COVINGTON

2021 End-of-Year Summary of FDA Advertising and Promotion Enforcement Activity

February 17, 2022

Food, Drugs, and Devices

This e-alert reviews trends emerging from warning letters and untitled letters concerning product advertising and promotion issued in 2021 by the Office of Prescription Drug Promotion (OPDP) of the Center for Drug Evaluation and Research (CDER), the Advertising and Promotional Labeling Branch (APLB) in the Office of Compliance and Biologics Quality (OCBQ) of the Center for Biologics Evaluation and Research (CBER), the Office of Product Evaluation and Quality (OPEQ) of the Center for Devices and Radiological Health (CDRH), and the Office of Medical Device and Radiological Health Operations (OMDRHO) in the Office of Regulatory Affairs (ORA). OCBQ did not issue any advertising and promotion enforcement letters in 2021. We examined the 25 advertising and promotion letters issued by OPDP, OPEQ, and OMDRHO, and analyzed the most frequently cited allegations. This alert summarizes the letters and other enforcement trends.

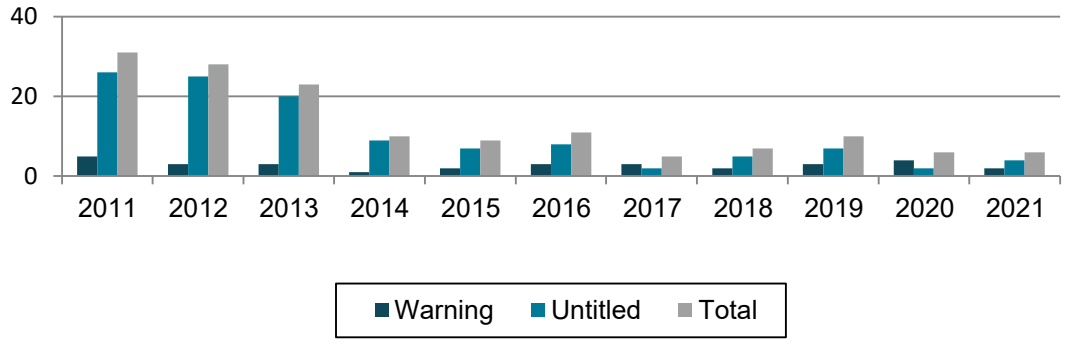
Office of Prescription Drug Promotion (OPDP)

I. Enforcement Activity

In 2021, OPDP issued six enforcement letters, the same number it issued in 2020, and four fewer than it issued in 2019. This figure remains consistent with the longer-term trend of OPDP issuing substantially fewer enforcement letters, a trend which likely reflects continued First Amendment pressure on FDA to allow truthful and non-misleading communications about prescription drugs. OPDP issued 52 letters in 2010 and continued to post over 20 letters a year through 2013.

In our 2019 alert, we noted that the slight increase in enforcement in 2018 and 2019 might indicate a recalibration of agency policy in a post-*Caronia* world. The slight dip in enforcement letters in 2020 and 2021, in comparison to recent years, may have been a result of FDA's focus on addressing the COVID-19 public health emergency.

OPDP Warning and Untitled Letters (2011-2021)*
Source: C&B tabulation, based on letters on FDA website

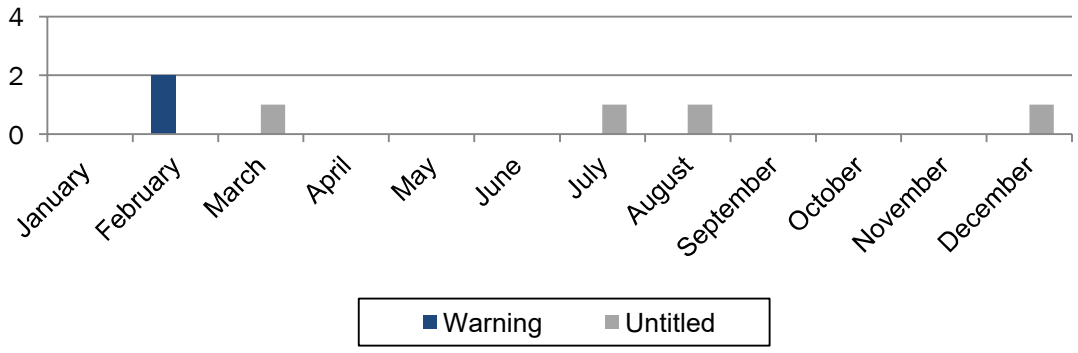


*In September 2011, FDA announced that the Division of Drug Marketing, Advertising, and Communications (DDMAC) would be reorganized into the Office of Prescription Drug Promotion (OPDP). For ease of reference, this alert refers only to OPDP.

