THE CALM BEFORE THE STORM: OPDP RELEASED TWO UNTITLED LETTERS BEFORE HHS'S REDUCTION IN FORCE, NOW WHAT?

The Food and Drug Administration's ("FDA") Office of Prescription Drug Promotion ("OPDP") started 2025 with two Untitled Letters, one in February and one in March, potentially signaling more enforcement for the year. OPDP issued only five enforcement letters in 2023 and 2024, with a heavy focus on influencer marketing. However, on April 1, 2025, most of OPDP's staff and leadership were part of the U.S. Department of Health and Human Services ("HHS") Reduction in Force ("RIF"), leaving the industry wondering about the future of the regulation of prescription drug advertising. While some believe that the RIF will not significantly impact overall enforcement against prescription drug advertising, the cuts will likely result in even fewer letters in 2025. This will undoubtedly also slow down innovation and potentially allow for violative campaigns to be disseminated for longer periods before OPDP takes action.

With Commissioner Martin A. Makary having just been sworn in earlier this month, more RIFs potentially on the horizon and Robert F. Kennedy's known stance on direct-to-consumer (DTC) advertising, the industry will need to wait and see what happens with OPDP within the next few months.

In the meantime, we provide some highlights below from each of the 2025 Untitled Letters. While these may no longer represent the OPDP's focus going forward, they do provide invaluable guidance for the industry in a time of great uncertainty.

FEBRUARY 3 LETTER – FALSE OR MISLEADING RISK PRESENTATION & CLAIMS ABOUT EFFICACY

The first Untitled Letter was issued on February 3, 2025, to a pharmaceutical company regarding misleading promotional claims in an exhibit booth panel for its dexamethasone oral tablets, which are indicated for adults with multiple myeloma ("MM"). The letter cited false or misleading claims about the drug's benefits and the omission of critical risk information as violating the Federal Food, Drug, and Cosmetic Act. The exhibit booth was submitted to the FDA for review under the cover of Form FDA 2253. The FDA also received a complaint about the exhibit booth panel via the FDA Bad Ad Program.

A major issue flagged by OPDP was the exhibit booth panel's complete omission of risk information. While the panel highlighted efficacy claims, such as "[DRUG] reduces up to 80% of the number of tablets required for a therapeutic dose of dexamethasone for the treatment of adults with MM" and "[DRUG] is a unique strength dexamethasone tablet bioequivalent to five 4 mg tablets of dexamethasone", it failed to include **any** risk information. Promotional communications misbrand a drug if they are false or misleading with respect to risk.

According to the FDA-approved prescribing information, the drug carries serious risks, including but not limited to endocrine dysfunction, immunosuppression, cardiovascular complications, gastrointestinal perforation, osteoporosis, musculoskeletal issues, behavioral and mood disturbances and embryo-fetal toxicity. OPDP determined that by omitting these risks, the exhibit panel failed to provide material information about the potential consequences of using the drug, creating a misleading impression about the drug's overall safety profile.

In addition to the claims mentioned above, the exhibit panel featured a table titled "REAL-WORLD COMPARISON OF ADHERENCE to [DRUG] and generic dexamethasone among patients with MM," which suggested that the drug had higher patient adherence rates compared to generic dexamethasone. However, OPDP identified significant flaws in the cited study, stating that its design and methodology did not support conclusions about comparative adherence between the drug and generic dexamethasone 4 mg in the treatment of MM patients.

Additionally, OPDP determined that the protocol did not specify whether the drug or generic dexamethasone 4 mg was administered as monotherapy or in combination with other treatments, which has the potential to introduce bias into adherence calculations. OPDP also found that other factors influencing adherence, such as the total number of medications prescribed, the number of pharmacies used and patient age, were not controlled for in the statistical analysis, which did not adjust for these or any other covariates.

