DIA Regulatory Affairs Community AdPromo Working Group

Web Meeting

March 16, 2022

Your WG Chairs: Renee Ambrosio (Merck & Co., Inc.) and Kimberly Belsky (Mallinckrodt Pharmaceuticals)

DIA Communities

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Reminder - Please Mute Your Line if You are Not Speaking Thank you!

Hold the Dates! The DIA AdPromo WG will generally meet on the 3rd Wednesday of each month at 12:00 pm eastern

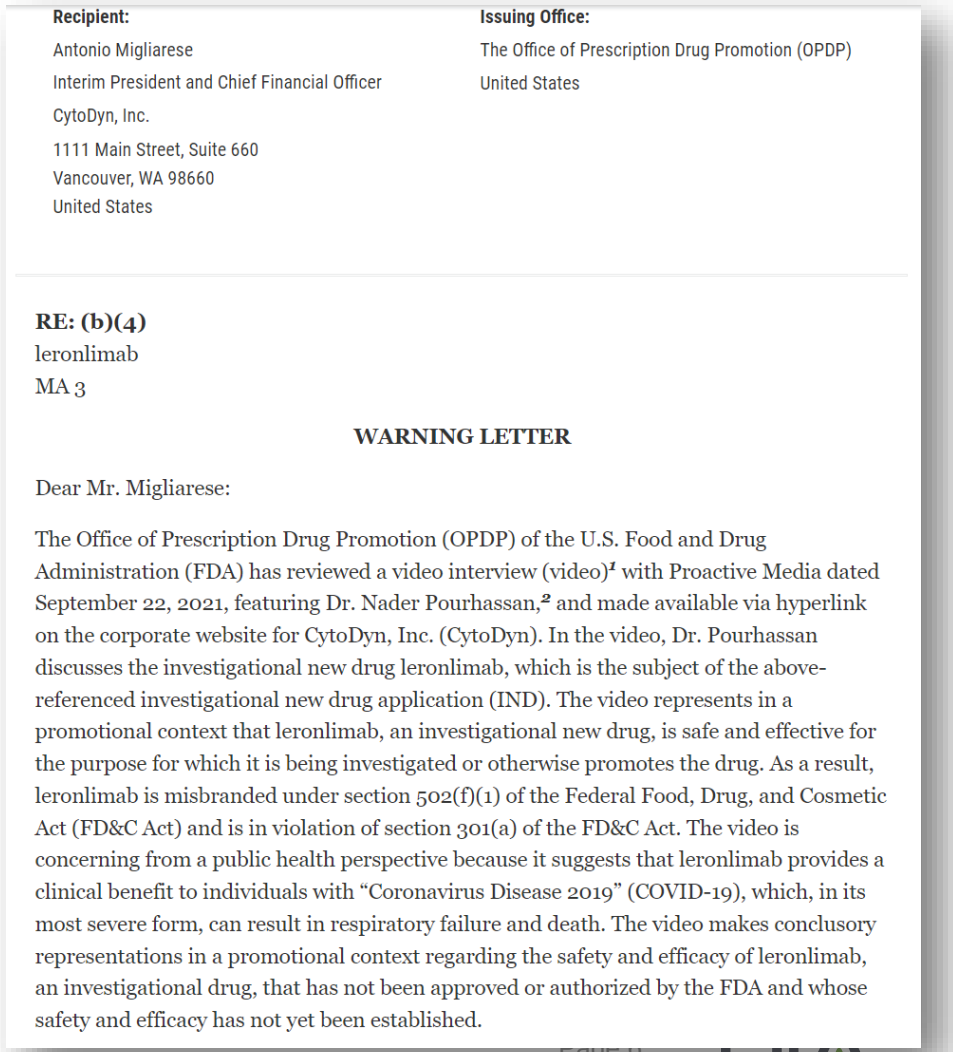
April 13 (NOTE this date change!), 2022 @ 12 pm – 1 pm ET	*Latest Happenings and* ***Guest Presenters*** • **Regulatory review of advertising on streaming media,** Shruti Gadhi (*Kyowa Kirin*) and Olivia Walker (*Jazz Pharmaceuticals*)	**Join Zoom Meeting** **https://diaglobal.zoom.us/j/94431294607** **Meeting ID: 944 3129 4607** **One tap mobile** **+16468769923,,9443129460 7# US (New York) 13126266799,,9443129460 7# US +(Chicago)**
May 18, 2022 @ 12 pm – 1 pm ET	*Topics to follow….*	Join Zoom Meeting https://diaglobal.zoom.us/j/94885304921 Meeting ID: 948 8530 4921 One tap mobile +16468769923,,94885304921# US (New York) 13126266799,,94885304921# US +(Chicago)

