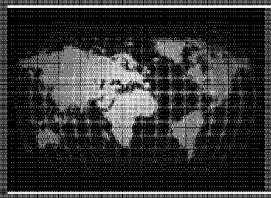

FDA MEETING

April 7, 2016
11:00AM - 12:00PM

Location: FDA White Oak Campus
Building 1, Conference Room 2102
10903 New Hampshire Avenue
Silver Spring, MD 20993
Commissioner's Office
Phone Number: 301-796-5000

DEBRA BARRETT
EXHIBIT
08154
Juliana Zajicek, CSR. 01/28/2021

PLAINTIFF TRIAL
EXHIBIT
P-23847_00001

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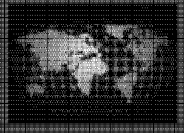


FDA Attendees

Robert Califf, M.D. FDA Commissioner

Douglas Throckmorton, M.D., Deputy Center Director for Regulatory Affairs, Center for Drug Evaluation and Research

Jeremy Sharp, Deputy Commissioner for Policy, Planning and Legislation

Bruce Kuhlik, Senior Advisor to the Commissioner

Tom Kraus, Chief of Staff

Teva Attendees

Erez Vigodman, President and Chief Executive Officer

Michael Hayden, CM OBC MB ChB PhD FRCP(C) FRSC, President of Global R&D and Chief Scientific Officer

Siggi Olafsson, President and CEO, Global Generic Medicines Group

James G. Ottinger, RPh, Senior Vice President and Head of Global Regulatory Affairs

Debra Barrett, Senior Vice President Global Government Affairs and Public Policy

Arrival Details

- Teva attendees should be dropped off in front of the main FDA entrance (Building 1).
    - Upon entering the campus from New Hampshire Avenue please proceed to the stop sign on Mahan Road. The circular driveway leading to Building 1 is straight ahead.
- Please allow 30 minutes to get from the visitor's area to the Commissioner's conference room and extra time to accommodate the security check-in and set up slide presentation.
- **All meeting participants are required to show picture identification (driver's license preferred) we will need to provide passports for non US citizens.**
- An escort will meet Teva attendees in the lobby of Building 1.

Meeting Context

This meeting with the FDA provides Teva an exceptional opportunity to meet with the newly appointed Commissioner and his senior advisors. Originally requested by Teva as a technical meeting to discuss process related to our opioid abuse deterrent pipeline, the meeting goals have evolved to allow for a more robust conversation on Teva's breadth and impact on the health of US Citizens; our commitment to science; focus on patients and interest in partnering with the FDA.

Notable in the attendee list is Douglas Throckmorton, M.D, Deputy Center Director for Regulatory Affairs, Center for Drug Evaluation and Research who has been a lead supporter of abuse deterrent technology as an important component in the progress to prevent the abuse of opioid drugs. He led the announcement on the label changes for Prude Pharma' reformulated extended-release OxyContin tablets and removal of Purdue Pharma's original formulation of OxyContin ER and has been the spokesperson in the media on the release of the FDA draft guidance to encourage the development of abuse-deterrent opioids. Regarding abuse deterrent products he has said, "We believe such products have promise to help reduce prescription drug abuse and improve public health." His attendance at the meeting provides us the opportunity to discuss in detail our desire to be a partner in the opioid abuse crisis.

Another notable attendee is Jeremy Sharp, Deputy Commissioner for Policy, Planning and Legislation. His attendance allows the opportunity to discuss policy barriers impacting innovation. Teva's US Government Affairs is currently supporting the introduction of abuse-deterrent technology (ADT) legislation that would impact the agency. The legislation removes a barrier to innovation by making the abuse deterrent property a condition of approval—allowing for more types of ADT medications to come to market without blocking each other. This change would allow for greater diversity in ADT products types while encouraging innovation by supporting exclusivity on those products with clinical abuse potential studies.

Additional Background

Be sure to review the Global Regulatory Intelligence & Policy Briefing: *FDA Activities & Significant Events Addressing Opioid Misuse & Abuse* prepared by Teva's Regulatory Intelligence team in support of this meeting.

