MINTZ

Guide to Advertising for Life Sciences Companies: Insights from Legal and Business Perspectives

November 10, 2022

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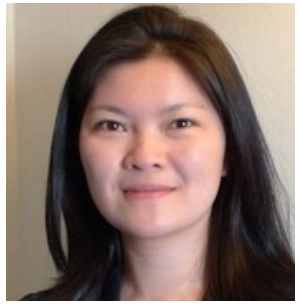
a wholly owned subsidiary of Bristol Myers Squibb Company



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Roadmap

- FDA Legal Framework
- FTC Legal Requirements
- Lanham Act – False Advertising
- Enforcement Examples
- Helpful Resources

Overview of FDA Legal Framework

FDA Promotion & Advertising Rules

Objective: Protect and advance the public health

The Federal Food, Drug, and Cosmetic Act (FD&C Act) prohibits, *for all product categories*:

- False or misleading *labels* or *labeling*
  - The label is any text or figure on the container (bottle, box, wrapper, etc.) that the product is in, which is usually the retail packaging
  - Labeling is a much more inclusive term, encompassing the "label" and any other printed material that either comes with the product (e.g., the package insert) or that is associated with the product (e.g., the product website)

Key Concepts to Keep In Mind

- FDA will consider a company – manufacturer or distributor – responsible for materials intended to sell its products, when such materials:
  - It has direct ownership or control over (e.g., website)
  - It directs another party to create and/or disseminate on its behalf
  - Are presented by speakers paid by the company, whether in public or private venues
- Always evaluate “the message,” not “the medium”
  - FDA’s requirements apply equally regardless of the medium of communication (e.g., social media platforms and other digital content vs. traditional paper-based materials)
  - Same rule applies when evaluating advertisements under the FTC’s framework

Prohibition on Pre-approval Promotion

Objective: (i) precluding commercialization of an unapproved product; and (ii) preventing potential customers from developing unsubstantiated beliefs about the product/technology's safety or effectiveness

> **21 C.F.R. § 312.7(a):** "*Promotion of an investigational new drug.* A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, **shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation** or otherwise promote the drug. This provision is **not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media**. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution."

**Comparable restriction for investigational devices found at 21 C.F.R. §812.7*

Promotional Labeling vs. Advertisements

- An **advertisement** is printed, graphic, or even spoken communications intended to help sell a drug or device and generally appear in print periodicals (journals, magazines, and newspapers) and broadcast media (television and radio).

- **Promotional labeling** is any written, printed, graphic, or even spoken communication that mentions or alludes to a drug or device and that is used to help sell such products. This definition encompasses **advertisements as well as additional types** of materials and distribution methods to consumers, e.g.:
  - *Brochures, booklets, mailings (both hard copy and e-blasts)*
  - *Websites, social media, or online videos that describe the product and its uses*
  - *Pens, magnets, cups, and other swag that display the product's name*
  - *Communications to payors regarding health care economic information*

FD&C Act Misbranding Provisions

- Section 502(a) of the Act (21 U.S.C. § 352(a)) establishes that a "drug or device shall be deemed to be misbranded. . . [i]f its labeling is false or misleading ***in any particular***." (emphasis added)
- Such particulars can include that:
  - The labeling fails to reveal material facts
  - The labeling omits or minimizes risk information or overstates the efficacy of the drug
  - The labeling lacks adequate directions for all "intended uses"
  - Claims are not adequately substantiated. . . among others!

Section 502(n) also sets baseline requirements for Prescription Drug Advertisements, which FDA has expanded upon via regulations. For Restricted Medical Devices, Section 502(q) expressly prohibits restricted device "advertising [that] is false or misleading in any particular" and Section 502(r) creates requirements for certain affirmative disclosures for such device ads that are similar to Rx drugs; however there are no parallel implementing regulations for restricted medical device advertisements. Many FDA policies/guidances apply to both classes of products even when not provided for in the statute (e.g., Health Care Economic Information safe harbor in 502(a)(1)).

21 C.F.R. §202.1 "Prescription-drug advertisements"

- FD&C Act does not define "advertisement" but these implementing regulations provide context
- Key requirements for ads and other promotional materials:
  - Required Information/Required Accompanying Information
    - Established name; quantitative ingredient list; at least on dosage form
    - Brief summary re. "side effects, contraindications, and effectiveness" (Reminder Ads exempt)
    - Full indication (if any benefit or other claims are made)
    - Prescribing information may be needed in some cases
  - Fair Balance "between information relating to side effects and contraindications and information relating to effectiveness of the drug" (Reminder Ads exempt)
  - Examples of "false, lacking in fair balance, or otherwise misleading" practices are in § 202.1 (*e.g.,* a drug comparison representing/suggesting that a drug is safer or more effective than another drug in some particular aspect when it hasn't been demonstrated as such by substantial evidence or substantial clinical experience)

Risk-Benefit Information / Fair Balance

- FDA requires manufacturers to describe the risks of using a medical product in comparable prominence, scope, depth, and detail as the product's therapeutic benefits.
  - E.g. The "major statement" in television advertisements for prescription drugs
- Attaching or linking to a brief summary of the risks to the package insert information does not automatically satisfy the Fair Balance requirement.
  - Risks must be described in the same manner and extent as the benefits
  - Risk info must accompany benefits info wherever they appear in promotional labeling (e.g., fine print statement of risks at the bottom of a website is not fair balance to prominent statement of benefits at the top)
  - The "net impression" of the promotional labeling must equally present benefits and risks

For a detailed discussion, see FDA's 2009 draft guidance, *Presenting Risk Information in Prescription Drug and Medical Device Promotion*

Substantiation Differs Based on Type of Claim

- All promotional claims about the safety or efficacy must be supported by ***Substantial Scientific Evidence***.
  - For almost all drugs, such evidence is in the form of two adequate and well-controlled clinical trials
  - 21 C.F.R. §314.126 describes the essential characteristics of adequate and well-controlled trials for prescription drugs
  - FDA's December 2019 revised draft guidance on substantial evidence is also important and discusses exceptions from the general rule
- Comparisons to other drug/device products typically must be supported with head-to-head clinical studies.

