilarity messaging is consistent with this finding, and FDA should not go beyond that, because it risks running afoul of FDCA's authority. In fact, the draft guidance on biosimilarity messaging guides manufacturers on both sides to ensure their product promotion does not go beyond what a finding of biosimilarity entails.[365] For example, it clarifies that there can be no superiority claim to one another without the appropriate evidence.[366] It also explains that the finding of biosimilarity does not justify a promotional claim that the biosimilar and reference products are identical.[367] FDA is the most important agency in protecting the public from potential harm that misbranded, ineffective, unsafe, and adulterated products can bring. However, the agency is not a guardian against every potentially misleading communication and cannot innovate to regulate speech beyond product-specific promotion and for extraneous purposes not stated in the FDCA. As much as FDA cannot force disclosure of product pricing, it cannot push private stakeholders to

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[362] The Tweet and link are no longer available.

[363] U.S. FOOD & DRUG ADMIN., PUBLIC WORKSHOP: FDA/FTC WORKSHOP ON A COMPETITIVE MARKETPLACE FOR BIOSIMILARS (Mar. 9, 2020), https://www.fda.gov/drugs/news-events-human-drugs/public-workshop-fdaftc-workshop-competitive-marketplace-biosimilars-03092020-03092020 [https://perma.cc/7N34-N53F].

[364] 42 U.S.C. § 262(k).

[365] FDA, GUIDANCE ON PROMOTIONAL LABELING AND ADVERTISING, *supra* note 6.

[366] *Id.*

[367] *Id.*

convey messages that support biosimilars' market uptake. Pfizer's request for issuance of guidance establishing standards for truthful and not misleading communication on the "nature and properties" of biosimilars cannot be fulfilled. As such, FDA does well by not venturing into that space and opening the door for distraction and judicial challenge that can undermine its regulatory power.

Secondly, while FTC may successfully require additional disclosures in commercial advertisements, whether employing resources on this front would yield the best results for patients is debatable.

Education on biological medical products and biosimilars remains needed. It is natural that some physicians treating life-threatening or debilitating diseases may still resist switching patients to biosimilars. Such resistance is primarily due to a lack of clinical experience and evidence, and likely not because biologics manufacturers deceive patients and healthcare professionals.

Biosimilars are a yet unfulfilled promise of lower drug prices in the United States, but the most recent market data suggests biosimilars are heading in that direction. The recent approval of the first two interchangeable biosimilars in the United States could be a significant turning point. Also, the Advancing Education on Biosimilars Act of 2021 will likely allow FDA to direct more funds to develop meaningful educational content that will help turn the table. Still, multiple complex barriers permeate the U.S. healthcare system and require strategic planning and better regulation in other spaces. Spending valuable FDA and FTC resources to shape commercial speech around biologics and biosimilars in the battle for market share will likely yield little value to the healthcare system and patients at this point. In addition to future FDA education fostering biosimilars, manufacturers have their own cause of action against false advertisement and commercial disparagement, and should seek remedy themselves, where they feel a strong case exists.

Moreover, major players in the biologics space have already changed their communication approach about biosimilars. Amgen is perhaps the best example to illustrate this change. The biosimilarity messaging that Pfizer alleged was misleading cannot be found online any longer. In fact, today Amgen maintains multiple campaigns online to highlight its capacity to innovate and manufacture both biologics and biosimilars better than others. Amgen currently seeks to differentiate itself from any competitor, biologics or biosimilars manufacturer, based on its advanced manufacturing technology and quality control. But Amgen has not needlessly disclaimed in its communication that other manufacturers have also successfully obtained FDA approval to produce drugs and biologics. Would FTC conclude that Amgen's new campaign also deceives reasonable patients? Excessive consumer paternalism can lead to important inefficiencies in the search for truth and stresses the perils of improperly abridging free speech, even when commercial in nature. More likely, most reasonable American patients undergoing a complex biologics treatment are used to and capable of weighing truthful commercial claims appropriately and are not typically deceived by general statements, especially where advertisement calls for patients to consult with their doctors.

Highlighting that a biosimilar is not identical and may not have the same clinical effect in any patient is consistent with the interchangeability requirement, which, so far, only two biosimilars have achieved in the United States. On its face, such messaging can hardly be perceived as deceptive especially where it calls for potential patients to discuss options with their healthcare professionals. Rather, it is educational, constitutionally protected, and salutary speech.

Market participants are well-established, monitor each other for anti-competitive and deceptive practices, and are entitled to their day in court when proper. Conversely, FDA and FTC would likely make the best use of their resources by addressing more critical market barriers to biosimilars, including eliminating anti-competitive price behavior and fostering interchangeability studies, to name two.