Topics Covered Today

- OPDP WL Issued to CytoDyn Inc for Video - Investigational New Drug
- In Brief Summary (March 2022) - Select Info
- *CDER Conversations:* OPDP's Social Science Research Program: Aiming to Understand How Health Care Providers and Patients Interpret Prescription Drug Information
- Lanham Act Case Between CareDx and Natera
- Heard (and/or presented) at the DIA AdPromo Conference March 8-9, 2022
- Future WG Topic Idea

leronlimab OPDP Warning Letter

- On **February 11, 2022,** OPDP issued a Warning letter to **CytoDyn, Inc.**. addressing a video interview with proactive media featuring a doctor discussing the investigational new drug leronlimab.
  - The Close-out letter was posted on Feb 25, 2022 Close-Out Letter (PDF)
- The video presented information about leronlimab in a promotional context, which **misbranded leronlimab.**
- OPDP stated that the video was particularly concerning because it suggested that leronlimab provides a **clinical benefit to individuals with COVID-19** when it has not been approved or authorized by the FDA for that purpose. As such, FDA is taking measures to protect consumers from certain products that, without approval, clearance, or authorization by FDA, **claim to mitigate, prevent, test diagnose, or cure COVID-19 in people**



Recipient:
Antonio Migliarese
Interim President and Chief Financial Officer
CytoDyn, Inc.
1111 Main Street, Suite 660
Vancouver, WA 98660
United States

Issuing Office:
The Office of Prescription Drug Promotion (OPDP)
United States

RE: (b)(4)
leronlimab
MA 3

WARNING LETTER

Dear Mr. Migliarese:

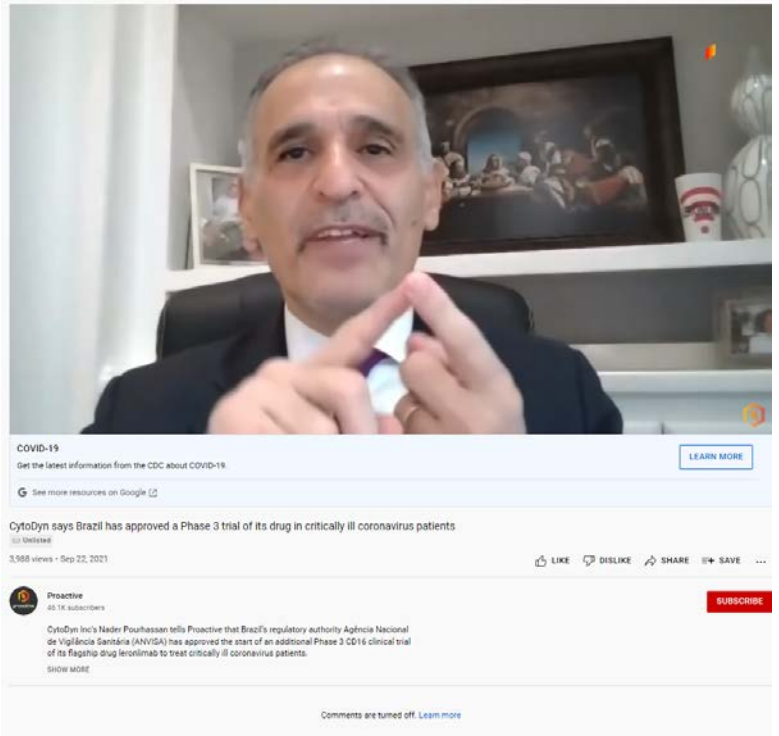
The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a video interview (video)[1] with Proactive Media dated September 22, 2021, featuring Dr. Nader Pourhassan,[2] and made available via hyperlink on the corporate website for CytoDyn, Inc. (CytoDyn). In the video, Dr. Pourhassan discusses the investigational new drug leronlimab, which is the subject of the above-referenced investigational new drug application (IND). The video represents in a promotional context that leronlimab, an investigational new drug, is safe and effective for the purpose for which it is being investigated or otherwise promotes the drug. As a result, leronlimab is misbranded under section 502(f)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and is in violation of section 301(a) of the FD&C Act. The video is concerning from a public health perspective because it suggests that leronlimab provides a clinical benefit to individuals with "Coronavirus Disease 2019" (COVID-19), which, in its most severe form, can result in respiratory failure and death. The video makes conclusory representations in a promotional context regarding the safety and efficacy of leronlimab, an investigational drug, that has not been approved or authorized by the FDA and whose safety and efficacy has not yet been established.

leronlimab OPDP Warning Letter

- The video included several claims that **promoted leronlimab as safe and effective for COVID-19** with the following:
  - "In the United States, we did a trial of 394 patients which included severe and critically ill population. In the critically-ill population, **our results were really strong…**"
  - "Our critically-ill population that we did in the United States when we gave a dose of leronlimab**, the survival rate was 78%.** Once we gave them another dose, **the survival rate went up to 82%**."
  - "Imagine, if 78% went to 82, the next one would be maybe 88, and then 95. I am making up numbers, but if it goes to that kind of numbers, if it just follows the same pattern what we learned, this is going to be the most fantastic results anybody could ever imagined to have. Now I'm not saying that's what we're going to get, but I'm saying that's what the results are showing."
  - "The primary endpoint…is the discharge, the rate of patients who get on ventilator and get discharged. **That endpoint was 166% better in our trial that we did in the United States versus placebo…166%.**"

- OPDP stated that the above claims made **conclusory statements** that suggest the leronlimab **has been established as safe an effective** for the treatment of COVID-19