Substantiation Differs Based on Type of Claim

- "Health Care Economic Information" (HCEI) = substantiation standard is ***Competent and Reliable Scientific Evidence*** (see June 2018 final guidance)
  - HCEI is defined in Section 502(a) of the Act as "any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug."
- Claims that are "consistent with the FDA-required labeling" (CFL) = substantiation standard is ***Scientifically Appropriate and Statistically Sound*** (see June 2018 final guidance)
  - In addition, "To be considered truthful and non-misleading, firms' product communications should not overstate the findings of or the conclusions that can be drawn from such studies or analyses, or fail to disclose their material limitations."

Common Risk Areas / Keep a Lookout For:

Presentation of Risk Information & Safety Claims are always important to review closely!	
Abbreviation of Indication	Clinical Practice Guidelines / Third-Party Links
Absence of Context / Selective Presentation of Data	Patient Case Studies
Pre-Clinical Data	Duration of Use Claims
Convenience Claims	Quality of Life (QOL) Claims
Compliance / Adherence Claims	Cost Claims
Investigational Products	MOA Selling / Symptom Selling
Imagery	Other Comparative Claims

FDA Social Media History

October 1996

Public meeting: Internet promotion

- Investigational use
- Chat rooms and newsgroups
- Website links
- General regulatory issues

November 2009

Public hearing: Internet promotion

- "General concept of Internet promotion"
- "Any aspect of Internet promotion that is of interest"

December 2010

CDER statement: Guidance topics

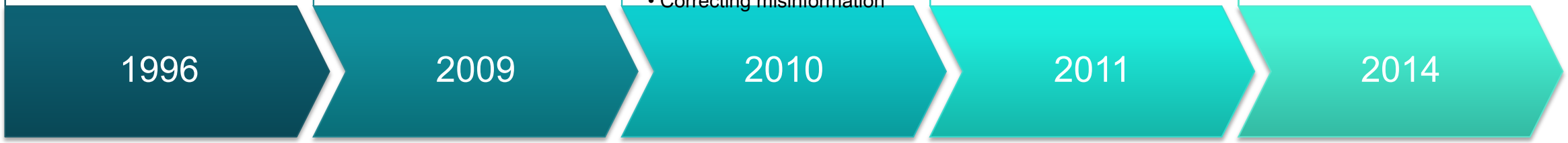
- Responding to unsolicited requests
- Fulfilling regulatory requirements when using tools with space limitations
- Fulfilling postmarketing submission requirements
- Online communications for which manufacturers, packers, or distributors are accountable
- Use of links
- Correcting misinformation

December 2011

- Draft guidance for responding to unsolicited requests

January & June 2014

- 3 new draft social media guidances



Adapted from: Bañuelos - FDA's Evolving Approach to Testimonials, Endorsements, and Influencer Marketing; DIA Advertising & Promotion Conference; March 8, 2021

FDA Social Media Guidance

- Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices – June 2014
- Internet/Social Media Platforms with Character Space Limitations— Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices – June 2014
- Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics – January 2014
- Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices – December 2011 (includes examples of *online requests* and how to respond)
- Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers; Guidance for Industry – June 2018 (the "CFL Guidance")

All posted on OPDP's Regulatory Information page:
https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm109905.htm

Selected OPDP Research Projects

Completed

- **Interactive Advertising Literature Review (Completed in 2022)**
- **Web and Mobile Technology DTC Content Analyses (Completed in 2017)**
- **Examination of Online DTC Drug Promotion (Completed in 2016)**

Pending

- **Character-Space-Limited Online Prescription Drug Communications**

In Progress

- **Endorser Status and Explicitness of Payment in Direct-to-Consumer Promotion**
  - Examining 4 types of endorsers in 2 separate studies (celebrity, physician, patient, influencer)
  - Examining whether the presence of a disclosure of their payment status influences participant reactions

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-prescription-drug-promotion-opdp-research

Overview of FTC Requirements

FTC Advertising Rules

Objective: Police deceptive advertising claims

- Section 5 of the FTC Act (15 U.S.C. § 45): **"Unfair methods of competition in or affecting commerce, and unfair or deceptive acts or practices in or affecting commerce, are hereby declared unlawful."**
  - Section 5 does not just prohibit outright lies by advertisers; it covers both explicit and implicit claims and any ad that has the *capacity to deceive* the public, even if no one was *actually* deceived.
  - Section 12(a) prohibits false advertisements ("misleading in a material respect," per Section 15) that are likely to induce the purchase of food, cosmetics, drugs, or devices

“Unfair or Deceptive Acts” Under Section 5

- Does the ad contain a representation or omission that is likely to mislead the consumer?
- From perspective of a reasonable consumer
- Representation/omission/practice must be “material” = likely to affect the consumer’s conduct or decision with regard to a product or service
  - Express claims generally are presumed to be material
  - In other cases, evidence of consumers’ expectations may be needed (i.e., implied claims).

Basic test is whether the NET impression of the ad, taken as a whole, is false or misleading.

“Unfair” Advertisements or Trade Practices

- Whether or not “deceptive,” an advertisement or trade practice may be unfair if it:
  - Causes or is likely to cause substantial consumer injury;
  - Is not reasonably avoidable by consumers themselves; and
  - Is not outweighed by countervailing benefits to consumers or competition.

Examples of “Deceptive” Practices

- ***Comparative claims when two products actually have no meaningful difference*** (i.e. consumers must actually benefit from a discernible difference).
  - Not specifying exact product involved in the comparison claim will be presumed to be a comparison to ***all*** competing products on the market.
- ***Exaggerated statements that are not merely “puffery”*** (puffery: claim that no ordinary consumer would take seriously or understand as being actual facts).
- ***Marketing presented in “native advertising” or “sponsored content” format without clearly disclosing to consumers that it is commercial content.***
- ***Representations that are not substantiated*** when consumers are made to believe that they are, based on explicit statements in the ad or its net impression.
- ***Endorsements or testimonials with insufficient disclosure***

FTC Advertising Substantiation Principles

- Substantiation requires reasonable basis for claims ***before*** dissemination.
- An advertiser must have ***at least*** the amount of substantiation expressly or implicitly claimed in the ad. (E.g. “tests prove”; “doctors recommend”; “studies show”)
- Degree of substantiation required is directly related to the question of what exactly the claims are – how to interpret express vs. implied representations.
  - Compare soft/general claim that lipstick “won’t come off until you want it to” to the more specific/hard claim that the lipstick “looks fresh hour after hour” (they are both color retention claims, but with very different substantiation requirements).
- Implied claims for which the advertiser is expected to have prior substantiation are only those that are reasonable interpretations (i.e. advertiser won’t be held responsible for “outlandish” or “tenuous” interpretations).

