Arnall Golden Gregory LLP

FDA ENFORCEMENT WITH PRODUCT PROMOTION:

Year in Review (A Little Late) and Issues to Consider for 2022

Alan G. Minsk and Laura S. Dona | February 23, 2022

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Letters in 2021 Issued by OPDP

- FDA's Office of Prescription Drug and Promotion
  - Six letters total: Two Warning Letters and Four Notice of Violations/Untitled Letters
  - OPDP issued Four Warning Letters and Two Untitled Letters in 2020
- Some common mistakes from the past; some a little newer
- We will highlight some of the key issues raised by OPDP (without identifying any companies)
- Medical device folks, we will get to you

Meet the New Boss, Same as the Old Boss: OPDP Issues Its First Warning Letter of 2021

- February 2021
- OPDP objected to a banner ad and tabletop display for a Schedule II controlled substance, a prescription opioid drug that was submitted to FDA under Form FDA 2253
- The agency said that promotional materials made false and misleading representations about the risk and efficacy of the drug
- The Boxed Warning product, with a Risk Evaluation and Mitigation Strategy Program, claimed “TONGUE AND DONE” in connection with an image of the single-dose applicator, suggesting that the product might be, according to OPDP, “a simple, one-step process when this is not the case”
  - OPDP noted that the Prescribing Information described multiple administration steps

Meet the New Boss, Same as the Old Boss: OPDP Issues Its First Warning Letter of 2021 *(cont'd)*

- The banner omitted information from the PI's Dosing and Administration section about the maximum daily dosage: the banner created a "misleading impression about the safe use of [the product]"
- The banner provided a claim that failed to include the product's limitations of use, which was misleading
  - While the limitations of use were included with the full indication further below, as part of the full Important Safety Information (ISI), OPDP said that this was "intermingled with risk information in a paragraph format in a much smaller font size and a plain white background" and was accessible only if the viewer "scrolled" down the banner
  - OPDP concluded that "this does not mitigate the misleading impression"
- The banner and display did not include the risk information, such as the Boxed Warning, Contraindications and Warnings, and Precautions, with a prominence and readability that was comparable as the presentation of the benefit information; OPDP said, "the risk information is relegated farther down in paragraph format with less prominence"

Meet the New Boss, Same as the Old Boss: OPDP Issues Its First Warning Letter of 2021 *(cont'd)*

AGG Observations

- OPDP focuses on high-risk drugs, such as those with Boxed Warnings
- Do not forget to include the limitations of use in the text; omission or truncation can make the promotion misleading.
  - The limitations of use are part of the indication; it is insufficient to merely place the limitations of use in the ISI at the bottom of the page
- Fair balance includes the presentation of risk information in a comparable manner to the benefit information

Déjà Vu, We Have All Been Here Before: OPDP Issues Its Second Warning Letter in 2021

- February 2021
- OPDP sent the Warning Letter to the drug company a day after issuing the first
- The second Warning Letter included many recurring themes of unlawful promotional areas
- In addition, OPDP sent an Untitled Letter to the company in 2019 for similar concerns
- The promotional piece was a direct-to-consumer video, shown on a television station

Déjà Vu, We Have All Been Here Before: OPDP Issues Its Second Warning Letter in 2021 *(cont'd)*

- The company did not submit the video to OPDP on a Form FDA-2253, which is required for all promotional materials at the time of initial dissemination of the labeling or at the time of initial publication of the advertisement

- OPDP became aware of the video through a Bad Ad complaint

- The video did not provide <u>any</u> risk information, even though it promoted the product's efficacy; while the video referred the viewers to the product website for additional information, OPDP found "that does not mitigate the complete omission of risk information from the video"

Déjà Vu, We Have All Been Here Before: OPDP Issues Its Second Warning Letter in 2021 *(cont'd)*

AGG Observations

- It is inadequate for companies to promote positive safety and efficacy claims and then direct users to another place to view risk information; one must provide a fair balance at the same time
- Bad Ad complaint
- Previous correspondence from FDA about promotion
- No 2253

A Drug Company Finds Itself With a Headache and Over Its Head With Unlawful Promotional Messaging

- March 2021
- OPDP took exception in an Untitled Letter to a direct-to-consumer promotion that marketed a prescription drug product for acute treatment of migraine with or without aura in adults
  - The video originally appeared on the television show *The View* and could be accessed on its YouTube page
  - The drug company was identified as a sponsor of the television program
  - The video also included a web address to direct the viewer to the sponsor's website
  - The letter brought up the challenges of product promotion in live, often unrehearsed settings