- **FDA noted that a trial conducted by CytoDyn previously failed to find any effect of the drug on the primary or any predefined secondary endpoints of the trial**
  - *Prior Communications* - On May 17, 2021, following public communications by CytoDyn regarding differences in small subgroups in one of the clinical trials CytoDyn conducted with leronlimab for the treatment of patients with COVID-19, including those with severe outcomes from COVID-19, **FDA issued a statement** addressing CytoDyn's development of leronlimab. The statement reviewed the results of two clinical trials, CD10 and CD12, conducted by CytoDyn investigating leronlimab for the treatment of COVID-19**.**
  - **In part, the statement provided, "*With the conclusion of both the CD10 and CD12 clinical trials, it has become clear that the data currently available do not support the clinical benefit of leronlimab for the treatment of COVID-19.*"**



https://www.youtube.com/watch?v=IeUGEMtcmPs Still posted as of March 16, 2022 (7:30 am ET)
FDA acknowledges in Footnote 2 "until January 24, 2022, Dr. Pourhassan was the President and Chief Executive Officer of CytoDyn, Inc."

leronlimab OPDP Warning Letter

- **Corrective Actions:**
  - OPDP requested that CytoDyn submit a **comprehensive plan of action** to **disseminate truthful, non-misleading, and complete corrective communication**(s) about the concern(s) discussed in the Warning Letter
    - disseminated to the same **audience(s)** that received the promotional communication(s)
    - include a **summary of the concern(s)** described in the Warning Letter
    - provide information to **correct each of these concern(s)**

- **Corrective communication**(s) should be **free of promotional claims and presentations and** distributed using:
  - the **same media**
  - generally for the **same duration** of time
  - the **same frequency** as the promotional communication(s) identified in the Warning Letter

- **Enforcement Trends:**
  - This reinforces OPDP's continued focus on enforcement regarding prescription drug promotional materials making **false or misleading claims about COVID-19 prevention or treatment**
  - In September 2020, OPDP issued a warning letter to Nephron Pharmaceuticals Corporation for Budesonide Inhalation Suspension, for inhalation suspension for falsely stating its drug could treat COVID-19 symptoms

Ieronlimab OPDP Warning Letter
A View From FDA Law Blog

Thoughts from FDA Law Blog, posted March 4, 2022 "Fake News? Fantastic Claims and Where to Find Them (or Where FDA Will)"

- "FDA is making one thing clear: OPDP will find your promotional content—even when it may not *look* like promotional content. While it's not mind-blowing that OPDP would find a series of videos while scrolling Instagram (particularly when it's flagged by FDA's Bad Ad program),…"

- "What *is* interesting is that **the video appeared on the YouTube channel of "one of the fastest growing financial media portals in the world," and the link to the video on the cytodyn.com website was included under an "In the News" page**. At first blush, we were deja vu-ing all over again to FDA's action against Aegerion back in 2013. But the CytoDyn interview was different.

- **Proactive**, the company behind the YouTube Channel that included the CytoDyn video, **describes itself as "enabl[ing] companies and investors to connect intelligently." Proactive's Terms and Conditions includes the following statement**:

  - *In exchange for publishing services rendered by the Company on behalf of any issuer named on the Site, including the promotion by the Company of the issuer in any Content on the Site, the Company receives from said issuer annual aggregate cash compensation in an amount equal to Twenty Five Thousand dollars ($25,000)…."*

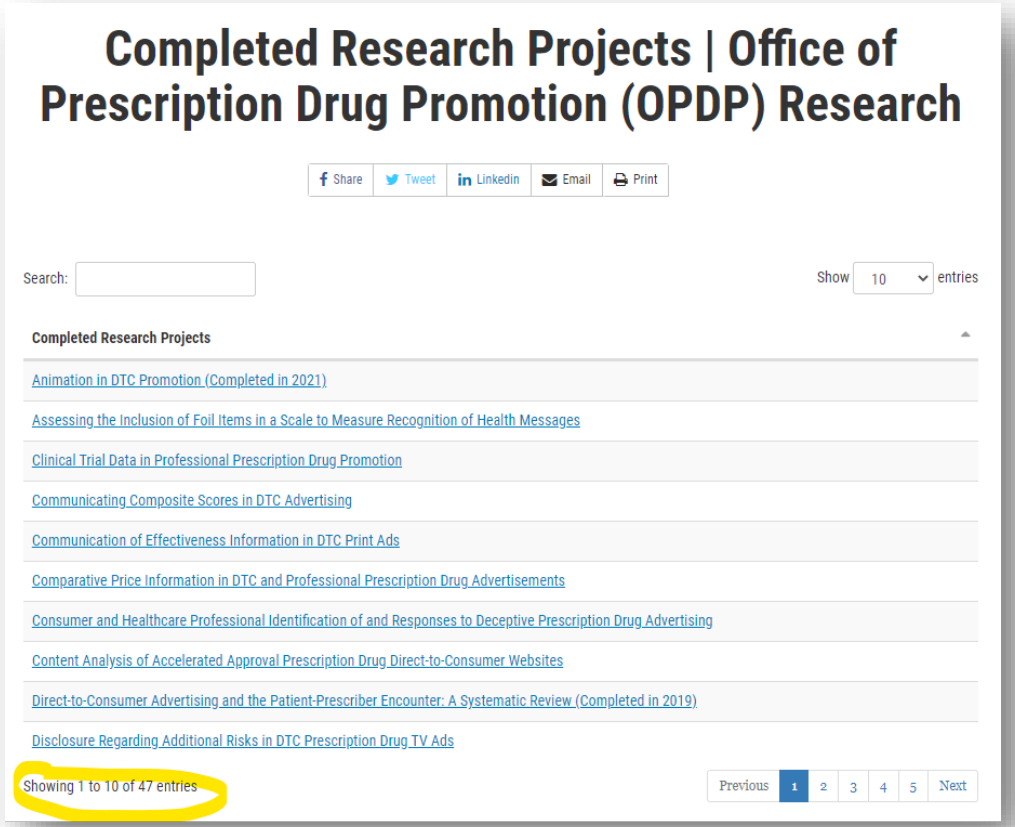
Ieronlimab OPDP Warning Letter
A View From FDA Law Blog