Competent and Reliable Scientific Evidence

- Health and safety claims require a high level of substantiation = “Competent and Reliable Scientific Evidence”
  - “Tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that has been conducted or evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the relevant field to yield accurate and reliable results.”
- Tests and surveys must be methodologically sound and be conducted on the product itself (or an essentially equivalent product), and relevant to the actual and ordinary use of the product.
- Ads must accurately reflect test results.

The bigger the claim, the better the testing has to be and the more tests you need to have.

Disclosures/Qualified Claims

- Disclosures must be “clear and conspicuous” (i.e. fine print disclosures won’t correct a misleading representation).
- 3P’s of disclosure = ***Prominence, Placement, Proximity***
- “Deception is unlawful no matter what medium.”
- **Disclosure cannot “cure” a blatantly false claim.**
- FTC orders may require an advertiser to cease and desist disseminating a certain claim, unless affirmative disclosures or qualified statements are included when such statements would prevent consumer deception.

FTC Polices Endorsements and Social Media as Advertising

- Follow FTC *Guides Concerning the Use of Endorsements and Testimonials in Advertising*, otherwise these types of ads are at risk of being deemed deceptive.
  - Originally issued in 1975 but amended several times, including most recently in 2009 to clarify application to social media, with additional FAQs released in May 2015 and September 2017.
  - In February 2020, FTC solicited public comments on whether to make changes to its *Endorsement Guides* as part of the agency's systematic review of current rules and guides.
  - In May 2022, the Commission released proposed updates to the *Endorsement Guides* that "reflect the extent to which advertisers have turned increasingly to the use of social media and product reviews to market their products," as articulated in the May 19th press release.

FTC announcement: https://www.ftc.gov/news-events/news/press-releases/2022/05/ftc-proposes-strengthen-advertising-guidelines-against-fake-manipulated-reviews

Request for comments on proposed changes: https://www.federalregister.gov/documents/2022/07/26/2022-12327/guides-concerning-the-use-of-endorsements-and-testimonials-in-advertising (comment period has closed)

Properly Using Endorsements and Social Media

- FTC's *Endorsement and Testimonial Guides* require, among other things:
  - That the person endorsing a product be an actual user and that their endorsement be honest, bona fide, and reflect their actual views;
  - That appropriate disclosures be made, in a clear and conspicuous way, about the connections between the endorser and the sponsoring advertiser (#ad or #sponsored);
  - That the experience of the endorser be "typical" for the product in question, otherwise it must be accompanied by a clear disclosure about what results should be expected; and
  - That any endorser held out as an expert must be qualified as such and their endorsement is supported by actual exercise of that expertise when evaluating the.
- Employees, company owners, shareholders, etc. always will be considered to have a material connection to the company and should disclose their relationship whenever endorsing the product.
- ***Endorsements/testimonials make claims that company could not make itself.*** A claim that is likely to be unsubstantiated if the company were to include it directly is also unsubstantiated if an endorser says it in content that is posted on company's website and becomes part of the ad.

Advertiser Obligations For Endorsements and Social Media

- Advertisers are responsible for adequately training and ensuring that all of their endorsers – whether consumers, celebrities, or experts – are in compliance with the *Endorsement Guides*. You should have policies and procedures in place to govern these activities.

- Companies also should be engaging formally with these individuals, though an Endorser Agreement or other contract, to ensure that they know their obligations to disclose the relationship, that they know what they can/cannot say about a product based on the advertiser's available substantiation, and that they promptly inform the advertiser if they cease using the product or otherwise no longer believe the statements made in their prior endorsement/testimonial.

- Advertisers are also responsible for monitoring the activities of their endorser network and should take action when, for example, unsubstantiated claims are being made about their products by a blogger with a material connection to the company.
  - Not responsible for statements made by completely independent people!
  - It does not matter if the person is a micro-blogger or a celebrity influencer – the principles contained in the *Endorsement Guides* apply to all of these arrangements.

Sampling of May 2022 Proposal to Update *Endorsement Guides*

- Definition of “endorser” will be expanded to include computer-generated influencers and those who fabricate reviews and endorsements; the act of tagging a brand in a social media post also will be expressly considered to be an endorsement
- Disclosures in advertisements targeting specific audiences would be evaluated through the lens of members of that group. FTC also plans to hold a virtual event in October 2022 to evaluate children’s capacity to understand online advertising and the efficacy of disclosures in advertising directed at children.
- New section of the *Guides* will be created to address consumer reviews, specifying that advertisers should not distort or misrepresent what their customers think of the products or services when presenting consumer reviews, and providing examples of practices that FTC considers to be misleading or unfair (e.g., deleting or not publishing negative reviews, buying fake reviews, “review gating”)

Sampling of May 2022 Proposal to Update *Endorsement Guides*

- Additional guidance will be given on material connections between advertisers and endorsers, and how those connections should be disclosed, including examples of relationships that could be considered material connections and where incentives are provided in exchange for reviews
- Clarifications regarding when advertisers, endorsers, intermediaries, and platforms can be held liable under the FTC Act for misleading endorsements
- Discussion of newer, built-in disclosure tools on social media platforms that endorsers may be able to use as part of their posts. This section is being added because some disclosure tools may be inadequate and may expose endorsers relying solely on those tools to potential liability for inadequate disclosures

FTC May Initiate Rulemaking Specific to Reviews

- In October 2022, FTC announced that it would be "exploring a potential rule to combat deceptive or unfair review and endorsement practices," and in November it published an ANPR and request for public comments in the Federal Register; comment period closes on **January 9, 2023**
- Commission is seeking information on the pervasiveness and potential harms to consumers and competition from certain clearly deceptive/unfair practices involving reviews and endorsements for any products or services in commerce (including Rx medical products). Some practices specifically called out in the ANPR include:
  - The use of fake reviews and fake review websites
  - Insider reviews (i.e., those written by a company's executives or solicited from its employees that don't mention their connections to the company)

FTC announcement: https://www.ftc.gov/news-events/news/press-releases/2022/10/ftc-explore-rulemaking-combat-fake-reviews-other-deceptive-endorsements