Consistent with historical trends, and in a reversal from 2020, OPDP relied more heavily on untitled letters than warning letters in 2021. Of the six letters OPDP issued, four were untitled letters, and only two were warning letters.

Both warning letters were published in February. The four untitled letters were issued in March, July, August, and December, respectively. By contrast, in 2020 and 2019, OPDP's enforcement letters were clustered in the second half of the year.

OPDP Letters Issued by Month (2021)
Source: C&B tabulation,
based on letters on FDA website



The average number of allegations decreased compared to 2020 but was consistent with recent trends. Three of the six letters included only one allegation, one letter included two allegations,

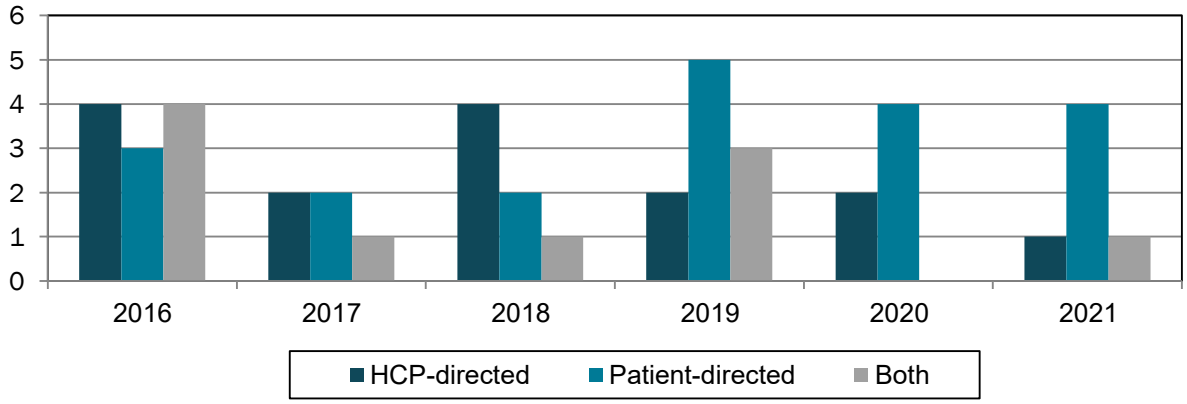
and two letters included three allegations, for an average of 1.8 allegations per letter (counted by the number of headings in each letter). By contrast, the average number of allegations in each letter was 2.2 in 2020 and 1.7 in 2019.

II. Content of Enforcement Letters

A. Nature of Promotional Pieces

Five out of the six enforcement letters addressed materials directed at patients, as opposed to materials intended solely for health care professionals (HCPs). This is consistent with FDA's recent focus on patient communications. In 2020, 67% of letters addressed materials directed at patients.

Number of Letters by Audience (2016-2021)
Source: C&B tabulation, based on letters on FDA website