- **"…FDA notes this point in Footnote 1 of the Warning Letter**, calling out the video and Proactive with the quote, "Proactive is a publisher and **receives compensation for publishing content on this account for and on behalf of its clients**."
  - This footnote call-out may be easily missed, **but it is critically important for FDA in establishing that the objectionable content is, in fact, promotional content that may be separate and apart from "the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media." 21 C.F.R. §312.7**."

- **Concluding thoughts from FDA Law Blog, "Aside from the obvious lessons** here (e.g., don't call subgroup analyses from failed studies "really strong" results), **it's important to consider the different approaches taken by FDA based on the types of communications. FDA's initial approach was to correct misinformation through a public statement—sending an OPDP Warning Letter only when the communications could more clearly be tied as "promotional." And FDA did its research—it called out Proactive Media's platform as a sponsored publication.**
  - **Given the rise in sponsorship "opportunities" on news platforms, and FDA's interest in sponsored news segments, companies should be treating these opportunities the same way they would treat more traditional promotional communications** and ensure truthful communications"

In Brief Summary March 2022
Selected Content

- **The March issue is posted here: https://www.fda.gov/media/156635/download**
- **The OPDP Research Team Website**
  - The OPDP Research Team develops, conducts, and publishes numerous research projects each year. In 2021, OPDP restructured the Research Team website and added new search functionality to assist stakeholders. The OPDP Research website is the one-stop hub that provides stakeholders with an overview of the research team in addition to links to recent FDA publications related to OPDP research. **Our research projects are displayed on the Research Team website and are separated into three categories: Completed Research, Research Pending Peer Review and Publication, and Research in Progress**. ….
  - **OPDP research projects are added to the Research in Progress webpage in conjunction with the public availability of a 60 Day Federal Register Notice** announcing the planned study and inviting public comment. Research projects will remain on the Research in Progress webpage until the completion of the study. Once a project is complete and submitted for Peer Review, the project description is moved to the Research Pending Peer Review and Publication webpage. Finally, after a research project has been peer reviewed and published, the project description is moved to the **Completed Research page**. **This page is the largest of the three pages and includes descriptions and links to publications completed by the OPDP Research Team**.
  - **To make searching easier, especially when viewing the Completed Research page, a searchable table of contents has been added to each Research webpage**. The table of contents can be filtered by entering a keyword or phrase from the Research Study Title. The table of contents will automatically filter as a user enters keywords and the user can jump to the research project by clicking on the link in the table of contents.



OPDP's Social Science Research Program: Aiming to Understand How HCPs and Patients Interpret Rx Drug Information

- ***CDER Conversations***: **OPDP's Social Science Research Program: Aiming to Understand How Health Care Providers and Patients Interpret Prescription Drug Information**
  - Posted 2/22/2022
- CDER's Office of Prescription Drug Promotion (OPDP)'s four-person research team **investigates issues in DTC and HCP-directed prescription drug promotional communications**.
  - The team uses methodologies such as surveys, experimental research, and qualitative research in their endeavors
- The team also provides technical assistance within FDA and to stakeholders, as appropriate, on the design and implementation of studies concerning Rx drug promotion. **The team's brochure** explains the work in more depth.

- **The "Conversation" covers:**
  - *What is social science research in the OPDP context?*
  - *How do you come up with your study ideas? How many studies are you working on at any given time?*
  - ***What have been recent interesting research findings?***
  - ***Have you found anything counterintuitive in your research?***
  - *How are your research priorities changing in the time of technological change and the COVID-19 pandemic?*
  - ***What is on the 2022 research agenda?***
  - ***Any final thoughts on social science research?***

In this CDER Conversation, we speak to Kathryn (Kit) Aikin, PhD, senior social science analyst and research team lead in OPDP, about this important work.

OPDP's Social Science Research Program: Aiming to Understand How HCPs and Patients Interpret Rx Drug Information

What have been recent interesting research findings?