Advance Notice of Proposed Rulemaking: https://www.federalregister.gov/documents/2022/11/08/2022-24139/trade-regulation-rule-on-the-use-of-reviews-and-endorsements

Lanham Act – False Advertising

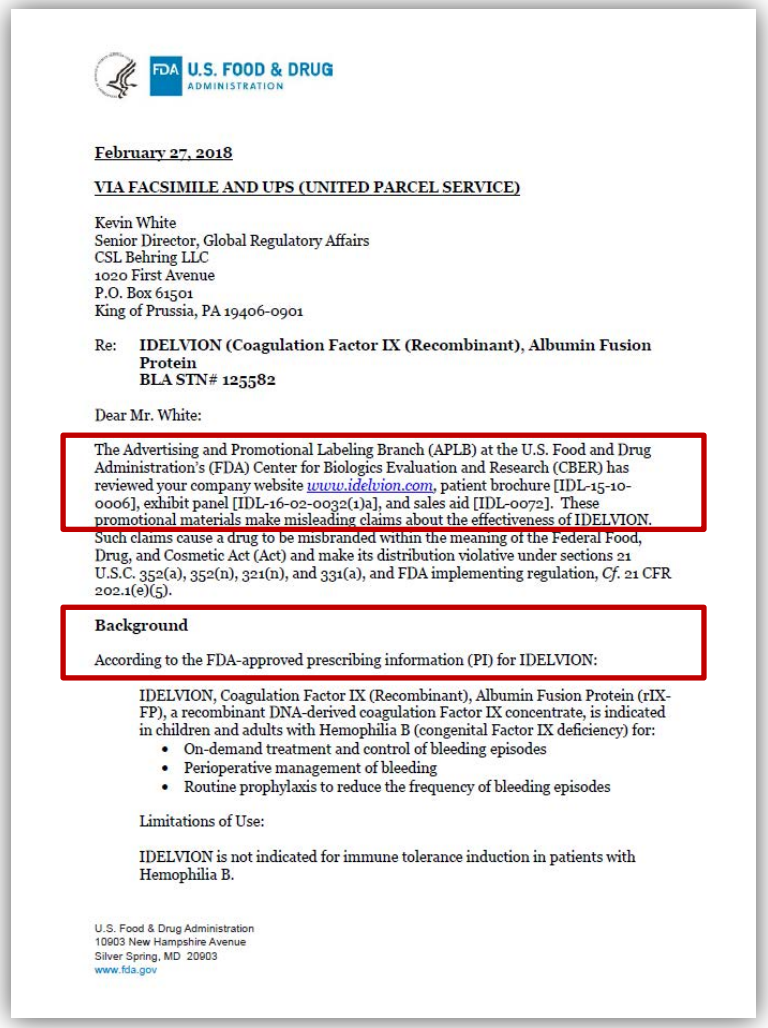
Private Cause of Action Under Lanham Act

- Provides for private cause of action by competitors
- To prevail on a false-advertising claim under the Lanham Act (41 U.S.C. § 1125(a)(1), “Section 43(a)”), plaintiff must show:
  - (1) a false or misleading statement of fact; that is
  - (2) used in a commercial advertisement or promotion; that
  - (3) deceives or is likely to deceive in a material way;
  - (4) in interstate commerce; and
  - (5) has caused or is likely to cause competitive or commercial injury to the plaintiffs.

Enforcement Examples

https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/February-27--2018-Untitled-Letter---IDELVION.PDF

IDELVION® Coagulation Factor IX (Recombinant) Untitled Letter



U.S. FOOD & DRUG ADMINISTRATION

February 27, 2018

VIA FACSIMILE AND UPS (UNITED PARCEL SERVICE)

Kevin White
Senior Director, Global Regulatory Affairs
CSL Behring LLC
1020 First Avenue
P.O. Box 61501
King of Prussia, PA 19406-0901

Re: **IDELVION (Coagulation Factor IX (Recombinant), Albumin Fusion Protein**
BLA STN# 125582

Dear Mr. White:

The Advertising and Promotional Labeling Branch (APLB) at the U.S. Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) has reviewed your company website *www.idelvion.com*, patient brochure [IDL-15-10-0006], exhibit panel [IDL-16-02-0032(1)a], and sales aid [IDL-0072]. These promotional materials make misleading claims about the effectiveness of IDELVION. Such claims cause a drug to be misbranded within the meaning of the Federal Food, Drug, and Cosmetic Act (Act) and make its distribution violative under sections 21 U.S.C. 352(a), 352(n), 321(n), and 331(a), and FDA implementing regulation, *Cf.* 21 CFR 202.1(e)(5).

Background

According to the FDA-approved prescribing information (PI) for IDELVION:

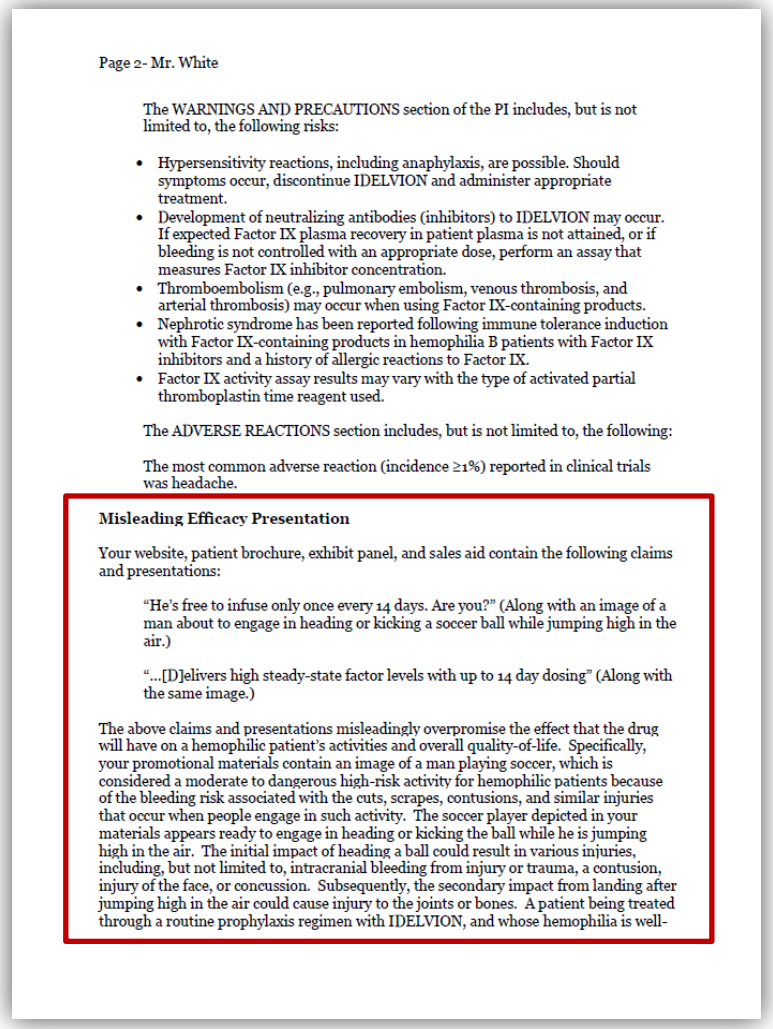
IDELVION, Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP), a recombinant DNA-derived coagulation Factor IX concentrate, is indicated in children and adults with Hemophilia B (congenital Factor IX deficiency) for:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding
- Routine prophylaxis to reduce the frequency of bleeding episodes