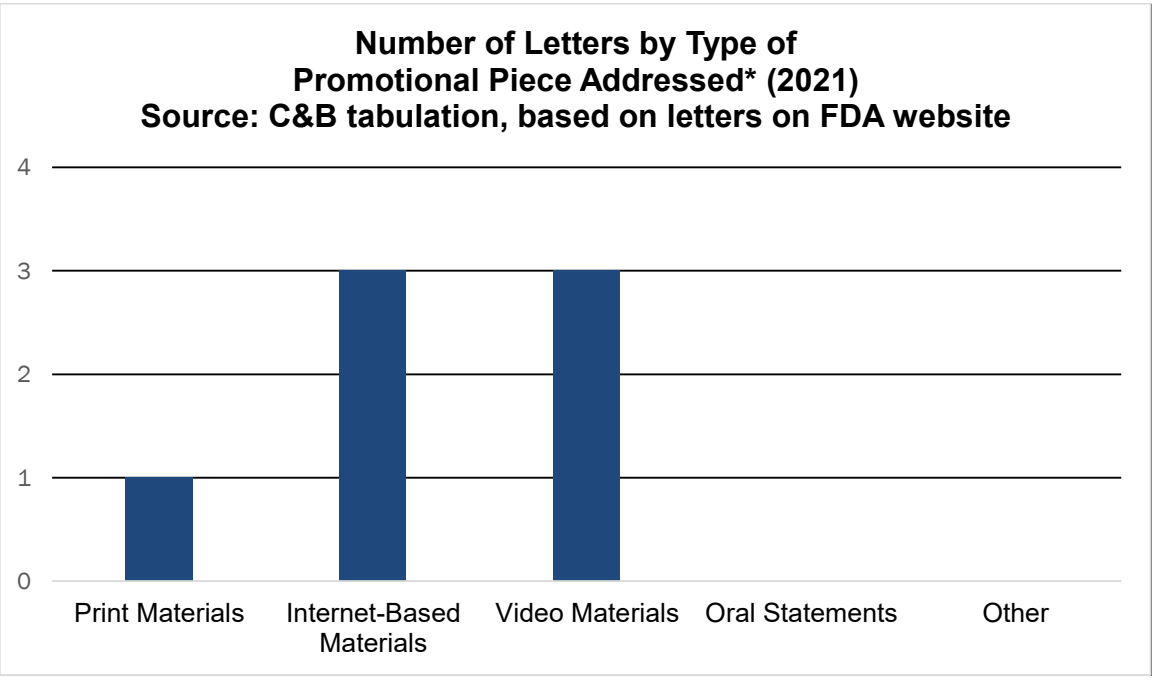


In 2021, OPDP's letters addressed three types of promotional materials: Video materials (television broadcasts[1]), internet-based materials (banner advertisements and sponsored links), and print materials (a tabletop display). Three of the letters addressed video materials, three letters addressed internet-materials, and one addressed print materials.[2] Consistent with recent years, no letters addressed oral statements by company representatives.[3]

[1] All three videos were also posted online.

[2] One letter addressed both a banner advertisement and a tabletop display.

[3] In 2015, 2016, 2017, 2019, and 2020, no letters addressed oral statements by company representatives. In 2018, a single letter addressed oral statements.



*Number of letters exceeds the total number of enforcement letters issued, as one letter addressed both a tabletop display and a banner advertisement.

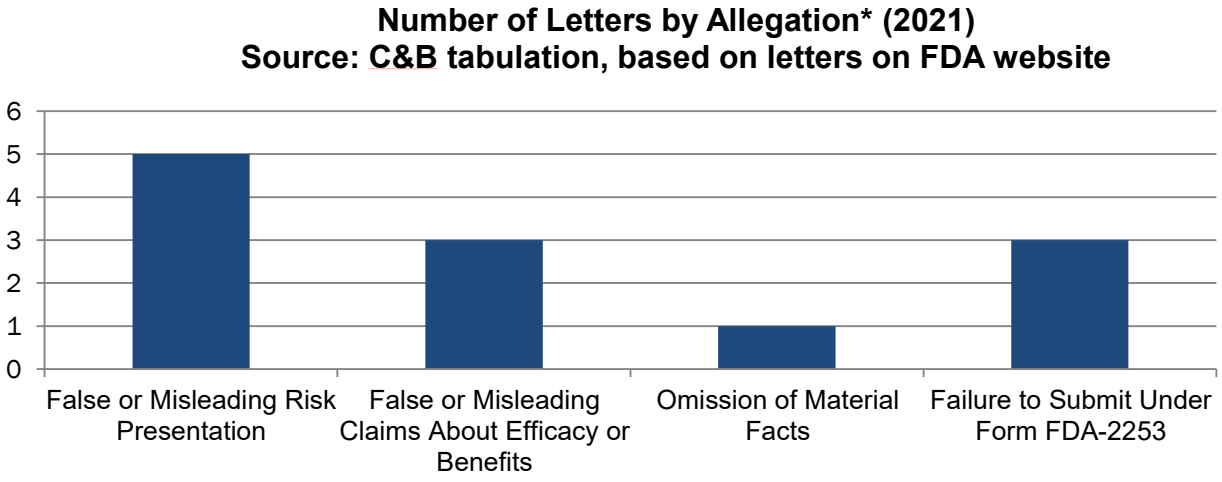
OPDP's letters related to video materials are noteworthy, as all three involved product endorsements. FDA has increasingly scrutinized the use of endorsements in direct-to-consumer (DTC) advertising. In 2020, OPDP announced the launch of two studies examining the use of celebrity, physician, patient, and influencer endorsements and whether the presence of a disclosure of their payment status impacts consumers' reactions.