- One recent project involved **patients' understanding of oncology clinical endpoints that measure a clinical benefit**, such as overall survival. Based on a literature review of relevant articles and abstracts, **we found that health care providers and patients with cancer generally do not discuss clinical endpoint concepts**. As a result, patients can be confused about the purpose of a particular treatment.
  - We followed up with a series of focus groups, or small group interviews. In these interviews, we asked 36 survivors of cancer and 36 adults in the general population about oncology clinical endpoints. Again, few participants were familiar with the term. We are now starting to set up an experimental study on this topic.
- But so far, **our research may be suggesting a need for more patient-friendly definitions of clinical endpoints**, which may help health care providers describe treatment benefits to patients and empower patients to make informed decisions among treatment choices.

OPDP's Social Science Research Program: Aiming to Understand How HCPs and Patients Interpret Rx Drug Information

- **Have you found anything counterintuitive in your research?**
  - …we had one **recent surprising finding involving superimposed text**, or text over an image that is generally displayed at the bottom of a screen or presentation that often describes risk information, in direct-to-consumer television advertising.
    - **The study authors were surprised that participants who viewed "low contrast" superimposed text** (white text over the video image) **were more likely to be aware of the text than participants viewing "high contrast" superimposed** text (white text over a black field). It would be interesting to see another study that explores the issue of "high contrast" and "low contrast" text.

Still frames from the study that show different levels of superimposition size and contrast

OPDP's Social Science Research Program: Aiming to Understand How HCPs and Patients Interpret Rx Drug Information

- **What is on the 2022 research agenda?**
  - ….We are going to be **looking at the effects of product endorsements and implied claims (or benefit claims that aren't overtly expressed but can be reasonably inferred).** We are also going to investigate **how descriptions of a drug's "mechanism of action"** (or how it works) **affect people's understanding and impressions of that drug.**
  - In addition, we are going to explore **how consumers and health care providers make trade-offs in terms of safety and efficacy**.
    - For example, are people willing to accept less benefits from a drug if it is easier to use? Will they trade one risk for another?
- **Any final thoughts on social science research?**
  - …It is important for FDA to understand how health care providers and patients perceive and make behavioral decisions based on prescription drug information. **These insights may help inform the agency's development of guidances, policies, and rulemakings. They may also influence how OPDP reviews promotional materials**. ….

OPDP's Social Science Research Program: Aiming to Understand How HCPs and Patients Interpret Rx Drug Information

- **The team's brochure (excerpt)**

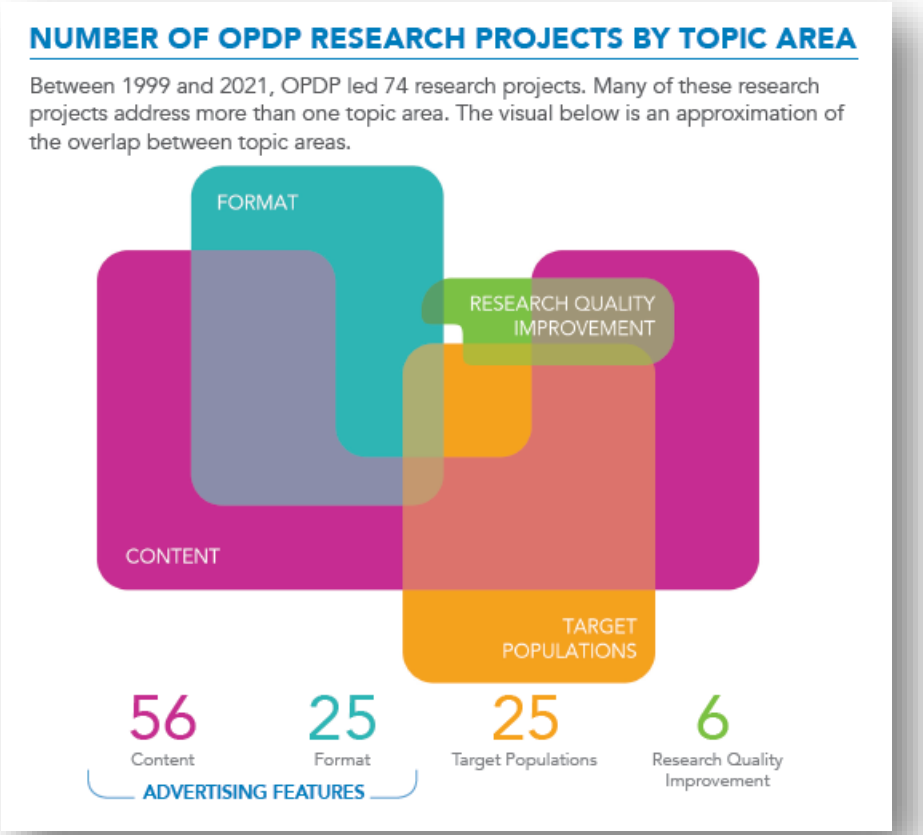
- **OUTCOMES OF RESEARCH**
  1. PEER-REVIEWED PUBLICATIONS
  2. GUIDANCE AND POLICY DEVELOPMENT
  3. RULEMAKING
  4. OTHER REGULATORY ACTIONS

- **Research Focus**

1. ADVERTISING FEATURES: Through the evaluation of advertising features, including content and format, we assess how elements such as graphics, layout, and disease and product characteristics impact the communication and understanding of prescription drug risks and benefits.