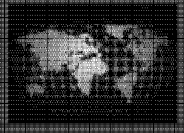
Agenda

Who is Teva?

- Profile and Presence
- Contributions to the US Healthcare System
- Generic Capabilities, Technology and Pipeline – Allergan Generics Acquisition

Key Therapeutic Areas

- Portfolio and Pipeline
- Beyond the Pill Capabilities and Innovation on Existing Molecules
- Innovation w/focus on Abuse-Deterrent Technology



Overall Goals of the Meeting	
• Leadership introduction of Teva to the FDA • Introduce FDA to breadth of Teva and impact on the health of US citizens • Underscore Teva's commitment to science, focus on patients, interest in partnering with the agency • Elevate Teva as a public policy thought leader with broad understanding of the pharmaceutical market both brand (specialty) and generic	
Meeting Flow	
Erez	What Makes Teva Different, Teva's Profile and Contribution, Generic Savings, Specialty and Beyond the Pill
Siggi	Generic Capabilities and Allergan Generics Acquisition
Michael Jim	Specialty Capabilities, Regulatory Affairs Capabilities, Innovation on Existing Molecules: Spotlight on ADs
Erez	Looking to the Future: the Space Between

DEEP DIVE: LOOK AT THE NEW COMMISSIONER

Key Characteristics

- Distinguished Cardiologist
- Registered Democrat
- One of the world's premier experts in clinical trial design.
- Has dedicated most of his career to improving the way clinical trials are run, and has specifically focused on groundbreaking trial designs for medicines to prevent blood clotting.
- He has donated all of his pharmaceutical/biotech consulting fees since the mid 2000s to non-profits; value is in the 6-figures.
- Founded and ran the Duke Clinical Research Institute, a $200M center that manages clinical trials in more than 65 countries, involving more than 1.2M patients.
- Ran a multimillion-dollar clinical research center at Duke University that received more than 60 percent of its funding from industry.
- Advocate for innovation and regulatory reform:
    - In a May 2014 presentation, Califf called attention to an unsustainable trend in drug development–that "the number of new drugs approved by the FDA per billion US dollars (inflation-adjusted) spent on research and development has halved roughly every nine years since 1950."
- Loves to workout, play golf, loves Duke basketball.

Nomination Background

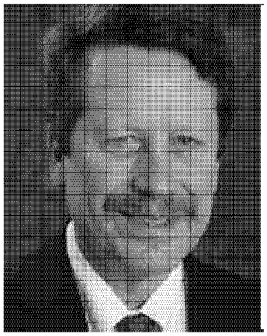
Characterized as an industry-insider Dr. Califf's was confirmed in February 2016 after weeks of opposition and delay from a handful of Senators who blocked his nomination over criticism of how the FDA has handled prescription painkillers. Chief among those in opposition was Senator Edward Markey (D-MA), who called on the FDA to take a harder stance in addressing the epidemic claiming the agency had "willfully blinded itself to the warning signs." Dr. Califf's nomination was confirmed only after the agency released a "far-reaching action plan to readdress the agency's approach to opioid medications." In the end four Senators voted against his confirmation Senators Markey, Joe Manchin III, Democrat of West Virginia; Kelly Ayotte, Republican of New Hampshire; and Richard Blumenthal, Democrat of Connecticut. More details on the FDA's comprehensive opioid action plan please read the Global Regulatory Intelligence & Policy Briefing: *FDA Activities & Significant Events Addressing Opioid Misuse & Abuse* accompanying this Government Affairs Policy Brief.

Industry Background Information

- He was the director of Portola Pharmaceuticals Inc from July 2012-Juanary 2015
- He has been a paid consultant for many companies including:

Teva	La Roche Ag
Merck Sharp & Dohme	Janssen Pharmaceuticals
Johnson & Johnson	Daiichi sankyo
GlaxoSmithKline	Sanofi-Aventis
AstraZeneca	Bristol-Myers Squibb
Eli Lilly	Astra Zeneca
Amgen	

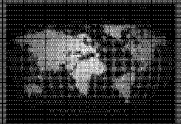
FDA Biographies



Robert M. Califf, MD, MACC, FDA Commissioner

Robert M. Califf, MD, MACC, is the Food and Drug Administration's commissioner of food and drugs. As the top official of the FDA, Dr. Califf is committed to strengthening programs and policies that enable the agency to carry out its mission to protect and promote the public health.