As in 2020, all of the letters issued in 2021 related to marketed products; none included allegations of preapproval promotion. OPDP issued two letters concerning investigational products in 2019, and one letter in 2018.

B. OPDP's Allegations

Five of OPDP's letters contained allegations of false or misleading risk presentation (including one letter that alleged "false or misleading risk and benefit presentations"). Three letters alleged false or misleading claims about efficacy or benefit (including the letter alleging "false or misleading risk and benefit presentations," a letter that alleged "false or misleading claims about efficacy," and a letter that alleged "false or misleading benefit presentation"). One letter cited omission of material facts.

All three letters addressing DTC product endorsements alleged failure to submit the promotional material to OPDP under Form FDA-2253, in addition to one or more of the allegations listed above. OPDP had not issued a letter citing the failure to submit under Form FDA-2253 since 2017.



*Allegations exceed the total number of enforcement letters issued, as many letters contained more than one allegation. Because OPDP does not use standardized headings in its letters, allegations on the X axis include headings with minor phrasing differences. The allegation "false or misleading risk and benefit presentations" is listed under both "false or misleading risk presentation" and "false or misleading claims about efficacy or benefits."

1. False or Misleading Risk Presentation

Five of the six letters issued in 2021, including both warning letters and all three letters addressing DTC product endorsements, alleged that the cited promotional material contained false or misleading risk information. In three such letters, OPDP alleged that the promotional materials failed to include "any risk information." In a warning letter issued to CooperSurgical, Inc. (CSI), OPDP acknowledged that a promotional video featuring a physician interview referred viewers to the PARAGARD® (intrauterine copper contraceptive) website for further information about the product. However, OPDP concluded that "this does not mitigate the complete omission of risk information from the video."

OPDP's untitled letter to Eli Lilly and Company (Lilly) alleged that TV advertisements featuring interviews with Olympic athletes Ryan Murphy and Allysa Seely did not convey risk information for EMGALITY® (galcanezumab-gnlm) and also failed to either provide adequate provision or a brief summary as required by federal regulations. OPDP published Lilly's response letter, which stated that the complete broadcasts "as designed and aired" included three components, including a full-product TV segment that provided indication and risk information. The company stated further that TV advertisements referenced in FDA's letter were posted online without the full-product TV segment "without Lilly's direction." OPDP's close-out letter noted that the TV advertisements "appeared [online] as a cohesive presentation," but OPDP ultimately concluded that it "consider[ed] this matter closed," in part because the videos cited were removed from the website and Lilly had discontinued use of the "complete TV broadcasts."

In the remaining two letters, OPDP alleged that promotional materials failed to present risk information with the prominence and readability reasonably comparable with the presentation of benefit information. In an untitled letter regarding a video for NURTEC® ODT (rimegepant), OPDP took issue with the fact that risk information was presented in text-only format and in small font, and also noted that the video did not alert the viewer that important risk information followed an interview with Khloé Kardashian. OPDP made similar allegations regarding the presentation of risk information in a warning letter to AcelRx Pharmaceuticals, Inc., regarding a banner advertisement and tabletop display for DSUVIA® (sufentanil) sublingual tablet, an oral

opioid. In addition, OPDP also stated that the banner advertisement omitted material risk information, including with respect to the maximum daily dosage and the drug's limitations of use.

2. False or Misleading Claims About Efficacy or Benefit

In three letters, OPDP contended that the promotional pieces at issue contained false or misleading claims about the drug's efficacy or benefit. The Dsuvia warning letter alleged that the banner advertisement and display misbranded the drug by "imply[ing] that the administration of Dsuvia consists of a simple, one-step process, when this is not the case." Both promotional pieces included the claim "Tongue and Done."

In the Nurtec ODT untitled letter, OPDP alleged that an interview with Khloé Kardashian made claims unsupported by clinical evidence. OPDP stated that Kardashian's claims about experiencing migraine relief within 15 to 30 minutes "may be an accurate reflection of [her] own experience," but that there were no pre-specified endpoints that evaluated the efficacy of the drug at 15 to 30 minutes after dosing. OPDP also stated that Kardashian's "personal experience [did] not support" comparative claims that created "the suggestion that Nurtec ODT is more advanced than or superior to other migraine drug products on the market."