2. TARGET POPULATIONS: Focusing on target populations allows us to evaluate how understanding of prescription drug risks and benefits may vary as a function of audience.

3. RESEARCH QUALITY: Our focus on research quality aims at maximizing the quality of research data through analytical methodology development and investigation of sampling and response issues.



OPDP's Social Science Research Program: Aiming to Understand How HCPs and Patients Interpret Rx Drug Information

Your Thoughts about the increased focus on OPDP Research?

Reminder- Discussed at the Jan 2022 AdPromo WG

New Division in the Drug Promotion Research Office

Division of Promotion Policy, Research and Operations (DPPRO)

(Published Jan 3, 2022)

- **Under the new reorganization, OPDP will get a new division: The Division of Promotion Policy, Research and Operations (DPPRO)**
  - "The reorganization will provide additional support and **increased focus on the regulatory counsel functions necessary to develop sound and legally supportable policy documents and surveillance activities,** particularly given First Amendment jurisprudence developments over the last few years,"

Caredx Wins $44.9 Million In Damages In False Advertising Trial Against Natera

- *Background…* CareDx alleged in 2019 that Natera used the results of a flawed clinical trial to make misleading statements about the effectiveness of Prospera, which Natera started selling later that year. CareDx said Natera used the study to falsely claim that Prospera was more effective than its competing AlloSure test.

- *In the News (CareDx Press Release)*… CareDx won its false advertising case against Natera **after a jury found Natera and its senior executives intentionally and recklessly misled the transplant community by deliberately engaging in false advertising in the promotion and marketing** of its Prospera kidney transplant rejection assessment test. CareDx received monetary damages totaling $44.9 million, including $21.2 million in compensatory damages and $23.7 million in punitive damages.
  - Overwhelming evidence came out at trial showing Natera made false statements that its senior executives knew were **based on unscientific, unreliable, and inappropriate conclusions** to market Prospera. GlobeNewswire (3/14/22)
  - **The jury found Natera liable for false advertising based on Natera's false comparisons of its kidney transplant assessment test, Prospera, to CareDx's market-leading AlloSure technology.** Specifically, the jury found Natera liable for:
    - False advertising under the **Lanham Act**
    - False advertising under the Delaware **Deceptive Trade Practices Act**
    - Intentional and willful engagement in **false advertising**
    - Intentional or reckless engagement in **unfair competition**

Caredx Wins $44.9 Million In Damages In False Advertising Trial Against Natera

- Commenting on the verdict, CareDx stated: “Today was **a landmark day for the transplant community because patient care and science won over false advertising**. … **We hope today’s verdict sends a clear message that CareDx will always fight for patients and work tirelessly to maintain trust in the transplant community**.”
  - **About CareDx – The Transplant Company:** CareDx, Inc., headquartered in South San Francisco, California, is a leading precision medicine solutions company focused on the discovery, development and commercialization of clinically differentiated, high-value healthcare solutions for transplant patients and caregivers. CareDx offers testing services, products, and digital healthcare solutions along the pre- and post-transplant patient journey and is the leading provider of genomics-based information for transplant patients. For more information, please visit: www.CareDx.com.

- Commenting on the verdict, Natera stated, “In reporting the jury's decision, **CareDx omits that CareDx itself was found to have engaged in false advertising, and makes unsubstantiated allegations**, including false assertions regarding Natera's executives. In addition, there has been no finding regarding the scientific validity of Natera's published data and test performance. In other litigation between the parties, a federal court recently invalidated all the patents that CareDx asserted against Natera. Natera continues to pursue its own patent enforcement action against CareDx.” Update on Lanham Act Case Between Natera and CareDx (prnewswire.com)

- The case is CareDx Inc v. Natera Inc, U.S. District Court for the District of Delaware, No. 1:19-cv-00662

DIA AdPromo Conference March 8-9, 2022
Heard at the Meeting (Selected)

A few select Q&As with the FDA Panel

- **Who mostly submits Bad Ad complaints?**
  - *What we heard…APLB is receiving complaints via Bad Ad too! And CDRH…*
- **Will the Instagram video be posted that was the subject of the Trulicity Untitled Letter?**
  - *What we heard… material submitted on the 2253 did not reflect the '35 scene changes in the 65 seconds' (or there abouts)*
- **Will OPDP take suggestions for what to cover in The Brief Summary?**
  - *What we heard… maybe. You can reach out to OPDP …*

Heard at the conference

- **Power Learning: DTCTV vs Online Video Ads Session**
  - ***Via Chat:*** *Ability to link to the labeling, length of content, how content will be displayed whether desktop v. mobile/app (determines if risk info will be clearly and fully viewable), etc. all must be considered.*
  - **Can you use a video intended for consumers in a HCP convention booth?** *May be considered minimization of risk if specific HCP info is not included … balancing risk could be achieved by presentation of HCP ISI in the booth … different perspectives on this topic.*
- *Common message* – **Context matters!**
- **Engaging with Patient Advocacy Groups:** Sponsor interactions with patient groups and their members, even when not promotional in nature, should always manage expectations and be "truthful and not misleading" – a standard that may differ depending on the content being shared and the goals of the interaction (e.g., receiving information from the patients vs. sharing information by the company).
- 21 CFR 312.7 Promotion of investigational drugs "…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**."
- Sound medical/scientific references do not have borders
- Use of social media can be tricky when it comes to posting on LinkedIn (for example)