Previously, Dr. Califf served as the FDA's Deputy Commissioner for Medical Products and Tobacco from February 2015 until his appointment as commissioner in February 2016. In that capacity, he provided executive leadership to the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, and the Center for Tobacco Products. He also oversaw the Office of Special Medical Programs and provided direction for



cross-cutting clinical, scientific, and regulatory initiatives, including precision medicine, combination products, orphan drugs, pediatric therapeutics, and the advisory committee system.

Prior to joining the FDA, Dr. Califf was a professor of medicine and vice chancellor for clinical and translational research at Duke University. He also served as director of the Duke Translational Medicine Institute and founding director of the Duke Clinical Research Institute. A nationally and internationally recognized expert in cardiovascular medicine, health outcomes research, healthcare quality, and clinical research, Dr. Califf has led many landmark clinical trials and is one of the most frequently cited authors in biomedical science, with more than 1,200 publications in the peer-reviewed literature.

Dr. Califf has served on the Institute of Medicine (IOM) committees that recommended Medicare coverage of clinical trials and the removal of ephedra from the market, as well as on the IOM Committee on Identifying and Preventing Medication Errors and the IOM Health Sciences Policy Board. He has served as a member of the FDA Cardiorenal Advisory Panel and FDA Science Board's Subcommittee on Science and Technology. Dr. Califf has also served on the Board of Scientific Counselors for the National Institutes of Health and the National Library of Medicine, as well as on advisory committees for the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Institute of Environmental Health Sciences and the Council of the National Institute on Aging.

While at Duke, Dr. Califf led major initiatives aimed at improving methods and infrastructure for clinical research, including the Clinical Trials Transformation Initiative (CTTI), a public-private partnership co-founded by the FDA and Duke. He also served as the principal investigator for Duke's Clinical and Translational Science Award and the NIH Health Care Systems Research Collaboratory coordinating center.

Dr. Califf is a graduate of Duke University School of Medicine. He completed a residency in internal medicine at the University of California, San Francisco and a fellowship in cardiology at Duke.

Douglas Throckmorton, Deputy Center Director for Regulatory Affairs, Center for Drug Evaluation and Research

As Deputy Director for Regulatory Programs, Dr. Throckmorton shares the responsibility for overseeing the regulation of research, development, manufacture and marketing of prescription, over-the-counter, and generic drugs in the United States. He is committed to ensuring that the benefits of approved drugs outweigh their known risks.

Dr. Throckmorton received his medical degree from the University of Nebraska Medical School and completed his residency and fellowship at Case Western Reserve University and Yale University, respectively. Prior to coming to the FDA in 1997, he conducted basic science research and practiced medicine at the Medical College of Georgia, Augusta, Georgia and Augusta Veterans Administration Hospital. He is a board-certified physician.

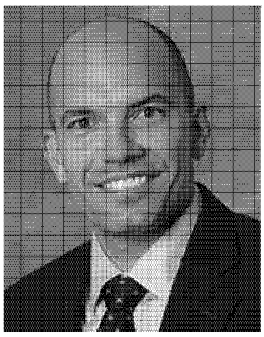
Jeremy Sharp, Deputy Commissioner for Policy, Planning and Legislation

Previously, Jeremy has served in two positions at the Department of Health and Human Services (HHS) during the Obama Administration. As Counselor to the Secretary for Science and Public Health he worked closely with Food and Drug Administration (FDA) leadership on various issues including opioid abuse, tobacco control, food safety, antimicrobial resistance, lab safety, pharmacy compounding, and drug safety. And as Deputy Assistant Secretary for Legislation, he worked with FDA's Office of Legislation and key Congressional offices on the Food and Drug Administration Safety and Innovation Act, the Pandemic and All-Hazards Preparedness Reauthorization Act, and the Drug Quality and Security Act, as well as other issues.