A Drug Company Finds Itself With a Headache and Over Its Head With Unlawful Promotional Messaging *(cont'd)*

- OPDP said that the spokesperson overstated efficacy when she claimed that the product could work in approximately 15-30 minutes
  - The clinical studies from the PI did not include any pre-specified endpoints that evaluated the efficacy of the drug at 15 or 30 minutes after dosing
  - Instead, the co-primary endpoints (freedom from pain and most bothersome symptoms) were measured beginning at two hours after dosing with the product and placebo; based on the studies, a claim that could be supported by the PI might be that relief should start in two hours (not 15 or 30 minutes)
  - OPDP acknowledged that this might have been the spokesperson's personal experience with the drug, and the video included a super that, "AS EVERYONE EXPERIENCES MIGRAINES DIFFERENTLY, TREATMENT RESULTS MAY VARY;" however, this disclaimer and the spokesperson's personal experience did not "mitigate the misleading impression" that the product could provide relief within 15-30 minutes when the PI and data said otherwise

A Drug Company Finds Itself With a Headache and Over Its Head With Unlawful Promotional Messaging *(cont'd)*

- The spokesperson also suggested that the product was a "game changer" and other products she took didn't work
  - OPDP said that there was no evidence to suggest the product was clinically superior to, more effective than, or a "gamechanger" compared to other prescription and over-the-counter products (i.e., they were unsupported comparative claims)
- The spokesperson did not include the full indication when she spoke; the indication also included a Limitation of Use
  - The product's full indication was that it is approved for acute treatment of migraine, and the Limitation of Use was that it is not indicated for the preventive treatment of migraine

A Drug Company Finds Itself With a Headache and Over Its Head With Unlawful Promotional Messaging *(cont'd)*

- The full indication was provided "briefly, at the end of the video, after the interview portion, in a script/text format on the screen," but OPDP said it did not mitigate the overall misleading impression
- The video did not provide risk information with the same prominence as the benefit information
  - The spokesperson provided the positive information in the audio and video, but the risk information was only presented in text format and in small format
  - OPDP noted that the risk information appeared only for four seconds at the end of the video, after the talk
  - The video did not inform the viewer that important risk information would follow the presentation when the spokesperson was done, but the television host said, "We'll be right back," which suggested the segment was over
- Bad Ad complaint
- The company failed to submit a 2253

A Drug Company Finds Itself With a Headache and Over Its Head With Unlawful Promotional Messaging *(cont'd)*

AGG Observations

- A Bad Ad complaint prompted the Untitled Letter
- Comparative claims must be supported by data, typically head-to-head studies
- Personal experience of a spokesperson, while it may be true for that individual, must be typical and consistent with what FDA has reviewed and approved in the PI; a qualifier and disclaimer are not sufficient to eliminate a potential false or misleading message

A Drug Company Finds Itself With a Headache and Over Its Head With Unlawful Promotional Messaging *(cont'd)*

- It is important that paid spokespeople, whether celebrities, patients, or doctors, are properly trained on FDA labeling and promotional requirements
  - Prepared speeches, presentations, and commercials leave less room for error
  - However, real-time interviews, active social media blogs, and interactive discussions are more prone to off-the-cuff mistakes and failure to follow the regulatory script
  - While it might be awkward for an individual to raise adverse event information during an interview and companies are hesitant to script others' talks, spokespeople are company agents
  - In addition, while adding supers after the fact may minimize the enforcement risk, as we see, they do not eliminate the risk
- Companies should not perpetuate potential regulatory problems by posting problematic live presentations on company-controlled forums without ensuring they are complaint
- After a thorough review, the presentation itself might not be used at all if it cannot be shown in an FDA-compliant manner

Real-World Data or Not So Accurate Data: OPDP Issues Letter to Company for Misplaced Reliance on Real-World Data

- July 2021
- OPDP sent an Untitled Letter regarding a professional animated banner; the banner ad made false or misleading claims and representations regarding the benefits of the prescription drug product
  - OPDP's primary concern was the company's use of a real-world study, which it found had many limitations

Real-World Data or Not So Accurate Data: OPDP Issues Letter to Company for Misplaced Reliance on Real-World Data *(cont'd)*