Updates from APLB

Issues Flagged in Recent APLB Advisories

- Broadening of Indication
- Overpromise of efficacy
- Failure to provide important safety information
- Failure to include adequate dosing difference for a represented specific population

Contact Information

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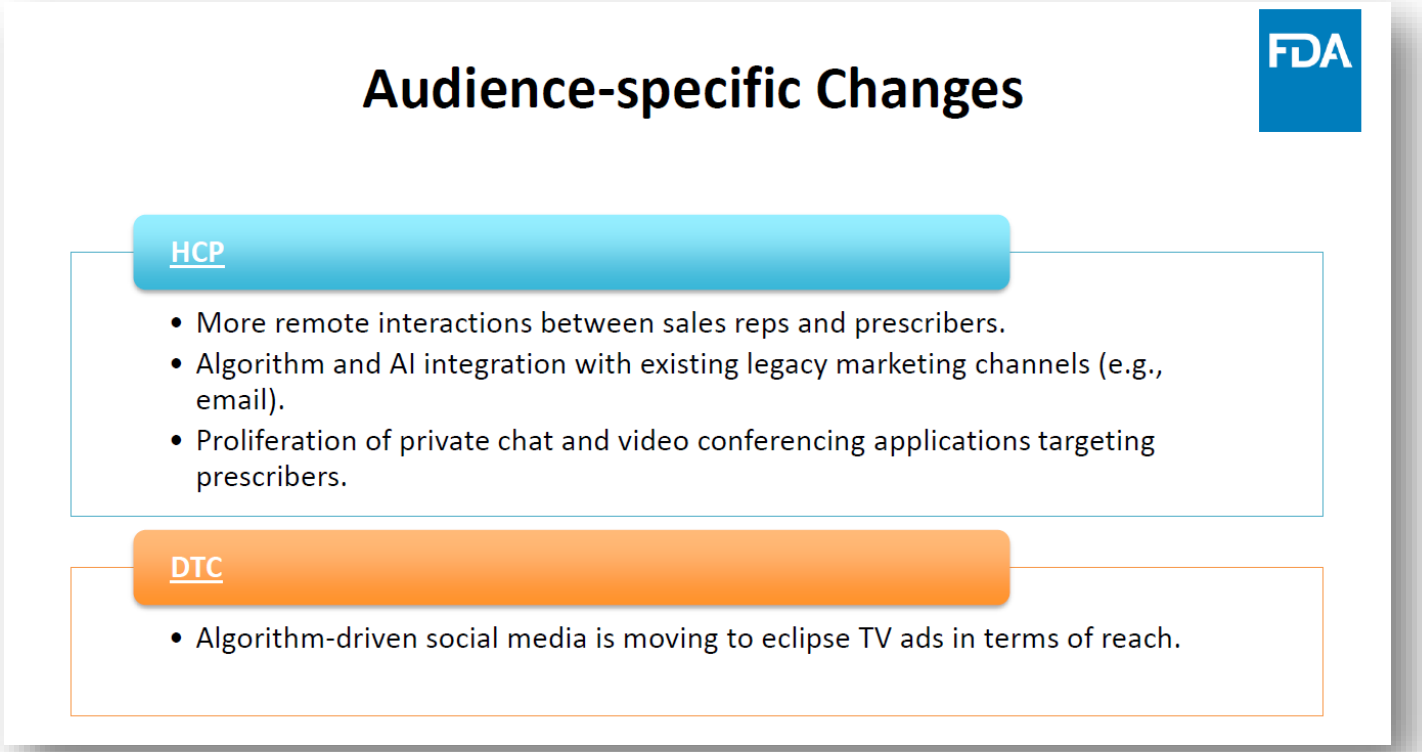
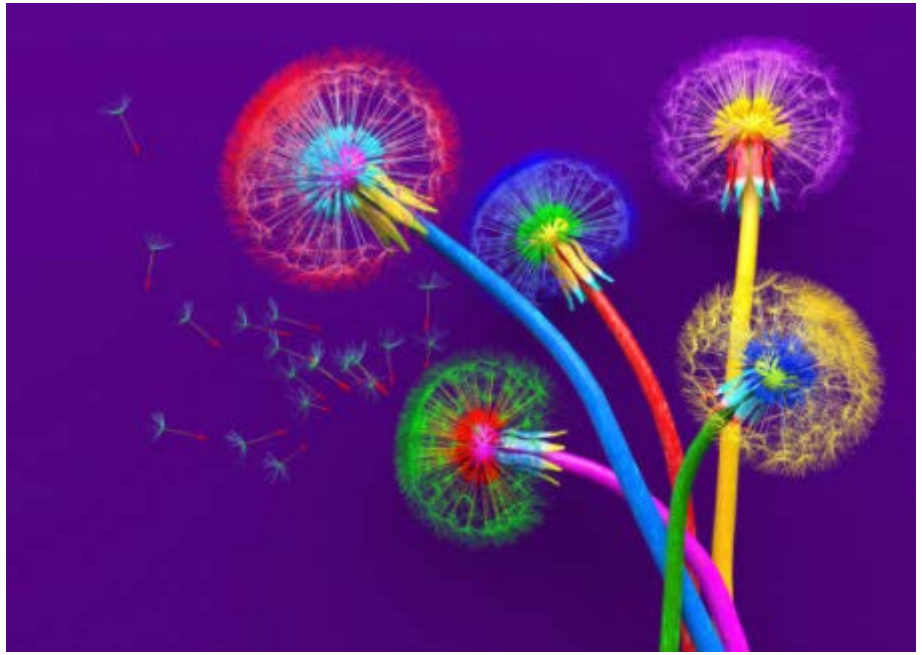
DIA AdPromo Conference March 8-9, 2022
Presented at the Meeting (Selected)