Another limitation was the significant disparity in sample sizes, with 3,775 patients in the generic dexamethasone 4 mg group compared to only 43 in the drug's group, resulting in a significantly unbalanced study population. OPDP found that this imbalance may contribute to an overestimation of adherence in favor of the patient group receiving the drug. Additionally, OPDP noted that the study protocol did not address how to avoid double-counting patients in the dexamethasone group who may have transitioned from NDMM to RRMM.

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Due to these flaws, OPDP determined that the study did not provide reliable evidence to support claims of improved adherence, rendering the promotional claims false and misleading.

MARCH 21 LETTER – FALSE OR MISLEADING BENEFIT PRESENTATION

The second Untitled Letter was issued to a pharmaceutical company on March 21, 2025, regarding the promotion of their futibatinib tablets for oral use. The letter addressed concerns over the representations about the benefits of the drug through a webpage titled "Efficacy Results" on the drug's Healthcare Provider Branded Website. This was not the first time the FDA raised concerns with this pharmaceutical company's promotion of the drug. In December 2022, OPDP issued advisory comments on draft claims and presentations for the drug. Despite these prior communications, the same representations were made in the "Efficacy Results" webpage, potentially prompting the Untitled Letter due to OPDP's concern that the company "appears to be promoting [the drug] using similar claims and presentations in a misleading manner."

OPDP expressed concern that the webpage made false or misleading claims about the drug's benefits, particularly regarding its efficacy in patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma ("iCCA") harboring fibroblast growth factor receptor 2 gene fusions or other rearrangements. Specifically, the webpage included Kaplan-Meier survival graphs showing progression-free survival ("PFS") and overall survival ("OS") data from the FOENIX-CCA2 trial. The OPDP highlighted that the FOENIX-CCA2 study was a single-arm trial, meaning there was no comparator group. As such, the results from this study could not be used to definitively show whether the drug's effects on PFS and OS were attributable to the drug or to other factors, such as the natural progression of the disease. Without a comparator, these time-to-event efficacy endpoints are deemed uninterpretable. While the webpage did include some disclaimers, such as warnings that the data should be interpreted with caution, OPDP deemed these insufficient to correct the misleading implications.

Another issue raised by OPDP was the presentation of the drug's disease control rate ("DCR"). The webpage presented an 83% DCR based on a composite of complete response ("CR"), partial response ("PR") and stable disease ("SD"), and also included similar results from an extended follow-up analysis. OPDP found that these presentations made these promotional communications misleading by suggesting that the drug improves DCR in patients with locally advanced or metastatic iCCA based on a composite of CR, PR and SD when the study from which the presentations were drawn could not demonstrate this result. Moreover, since FOENIX-CCA2 was a single-arm study, the study did not establish that the SD result was attributable to the effect of the drug. Therefore, the DCR data presented on the webpage could not be considered as proof of the drug's efficacy.

PRACTICAL TAKEAWAYS

1. Companies should ensure that all promotional materials contain a clear, prominent and easily understandable presentation of risks.
2. All efficacy and comparative claims should be supported by well-designed, peer-reviewed studies. When citing real-world data, companies should use consistent patient selection criteria, control for disease severity, treatment variations and confounding factors, and avoid sample size imbalances that could skew results.
3. A complete lack of risk information will not only attract OPDP's attention, but also that of a health care provider who may decide to report the advertising to the FDA as potentially false or misleading through the FDA's Bad Ad program.
4. If a company requests advisory comments from OPDP on certain promotional materials, it should ensure to implement those comments in any future promotions. Failure to incorporate OPDP's comments when using similar claims will catch the FDA's attention and most often result in an enforcement action.
5. These letters may be the only letters we see from OPDP for a while given the significant staff reduction. Companies will have to stay tuned to see what, if anything, happens with DTC advertising this year.

For more information on the advertising and promotion of drugs, biologics, or medical devices, please contact:

- Carolina Wirth at (202) 780-2989 or cwirth@hallrender.com;
- Jemalyn Harvey at (202) 780-2990 or jharvey@hallrender.com; or
- Your primary Hall Render contact.

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