- OPDP found that claims and presentations included in the banner ad created a misleading impression regarding the statistical significance of the risk of febrile neutropenia (FN) depending on the delivery method for the drug
  - The real-world study cited to make the claims included "multiple limitations" that would preclude such a conclusion
  - The data on file provided to OPDP (the agency requested the study) did not include information regarding the performance characteristics (e.g., sensitivity) of the algorithm or the diagnostic codes that were used
    - According to OPDP, the use of this unvalidated algorithm constituted a "significant limitation" because of the algorithm's unknown performance characteristics and potential for misclassification of patients at the beginning of the study
    - The data on file failed to describe "any measures taken to ensure the quality and accuracy of the results" generated by the algorithm
    - Therefore, the extent that patients in the study actually had FN could be over or underestimated

Real-World Data or Not So Accurate Data: OPDP Issues Letter to Company for Misplaced Reliance on Real-World Data *(cont'd)*

- OPDP found that the study was not designed to ensure that the patients utilizing the different delivery methods "were adequately balanced or controlled for potential bias," because the study failed to control for factors other than the delivery device that could influence the incidence of FN in the comparative groups (we won't get into the specifics)
- The agency also took exception to the use of the proper name of the drug in one instances, versus the use of the proprietary name of another product with a different delivery method that could be misleading

Real-World Data or Not So Accurate Data: OPDP Issues Letter to Company for Misplaced Reliance on Real-World Data *(cont'd)*

- According to the agency, one frame of the banner, which included certain qualifying language "less prominently and in smaller font" than the claims and presentations set forth in earlier frames, was not sufficient to mitigate the more prominent presentation of other frames
- OPDP also noted that two limitations to the study were presented in certain banner ad frames under the header "Real-World Study Limitations"
  - However, the agency found that the inclusion of the two major deficiencies of the study design did not mitigate the misleading claims and presentations in the banner
  - OPDP added that the misleading claims could undermine confidence in FDA-licensed biosimilar products, which are only delivered through a certain delivery method

Real-World Data or Not So Accurate Data: OPDP Issues Letter to Company for Misplaced Reliance on Real-World Data *(cont'd)*

AGG Observations

- This Untitled Letter should serve as an example of the type of scrutiny and review OPDP exercises to ensure the appropriate use of such data
- When evaluating real-world data and its appropriateness for use in promotional materials, companies should ensure all study limitations are considered and be comfortable that the conclusions drawn from the study are scientifically and statistically sound
  - It might be appropriate to add disclaimers and qualifiers, although this may minimize, but not eliminate risk

You Cannot Do It Any Way You Want It: FDA Issues an Untitled Letter for an Incomplete Journey Forward

- December 2021
- Untitled Letter to a drug company for unlawful promotion of its biologic product
- In particular, OPDP objected to two direct-to-consumer television advertisements about patient "journey forward" experiences, claiming the ads provided false or misleading risk information and failed to submit a Form FDA-2253 at the time of initial publication
- The TV ads provided claims about the product's use (e.g., migraine) and benefits, but did not include any risk information
- FDA also noted that the TV ads failed to provide adequate provision (for dissemination of the approved permitted package labeling in connection with the presentation) or a brief summary (of all required information related to side effects and contraindications)
- The TV ads did not include the material information regarding the full FDA-approved indication (e.g., preventive treatment of migraines in adults)

You Cannot Do It Any Way You Want It: FDA Issues an Untitled Letter for an Incomplete Journey Forward *(cont'd)*

- Shortly after FDA issued the Untitled Letter, the company responded, and OPDP found the corrections adequate
  - The company explained that it had intended to show the ads as part of a "complete TV broadcast," consisting of three components — the first component included disease state information concerning migraines, immediately followed by a second component that was presented in the format of a reminder advertisement for the product, and then the final component was a full product TV segment for the product (including indication and risk information)
  - These components were to be aired on television together in an immediate, sequential fashion, with all three viewed in totality
  - However, no "complete TV broadcast" was submitted to OPDP

You Cannot Do It Any Way You Want It: FDA Issues an Untitled Letter for an Incomplete Journey Forward *(cont'd)*

- In its Close-Out Letter, OPDP noted
  - The TV ads included a clear beginning, middle, and end to the presentation
  - The ads began with background music that played throughout
  - Each of the TV ads appeared as an organized presentation
  - The company acknowledged it did not submit the "complete TV broadcasts" to OPDP and none of the submissions referenced coordination with any other communication