Limitations of Use:

IDELVION is not indicated for immune tolerance induction in patients with Hemophilia B.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903
www.fda.gov



Page 2- Mr. White

The WARNINGS AND PRECAUTIONS section of the PI includes, but is not limited to, the following risks:

- Hypersensitivity reactions, including anaphylaxis, are possible. Should symptoms occur, discontinue IDELVION and administer appropriate treatment.
- Development of neutralizing antibodies (inhibitors) to IDELVION may occur. If expected Factor IX plasma recovery in patient plasma is not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures Factor IX inhibitor concentration.
- Thromboembolism (e.g., pulmonary embolism, venous thrombosis, and arterial thrombosis) may occur when using Factor IX-containing products.
- Nephrotic syndrome has been reported following immune tolerance induction with Factor IX-containing products in hemophilia B patients with Factor IX inhibitors and a history of allergic reactions to Factor IX.
- Factor IX activity assay results may vary with the type of activated partial thromboplastin time reagent used.

The ADVERSE REACTIONS section includes, but is not limited to, the following:

The most common adverse reaction (incidence ≥1%) reported in clinical trials was headache.

Misleading Efficacy Presentation

Your website, patient brochure, exhibit panel, and sales aid contain the following claims and presentations:

"He's free to infuse only once every 14 days. Are you?" (Along with an image of a man about to engage in heading or kicking a soccer ball while jumping high in the air.)

"...[D]elivers high steady-state factor levels with up to 14 day dosing" (Along with the same image.)

The above claims and presentations misleadingly overpromise the effect that the drug will have on a hemophilic patient's activities and overall quality-of-life. Specifically, your promotional materials contain an image of a man playing soccer, which is considered a moderate to dangerous high-risk activity for hemophilic patients because of the bleeding risk associated with the cuts, scrapes, contusions, and similar injuries that occur when people engage in such activity. The soccer player depicted in your materials appears ready to engage in heading or kicking the ball while he is jumping high in the air. The initial impact of heading a ball could result in various injuries, including, but not limited to, intracranial bleeding from injury or trauma, a contusion, injury of the face, or concussion. Subsequently, the secondary impact from landing after jumping high in the air could cause injury to the joints or bones. A patient being treated through a routine prophylaxis regimen with IDELVION, and whose hemophilia is well-

IDELVION® Coagulation Factor IX (Recombinant) Untitled Letter (continued)

controlled, will nevertheless still have a serious risk for bleeding while engaging in such activities.

In patients with hemophilia, once bleeding occurs, bleeding is prolonged, and such patients may experience bleeding even weeks after an injury. Persistent joint or muscle bleeding can lead to decreased mobility and function, or even permanent disability for these patients. Furthermore, one of the most serious types of bleeding that can occur within the body is intracranial bleeding from injury or trauma, possibly leading to strokes, which can threaten life, limb, and overall function. Without early recognition and treatment of a serious intracranial bleed, severe neurologic impairment or death can occur.

Overall, your claims and presentations misleadingly imply that hemophiliacs taking your product can engage in moderate to dangerous high-risk activity without consequences and that such activities are appropriate for typical patients with hemophilia using this product.

Conclusion and Requested Actions

For the reasons discussed above, your promotional materials misbrand IDELVION within the meaning of the Act and make its distribution violative under sections 21 U.S.C. 352(a), 352(n), 321(n), and 331(a), and FDA implementing regulation, *Cf.* 21 CFR 202.1(e)(5).

We request that CSL Behring immediately cease the dissemination of these promotional materials for IDELVION, as well as promotional materials with the same or similar claims and presentations. Please submit a written response within ten (10) business days of the date of this letter, stating whether you intend to comply with this request, listing all potentially violative promotional materials for IDELVION, and explaining your plan for discontinuing use of such materials.