OPDP's July untitled letter to Amgen, Inc. (Amgen), regarding a professional animated banner advertisement for NEULASTA® (pegfilgrastim) represented the agency's first enforcement letter on innovator promotion related to discussion of biosimilars. Neulasta can be delivered via the Onpro® on-body injector (OBI) or via prefilled syringe (PFS). OPDP alleged that Amgen created a misleading impression by "stating that there is a statistically significant higher risk" of febrile neutropenia (FN) when pegfilgrastim is administered via PFS versus the OBI. OPDP stated that "multiple limitations of the cited study preclude the drawing of such conclusions."

OPDP stated that "[t]he above misleading claims and presentations are particularly concerning from a public health perspective because they could undermine confidence not just in Neulasta delivered via PFS but also in FDA-licensed biosimilar pegfilgrastim products, which are only delivered via PFS." The agency stated further that the "prominent[]" display of "Pegfilgrastim PFS" as the comparator arm versus "Neulasta Onpro" and "Onpro" "could result in healthcare providers failing to understand that Amgen's Neulasta was used in both arms of the study" and "conclud[ing] that a biosimilar pegfilgrastim product delivered via PFS is not as effective as Amgen's OBI product (i.e., Neulasta Onpro)."

3. Omission of Material Facts

OPDP's untitled letter to Lilly also alleged that the TV advertisements were misleading because they did not provide material information regarding Emgality's full FDA-approved indication, the preventive treatment of migraine in adults. OPDP stated that one advertisement suggested use of the drug for the preventive treatment of migraine (without specifying that it is indicated for use in adults) while the other suggested the use of the drug for the treatment of migraine (without specifying that it is indicated for preventive treatment in adults). Lilly's response stated that it believed that the "full advertisement with all three components" provided the full FDA-approved

indication and that, even if viewed separately, the components published online complied with FDA regulations.[4]

4. Failure to Submit under Form FDA-2253

FDA regulations require companies to submit any labeling or advertising devised for promotion of the drug product at the time of first use. Each submission must be accompanied by a completed transmittal Form FDA-2253. In its enforcement letters related to Emgality, Paragard, and Nurtec ODT, OPDP stated that publication of the promotional materials violated these regulations because the materials were not submitted to FDA under cover of Form FDA-2253 at the time of initial dissemination. As discussed above, all three of these letters addressed DTC product endorsements.

FDA received complaints through the Bad Ad Program regarding the videos at issue in the Paragard and Nurtec ODT letters.[5] Created in 2010, the Bad Ad Program is an outreach program designed to help HCPs recognize and report potentially false or misleading drug promotion. In 2020, the program updated its free online education course and educational case studies to reflect changes to the prescription drug promotional landscape, and the program published additional engagement pieces in 2021.[6] Although the program is intended for HCPs, anyone can submit a complaint to FDA. According to an article published by OPDP reviewer Ankur Kalola, 47% of complaints are submitted by consumers, and an additional 12% are submitted by industry.[7]

CBER Office of Compliance And Biologics Quality (OCBQ)

Enforcement Activity

FDA's Office of Compliance and Biologics Quality (OCBQ) did not issue any enforcement letters in 2021 relating to advertising and promotion. This lack of enforcement continues a recent downward trend in enforcement letters that began in 2013, when the office issued only three letters total, after issuing between five and seven letters each year between 2008 and 2012. Since 2013, OCBQ has issued only two enforcement letters, one in 2015 and one in 2018.

---

[4] Specifically, Lilly stated that the interviews with the Olympic athletes contained appropriate disease state awareness information and the statement "brought to you by Emgality proud partner of Team USA" was a proper reminder advertisement.

[5] FDA also received complaints regarding "promotional communications with similar claims and presentations as the ones discussed" in the Neulasta letter.

[6] FDA Newsletter, *OPDP Bad Ad Update*, THE BRIEF SUMMARY at 4–5 (Jan 2022), https://www.fda.gov/media/155980/download.