AGG Observations

While the company quickly fixed OPDP's concerns, and it appears the company intended to provide all of the materials in an immediate, sequential matter, it did not execute properly

Freeze-Frame: FDA Issues an Untitled Letter for an Unlawful Instagram Post

- January 2022
- The Untitled Letter, the first for 2022, included a number of issues and concerns raised by OPDP in the past
- The company submitted a social post — an Instagram ad — on a Form FDA 2253, so OPDP saw the ad
- It appears OPDP learned of the post through the Bad Ad Program, an initiative by which healthcare professionals can contact the agency and share concerns about what they believe to be suspect prescription drug product promotion
- The labeling for the product included a Boxed Warning about a risk associated with the incidence of thyroid C-cell tumors associated with the use of the product (in addition to other noted contraindications and warnings)

Freeze-Frame: FDA Issues an Untitled Letter for an Unlawful Instagram Post *(cont'd)*

- Prior to issuing the Untitled Letter, OPDP provided advisory comments to the company on four separate occasions
  - The agency notified the company that it was provided advisory comments to the company on four separate occasions
- The agency determined the Instagram post was misleading, in part, because the video did not include the full FDA-approved Indication and Limitations of Use, which provided a misleading impression about the scope of the FDA-approved indication for the product while also displaying certain required information too fast and in a distracting, non-prominent manner:

> OPDP notes that the indication and the limitations of use are presented only in small, fast-paced scrolling font in a small window below the video, relegated to the bottom of the post, competing for the consumer's attention with several distracting video elements (fast-paced visuals, frequent scene changes, busy scenes, large-moving superimposed text, and a strong fast-moving musical beat) that detract from the communication of the indication and limitations of use. Therefore, this presentation does not mitigate the misleading impression created by the post.

Freeze-Frame: FDA Issues an Untitled Letter for an Unlawful Instagram Post *(cont'd)*

- OPDP expressed concern about the presentation of risk information
- Information was in a small font that was difficult to read and could not be adequately processed or comprehended by the consumers
- The Untitled Letter noted that the company did not provide sufficient information from a specific warning and precaution, so "the post creates a misleading impression about the drug's safety"

Freeze-Frame: FDA Issues an Untitled Letter for an Unlawful Instagram Post *(cont'd)*

AGG Observations

- The letter was the result of a nearly perfect storm of problems
  - Social media posts, such as Instagram ads, remain a high area of scrutiny because it can be difficult for such ads to meet FDA fair balance requirements due to limitations on the number of characters permitted on the platform
  - Products requiring Boxed Warning, because they have been determined to present a specific, high safety risk, remain a priority for agency review and, as warranted, enforcement actions

Freeze-Frame: FDA Issues an Untitled Letter for an Unlawful Instagram Post *(cont'd)*

- A Bad Ad Program complaint prompted, in part, the issuance of the Untitled Letter, so not only OPDP is watching
- The inadequate presentation of a product's Limitations of Use is a recurring theme in recent letters
- Not following OPDP's Advisory comments comes at a risk; while these comments are not legally binding and a company is not required to accept them, they should be seriously considered

- It is interesting that OPDP used "truthful and non-misleading" language, which is verbiage used by a few courts that have challenged past FDA enforcement letters
- Companies, through their Promotional Review Committees (or similar groups), should review the recent letter and consider the issues cited (here and in other letters) to see how to minimize the issuance of an OPDP letter concerning their own promotional materials

Recommendations to Minimize Risk

- While we have provided our observations along the way, we will note some here as well
- Testimonials and endorsements must be on-label and truthful and not misleading (even if the individual's personal experience is what it is)
- Limitations of Use statement must be noted prominently (part of the indication)
- A long-running ad doesn't mean FDA can't take action for past sins, so pull or fix the ad ASAP if problematic
- If a company uses social media/internet-sponsored links/banner ads, it must still comply with FDA requirements (space or character limitations are not an excuse) – the Song Remains the Same

Recommendations to Minimize Risk *(cont'd)*

- FDA advisory comments, if given, should be seriously considered
- Repetitive mistakes, even with begging for forgiveness, is not tolerated
- Disclaimers help minimize, but don't eliminate, risk
- Competitive claims, while not per se illegal, can be tricky
- Training, training, and training — auditing, auditing, and auditing
- Promotional Review Committees are a must