Prior to joining HHS, Jeremy served as Legislative Director to Senator Chris Dodd, and as a Professional Staff Member of the Senate Health, Education, Labor, and Pensions Committee, Subcommittee on Children and Families, chaired by Senator Dodd. During this time he was involved in the passage of landmark legislation such as the Family Smoking

Prevention and Tobacco Control Act, which gave FDA regulatory authority over tobacco products, the Food and Drug Administration Amendments Act reauthorizing the various user fee programs, and the Affordable Care Act.

Before that he worked for Rep. Lois Capps on health issues before the House Energy and Commerce Committee, Sen. Evan Bayh, and as a Manager of Government Relations at Trust for America's Health, working on various public health issues.



Tom Kraus, Chief of Staff

Tom Kraus is the Chief of Staff at the U.S. Food and Drug Administration (FDA). He previously served as the Associate Commissioner for Legislation, where he led legislative efforts to advance the FDA's public health priorities.

Prior to joining the FDA, he served as health policy advisor to Senators Tom Harkin and Edward Kennedy and as Deputy Staff Director for Health on the Senate Committee on Health, Education, Labor and Pensions. In that role he oversaw the development of legislation to protect the safety of the food supply and medical products and to improve health care quality. He has also served as a strategic advisor to public and private health systems and to medical product manufacturers in the health care and life sciences practices at McKinsey & Company and Ernst and Young.

He received a B.S. in biology from the University of Michigan, a J.D. from the Georgetown University Law Center and a Master of Health Sciences from the Johns Hopkins University Bloomberg School of Public Health.

Bruce Kuhlik, Senior Advisor to the Commissioner

Bruce Kuhlik serves as Senior Advisor to the Commissioner of Food and Drugs. He provides policy advice on significant issues before the FDA. He came to the agency in September 2015 after holding a variety of positions in industry, private law practice, and government.

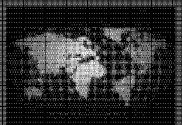
From August 2007 through June 2015, Mr. Kuhlik was general counsel of Merck & Co., Inc. In addition to leading Merck's legal department, Mr. Kuhlik had oversight responsibility for the company's public policy, communications, federal government relations, corporate responsibility, and security functions. From May 2005 through July 2007, he served as the company's associate general counsel. From 2002 through 2005, Mr. Kuhlik was general counsel of the Pharmaceutical Research and Manufacturers of America.

Mr. Kuhlik was a partner in the law firm of Covington & Burling from 1990 through 2002; previously, he was an associate at the firm. He chaired the firm's food and drug and healthcare practice groups, providing advice and representation on the full range of issues facing industries regulated by the FDA.

From 1984 through 1986, Mr. Kuhlik served as an assistant to the Solicitor General in the Department of Justice, where he briefed and argued cases before the U.S. Supreme Court. From 1981 through 1982, he was a judicial clerk to the Hon. Levin H. Campbell of the U.S. Court of Appeals for the First Circuit.

Mr. Kuhlik also has served as an adjunct professor of law at NYU and the University of Pennsylvania and has been a guest lecturer at other law and medical schools. He is a member of the American Law Institute and a recipient of the Food and Drug Law Institute's Distinguished Service and Leadership Award.

Mr. Kuhlik received his bachelor's degree in economics from Harvard College and his law degree from Harvard Law School.



Global Regulatory Intelligence & Policy Briefing:
FDA Activities & Significant Events Addressing Opioid Misuse & Abuse

Background:

Teva continues to demonstrate our commitment to patients in pain with our ongoing development of branded and generic ADF opioids and non-opioid analgesic medicines. The FDA has been making efforts to address opioid misuse and abuse since 2001 when they required Purdue Pharma to modify the label for OxyContin to add and strengthen warnings about the drug's potential for misuse and abuse. Since that time, the public scrutiny that FDA has undergone has resulted in the modification of statutory requirements for the development and approval of opioids as well as post approval surveillance to maintain these medicines on the market. This brief provides an overview of the regulatory history, as well as the most current changes in the regulatory landscape, and the implications to Teva.