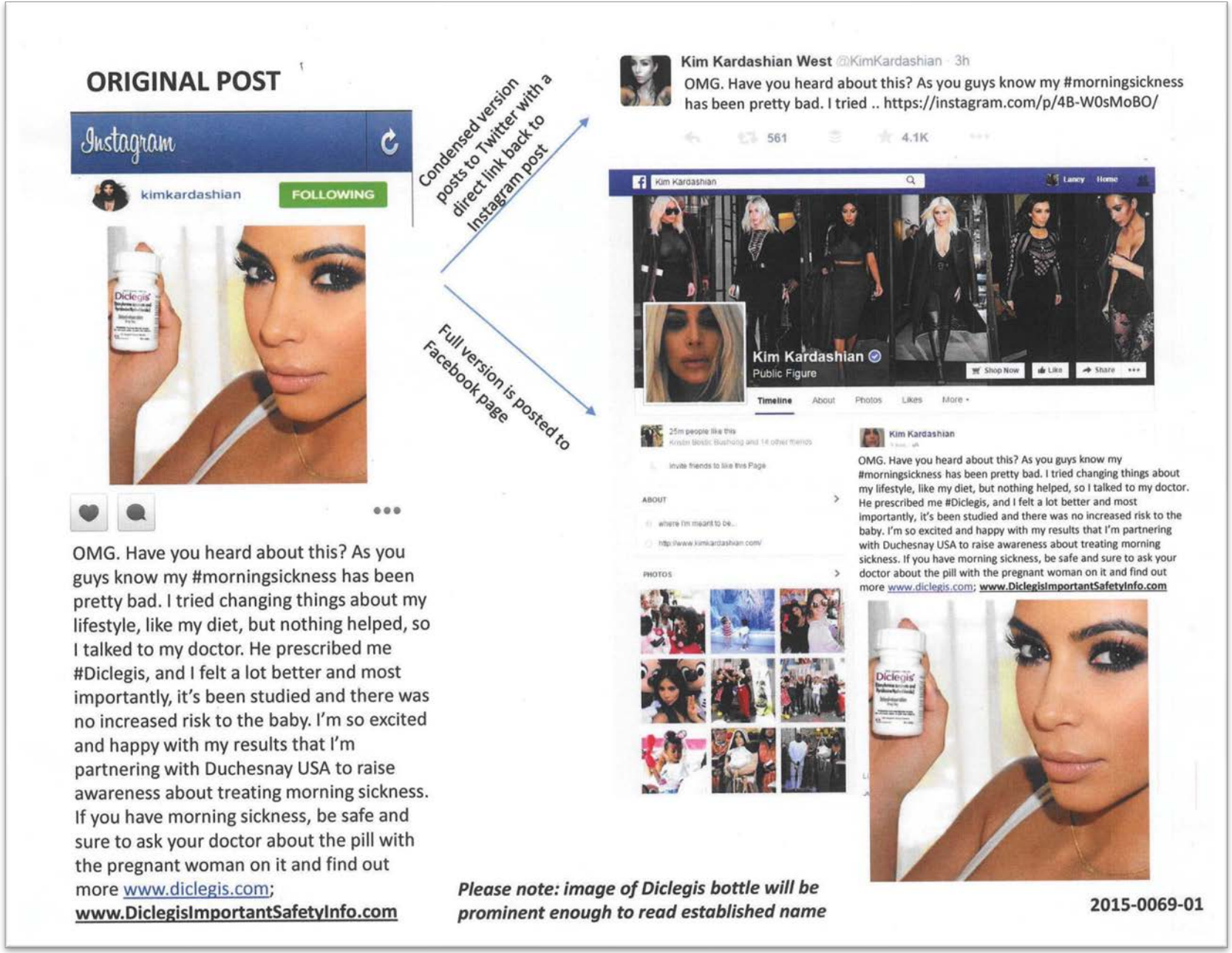
Please direct your response to Lisa Stockbridge, Ph.D., Branch Chief at the Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Compliance and Biologics Quality, Division of Case Management, Advertising and Promotional Labeling Branch, 10903 New Hampshire Ave., WO71-G112, Silver Spring, MD 20993-0002. In all future correspondence regarding this matter, please refer to the BLA/STN number. We remind you that only written communications are considered official responses.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for IDELVION comply with each applicable requirement of the Act and FDA implementing regulations.

If you choose to revise your promotional materials, APLB is willing to assist you in assuring that your revised materials comply with applicable provisions of the Act by reviewing your revisions before you use them in promotion.

Sincerely,

Robert A. Sausville
Director, Division of Case Management
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research



Letter: https://pink.pharmaintelligence.informa.com/-/media/pmbi-old-site/supporting-documents/the-pink-sheet-daily/2015/august/duchesnay-warning-letter-08-07-2015.pdf ; Promo: N/A

Enforcement Options

- When FDA determines that a product is misbranded or adulterated, it can:
  - Issue Warning Letters or Untitled Letters;
  - Require the product to be recalled;
  - Impose civil money penalties;
  - Seize the violative product;
  - Seek an injunction to prevent the company from operating;
  - Require companies to enter into consent decrees regarding future behavior; and
  - Criminally prosecute offenders.

Warning vs. Untitled Letter

Warning Letter

- Clearly titled: “WARNING LETTER”
- Addressed to highest known official in company, sent overnight by trackable method
- Establishes a response period
- Cites the section of the law and, where applicable, the regulation violated
- Describes the violative condition, practice, or product in brief but sufficient detail to provide the respondent the opportunity to take corrective action
- Issued for violations of regulatory significance that may lead to enforcement action if not promptly and adequately corrected.