Medical Device Promotion

- Reorganization a few years ago where Center for Devices and Radiological Health's (CDRH) Office of Compliance was moved
- More than 50 Warning Letters issued in 2021 — most related to COVID-like claims or products
- Separate from Warning Letters, CDRH can send "We Have Become Aware Of"–type letters, often not public — (Cyberletters)
- Stay in your lane: As with drugs, FDA is focusing on those products promoted outside of the bounds of the device's clearance or classification
- Unlike OPDP, CDRH does not post Untitled Letters, and it's hard to find Warning Letters issued by CDRH
  - According to an informed discussion with a CDRH official, "We don't have the kind of program that OPDP has"

Oh, Baby: Medical Device Warning Letter Example

- A device company was sent a Warning Letter concerning the company's family of products used to monitor infants
- FDA had been in contact with the company since 2016, conveying that the products fell under the statutory definition of "medical device" and outside of FDA's low-risk General Wellness categorization
- Risky claims included:
  - "Track the most important indicators of your baby's health — like oxygen level, heart rate, and total hours slept"
  - "If your baby's readings leave preset 'safe' zones, the [product] will immediately notify you that your baby needs your attention"

Oh, Baby: Medical Device Warning Letter Example *(cont'd)*

AGG Observations

- When FDA reaches out privately, respond and react accordingly (or face public reprimand)
- Products for vulnerable populations are of a higher risk
- As noted, promotion outside of the product's approval/clearance or exempt status is high risk

Not Too Bright: Another Medical Device Warning Letter

- In February 2021, CDRH sent a company a Warning Letter addressing the company's light therapy devices that made various claims relating to skin conditions
- The letter outlined that FDA had been in contact with the company (it sent the company an "It Has Come to Our Attention"-type letter in June 2020, requesting that the company provide FDA with either clearance or approval submission numbers for the devices)
- The company responded, providing a substantial equivalence determination letter, but FDA found the letter to be inadequate

Not Too Bright: Another Medical Device Warning Letter *(cont'd)*

- Where the company went astray:
  - The cleared device that the company referenced for substantial equivalence was indicated "to emit energy in the red and IR region of the spectrum for use in dermatology for the treatment of periorbital wrinkles"
  - However, the company made much further claims, including treatment of serious life-threatening diseases, such as cancers, dysplasia, jaundice, osteoporosis, heart disease, kidney and digestive tract diseases, emaciation, and anemia, without verification with clinical data

Ch-Ch-Ch-Ch-Changes: One More Example of a Medical Device Warning Letter

- FDA sent a Warning Letter in May 2021 for making significant changes to the device without submitting a PMA
- While the device had 510(k) clearance, the marketing materials indicated that the device had an intended use for dialysis with a physiological closed loop controller system, which FDA considered to be a significant change or modification to the device
- FDA previously corresponded with the company, sending an “It Has Come to Our Attention”-type letter in August 2019; while the company responded by providing validation testing and claiming that the function had been cleared, FDA disagreed and considered the product to be misbranded

Common Themes

- No 510(k) clearance at all – misbranding
  - no PMA approval – adulteration
- 510(k) clearance, but exceeding the scope of the clearance or regulation
  - e.g., general and specific use issues
- FDA had expressed concerns previously

Crystal Ball Time

- First Amendment issues will likely have FDA focus more on false or misleading concerns (e.g., presentation of risk information in a prominent and comparable manner, misleading comparative claims)
- As the world re-opens and there are more in-person medical conferences and trade shows, expect FDA to review more carefully materials at these venues
  - In 2021, OPDP said it would start a study on company interactions with doctors at medical conference exhibit halls at promotional booths (focusing on prescriptions of the promoted drugs by the doctors)
- High-risk products (e.g., COVID-19, opioids, biologics, Boxed Warning products) and direct-to-consumer ads (e.g., social media) will remain areas of scrutiny
  - Wide audience

Crystal Ball Time (*cont'd)*

- FDA might issue a letter on a topic where we haven't seen recent enforcement (e.g., pre-approval promotion, generic drugs, mobile apps, wellness products) to remind industry it cares about many areas
- Letter on testimonials or endorsements
- Continued focus on social science research activities/perception by HCPs and consumers
- More written guidance to industry
- More letters prompted by the Bad Ad campaign

Questions?

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THANK YOU

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