[7] Ankur Kalola, The FDA, Prescription Drug Promotion, and its Bad Ad Program, REGULATORY FOCUS at 4 (Mar. 2021), https://www.raps.org/RAPS/media/news-images/Feature%20PDF%20Files/21-3_Kalola.pdf.

CDRH Office of Product Evaluation and Quality (OPEQ) and ORA Office of Medical Device and Radiological Health Operations (OMDRHO)

I. Enforcement Activity

CDRH's OPEQ issued 19 warning letters related to advertising and promotion in 2021, one of which was cosigned by ORA's OMDRHO. This represented a significant increase from 2020 and 2019, when FDA issued one and eight warning letters, respectively. The letters addressed two types of allegations: (1) that the manufacturer promoted its device beyond the scope of its clearance, approval, or premarket exemption; and (2) that the manufacturer engaged in misleading promotion of products for COVID-19-related use.

II. Content of Enforcement Letters

1. Product Promotion Beyond 510(k) Clearance, PMA Approval, or Premarket Exemption

In a May warning letter to Nikkiso Medical America, Inc., OPEQ alleged that the company misbranded the Nikkiso DBB-06® by suggesting that the device was intended for dialysis with a physiological closed loop controller (PCLC) system, even though the PCLC function was not cleared under either of the device's 510(k) clearances. OPEQ stated that "[t]he introduction of a PCLC system is considered a change or modification in the device that could significantly affect the safety or effectiveness of the device, and therefore, requires clearance or approval."

2. Misleading Promotion of COVID-19 Products

The remaining 18 letters addressed the promotion of COVID-19 products that FDA alleged were being distributed without FDA approval, clearance, or authorization. Although this alert typically does not cover letters alleging distribution of devices without marketing approval, clearance, or authorization, these letters included additional allegations that we found notable.[8]

FDA issued one such letter in June to Innova Medical Group, Inc. (Innova), regarding the company's rapid antigen tests. FDA alleged that the 25T Configuration and 7T Configuration of the SARS-CoV-2 Antigen Rapid Qualitative Test were misbranded because the performance estimates in the labeling "d[id] not accurately reflect the performance estimates observed during the clinical studies." The Agency stated further that the clinical data Innova submitted in its emergency use authorization (EUA) request "was identical to data previously provided by other manufacturers in their separate EUA requests." FDA concluded that the "data reliability and accuracy issues . . . raise[d] significant concerns that the performance of the SARS-CoV-2 Antigen Rapid Qualitative Test has not been adequately established, and that the products distributed by Innova without FDA approval, clearance, or authorization could present a serious risk to the public health."

[8] Only those letters with additional allegations are covered here. FDA issued numerous other letters alleging that COVID-19 products were adulterated and misbranded because they were being distributed without marketing approval, clearance, or authorization from FDA that are outside the scope of this review.

In December, FDA issued a warning letter to DermaCare Biosciences, LTD., regarding its Easy Rapid Now COVID-19 Nasal Swab Antigen Test, alleging that the company was promoting the test for the screening or diagnosis of COVID-19. FDA cited statements on the company's website as evidence that the "test is intended for diagnosis of COVID-19 including screening for COVID-19 in asymptomatic individuals without known exposure with the intent of making individual decisions based on the test results (e.g., who may return or what protective measures to take on an individual basis)." FDA also alleged that the company's LinkedIn site displayed the FDA logo, stating that "[s]uch use may send a misleading message that the FDA favors or endorses your products."

Finally, FDA issued 16 letters with similar allegations regarding the distribution and labeling of face masks. OPEQ alleged that these products were misbranded not only because they were being distributed "without marketing approval, clearance, or authorization from FDA," but because their labeling suggested that they were in fact FDA approved, cleared, or authorized. Across these letters, OPEQ cites several ways in which the labeling can create a misleading impression. These include:

- Unauthorized use of FDA's logo;
- Representing masks as being "certified" by FDA; and
- Stating that the product is "FDA Approved."

***

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food, Drugs, and Devices practice:

Scott Cunningham	+1 415 591 7089	scunningham@cov.com
Scott Danzis	+1 202 662 5209	sdanzis@cov.com
Stefanie Doebler	+1 202 662 5271	sdoebler@cov.com
Michael Labson	+1 202 662 5220	mlabson@cov.com
Christina Kuhn	+1 202 662 5653	ckuhn@cov.com
Beth Braiterman	+1 202 662 5864	bbraiterman@cov.com