- **Research Status Updates, Kit Aikin, Senior Social Scientist Analyst/Team Lead, OPDP**

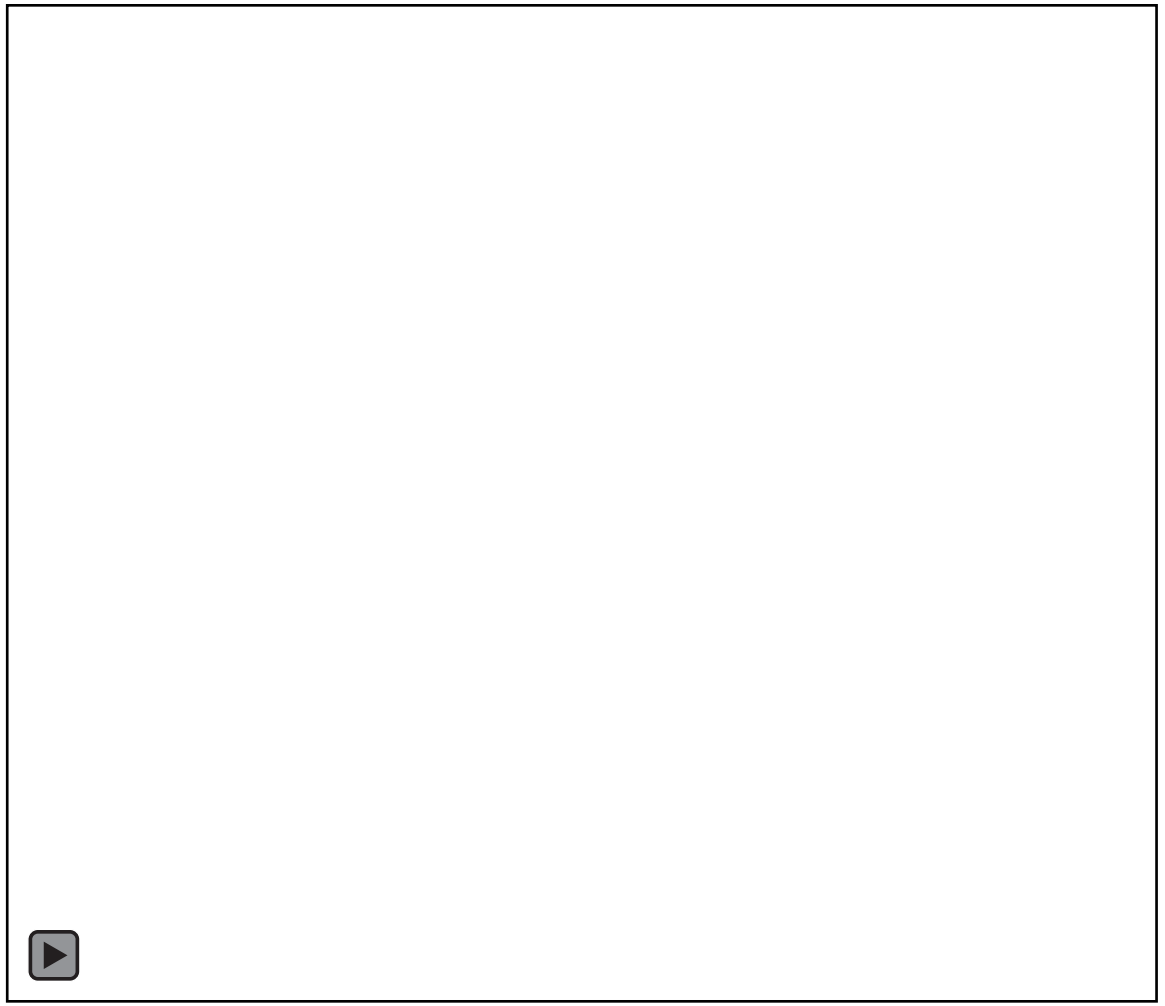


What else did you learn from the DIA AdPromo Conference?



Future Topic
(Suggested via the DIA AdPromo Conference)

- **In the AdPromo Space…XF Team Building**
  - Tips? What have you done? What works? What doesn't work?
- Anyone want to lead that discussion?



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