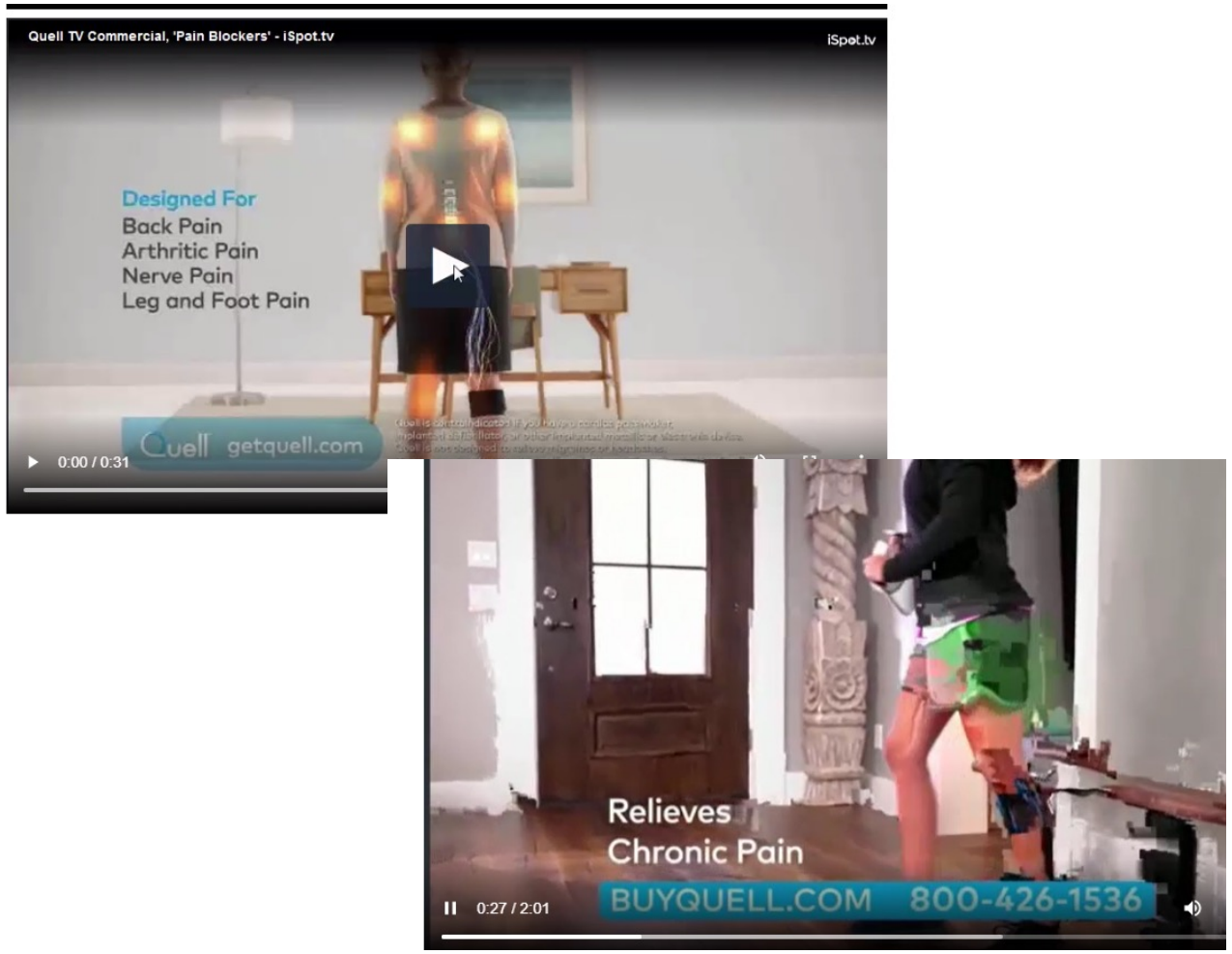
Untitled Letter

- Addressed to the RA lead
- Serves as an initial notification to firms that FDA is aware of their violations of federal law
- Cites violations that do not meet the threshold of regulatory significance for a Warning Letter
- Often serves to document formal notification by FDA to the person or firm
- Requests, rather than requires a response

Typical Structure of OPDP & APLB Letters

- Introduction paragraph
- Background
  - Indication, limitation of use (if applicable)
  - Boxed Warning (if applicable)
  - Safety Information
    - Any relevant warnings, precautions, or contraindications
- Prior Communication?
- List Violations
  - Overstatement of Efficacy
  - Omission and/or Minimization of Risk
  - False and/or Misleading Risk and/or Benefit Presentation
  - Unsubstantiated Effectiveness/Superiority Claims
  - Misleading Product/Safety Claims
  - Failure to Reveal Material Facts
  - Broadening of Indication/Promotion of Unapproved Use
  - Promotion of an Investigational New Drug
  - Failure to Submit under Form FDA 2253
  - Lack of Adequate Directions for Use
  - Use of Outdated Product Labeling
- Conclusion and Requested Action

Transcutaneous Electrical Nerve Stimulation Device (TENS) – Quell and Quell 2.0



ANNOUNCER: Reclaim your life from chronic pain . . .

ON SCREEN: Quell 2.0 Wearable Pain Relief Technology

[*Video depicts Quell device and packaging*].

ANNOUNCER: with Quell 2.0.

ON SCREEN: 100% Drug-Free
FDA Cleared

Quell 2.0 BUYQUELL.COM

[*Video depicts a woman in athletic attire attaching Quell 2.0 to her lower left leg, below the knee, and then getting up to go outside*].

ANNOUNCER: Quell is 100% drug free and FDA cleared.

ON SCREEN: Designed for People with a Wide Range of Chronic Pain Conditions

Quell 2.0 BUYQUELL.COM

ANNOUNCER: It's designed for people with a wide range of chronic pain conditions.

ON SCREEN: [*Animation depicts a Quell 2.0 wrapping around a woman's right lower leg, below the knee, then sending electrical pulses up the leg and into the central nervous system*].

Dramatization of Quell mode of action. * * * [small print, bottom of screen].

ANNOUNCER: Worn just below the knee, the Quell technology accesses the central nervous system.

https://www.ftc.gov/legal-library/browse/cases-proceedings/172-3130-neurometrix-inc

March 2020 settlement announcement - *FTC v. NeuroMetrix*

- TENS device was FDA-cleared for the symptomatic relief and management of chronic intractable pain.

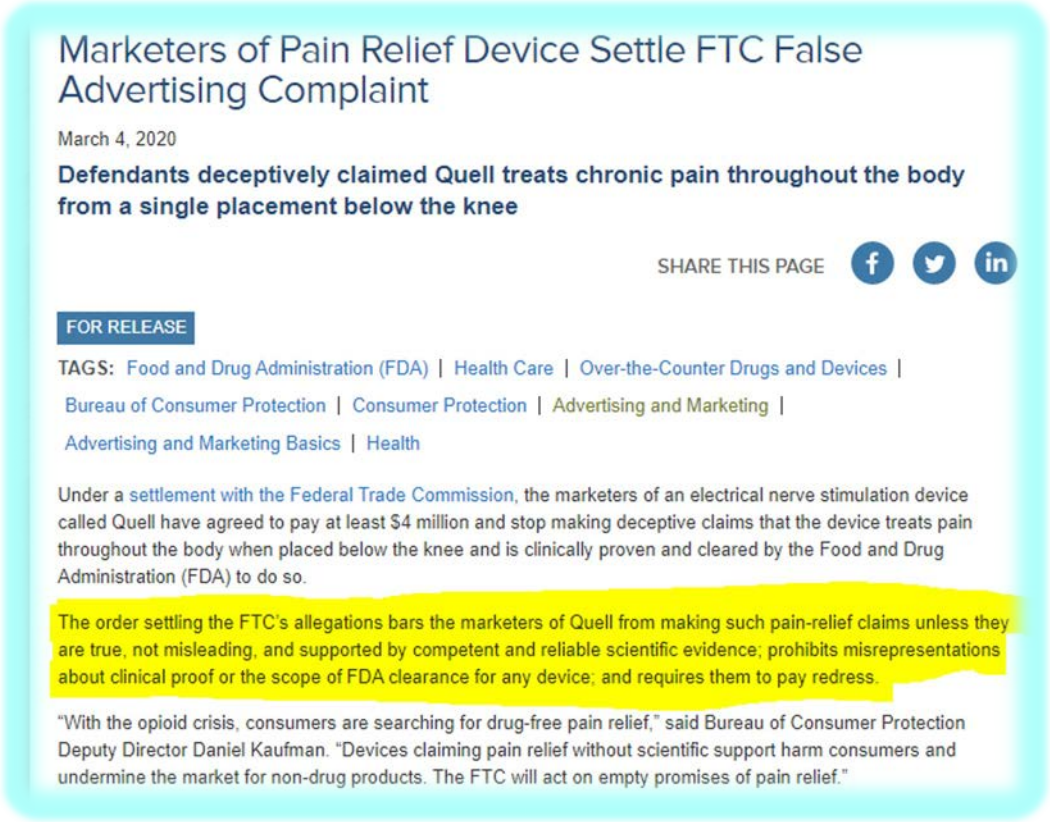
- Complaint alleges that the Device's 510(k) did not include "clinical testing demonstrating its safety or efficacy" and that the Company and its CEO made claims about clinical effectiveness that were not supported by CARSE.

- Per the Complaint: "Advertising claims for Quell were not substantiated and went beyond claims the FDA allowed for similar devices…" such as claims about "widespread chronic pain relief."

March 2020 settlement announcement - *FTC v. NeuroMetrix*

- Settlement provided that NeuroMetrix and its CEO would pay $4 million to the FTC for consumer refunds and would stop making the allegedly deceptive claims, and ongoing compliance reporting requirements were put in place for 10 years.

This case is an important reminder that FDA clearance/approval does not eliminate separate legal requirements to comply with the FTC Act!



Marketers of Pain Relief Device Settle FTC False Advertising Complaint

March 4, 2020

Defendants deceptively claimed Quell treats chronic pain throughout the body from a single placement below the knee

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FOR RELEASE

TAGS: Food and Drug Administration (FDA) | Health Care | Over-the-Counter Drugs and Devices | Bureau of Consumer Protection | Consumer Protection | Advertising and Marketing | Advertising and Marketing Basics | Health

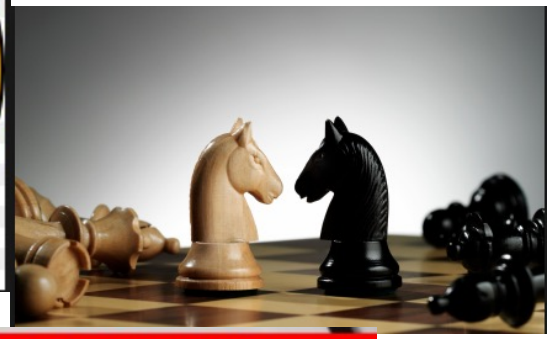
Under a settlement with the Federal Trade Commission, the marketers of an electrical nerve stimulation device called Quell have agreed to pay at least $4 million and stop making deceptive claims that the device treats pain throughout the body when placed below the knee and is clinically proven and cleared by the Food and Drug Administration (FDA) to do so.

The order settling the FTC's allegations bars the marketers of Quell from making such pain-relief claims unless they are true, not misleading, and supported by competent and reliable scientific evidence; prohibits misrepresentations about clinical proof or the scope of FDA clearance for any device; and requires them to pay redress.

"With the opioid crisis, consumers are searching for drug-free pain relief," said Bureau of Consumer Protection Deputy Director Daniel Kaufman. "Devices claiming pain relief without scientific support harm consumers and undermine the market for non-drug products. The FTC will act on empty promises of pain relief."

Other Implications

- Bad publicity
- Whistleblower complaints
- Product liability
- State prosecution
- Fraud and abuse prosecution
  - Including False Claims Act, Anti-Kickback, etc.
- Loss of good reputation in the medical and patient communities
- Other regulatory agencies (e.g. SEC, State Ags)
- Competitor challenges (e.g., Lanham Act, NAD)
- Individual liability



Helpful Resources

Helpful Resources

- Understanding the Influence of Prescription Drug Advertising - https://www.fda.gov/drugs/news-events-human-drugs/understanding-influence-prescription-drug-advertising
- Marketing or Medicine – 2008 Senate Hearings – History of Advertising and Promotion https://www.govinfo.gov/content/pkg/CHRG-110shrg49768/html/CHRG-110shrg49768.htm
- OPDP Regulatory Information – Laws, Regulations, Guidances, and Compliance Actions – https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/opdp-regulatory-information

Helpful Resources

- Prescription Drug Advertising - https://www.fda.gov/drugs/information-consumers-and-patients-drugs/prescription-drug-advertising
  - Background on Drug Advertising - https://www.fda.gov/drugs/prescription-drug-advertising/background-drug-advertising
  - Basics of Drug Ads - https://www.fda.gov/drugs/prescription-drug-advertising/basics-drug-ads
  - Prescription Drug Advertising Q&A - https://www.fda.gov/drugs/prescription-drug-advertising/prescription-drug-advertising-questions-and-answers
  - Sample Prescription Drug Advertisements - https://www.fda.gov/drugs/prescription-drug-advertising/sample-prescription-drug-advertisements

Helpful Resources

- Off-Label and Investigational Use - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/label-and-investigational-use-marketed-drugs-biologics-and-medical-devices
- Using Social Media - https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/industry-using-social-media
- Other Advertising and Promotion Guidances by Industry
  - Animal Vet - https://www.fda.gov/animal-veterinary/guidance-industry/advertising-and-promotion-guidances
  - CBER - https://www.fda.gov/vaccines-blood-biologics/labeling-cber-regulated-products/guidances-federal-register-notices-standard-operating-policy-procedure-advertising-promotional

Helpful Resources

- Other Advertising and Promotion Guidances by Industry
    - FDA Guidance Search - https://www.fda.gov/regulatory-information/search-fda-guidance-documents
  - Industry Conferences & Groups
    - Food & Drug Law Institute - https://www.fdli.org/
    - Regulatory Affairs Professional Society - https://www.raps.org/
    - DIA - https://www.diaglobal.org/
- American Conference Institute FDA Boot Camp - https://www.americanconference.com/fda-boot-camp/
- Sample policies and SOPs
  - Pfizer's White Guide: https://cdn.pfizer.com/pfizercom/White-Guide-Combine-01-20-2022.pdf
  - GSK's Global Guide: https://pk-consumerhealthcare.gsk.com/media/1257500/global-code-of-practice-for-promotion-and-customer-interactions.pdf