FDA Comprehensive Action Plan:

In early February, FDA Commissioner Robert Califf announced the Agency's Comprehensive Action Plan, a multi-prong approach to mitigate the risks of abuse and misuse of opioid medicines. The plan is comprised of four main pillars: 1) greater Agency transparency to the approval process for opioids; 2) improving communications with the medical community about opioids; 3) improving the information that is available about opioid use; and 4) focusing efforts on approving drugs that have the potential to mitigate opioid abuse (abuse deterrent formulations).

More specifically, the plan requires FDA to:

- Expand the use of advisory committee (effective February 5, 2016) such that they will convene an expert advisory committee before approving any NDA for an opioid that does not have abuse-deterrent properties as well as consulting an advisory committee on ADF opioids when they raise novel issues. The Pediatric Advisory Committee will make recommendations regarding a framework for pediatric opioid labeling before any new labeling is approved.

- Develop warning and safety information for immediate-release (IR) opioid labeling comparable to that of the ER/LA opioid analgesics labeling update from 2013.

- Strengthen the post marketing requirements associated with approval of all opioids to ensure sponsors generate sufficient post market data on the long-term impact of using ER/LA opioids.
- Update the risk evaluation and mitigation strategy (REMS) program requirements associated with the ER/LA opioids after taking into consideration advisory committee recommendations and review of existing requirements.

- Expand access to abuse deterrent formulation (ADF) opioids to discourage abuse and issue draft guidance for the approval standards for generic abuse-deterrent formulations.

- Reassess the risk-benefit approval framework for opioids by obtaining advice from the Agency's Science Board in March 2016 and also current engagement with the National Academies of Sciences, Engineering, and Medicine on how to take into account the evolving understanding of the risks of opioids, not only to the patient but also risks of misuse by others who obtain them.

Since publication of the Plan, FDA modified the former post marketing requirements (PMR) from five studies and replaced them with eleven PMRS (ten post marketing studies and one clinical trial) to include refined measures for assessing the known serious risks of misuse, abuse, addition, overdose, and

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death; held the Science Board Meeting, scheduled six upcoming Advisory Committee meetings related to these opioid medications, and released draft guidance for generic AD formulations.

Teva Impact Statement:

The action plan has resulted in the delay of FDA's approval of our Vantrela application, the first AD hydrocodone to demonstrate abuse deterrent properties in all categories of abuse as described in the FDA's brand guidance.

Teva will be presenting Vantrela ADF data before an FDA Advisory Committee on June 7, 2016, the requirement of this Ad Com is a direct impact from the recent agency Comprehensive Action Plan.

Teva has also been advised that the post marketing requirements for evaluating Vantrela have increased and been made more comprehensive than previously advised. The actions described in this plan will impact seven of Teva's approved ANDA generic medicines, warranting labeling changes to these medicines. The additional post marketing requirements and the new labeling will also impact three branded products in the pipeline as they will have to modify their development plans for inclusion of these recent changes.

Safety Labeling Changes:

On March 22, 2016, FDA announced class-wide safety labeling changes for the immediate release (IR) opioids. Among the changes, FDA requiring a new boxed warning communicating the serious risks of misuse, abuse, addiction, overdose and death. Additionally, FDA is requiring updated labeling for all opioids (both ER/LA and IR) to include safety information about potentially harmful drug interactions with other medicines that can result in serotonin syndrome. FDA is also requiring updated labeling that will include information about opioid effects on the endocrine system, including a rare but serious disorder called adrenal insufficiency and androgen deficiency. Lastly, the FDA is aware of and carefully reviewing available scientific information about potentially serious outcomes related to interactions between benzodiazepines and opioids. Once the review is complete, FDA will communicate their findings to ensure prescribers and the public are appropriately informed.

Draft Guidance for Generic Abuse Deterrent Opioids:

Most recently, on March 25, 2016, FDA published their long-awaited draft guidance entitled '***General Principles for evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products***'. This draft guidance is a nice parallel to that of the brand-side guidance, finalized in 2015, and provides the principles for ANDA applicants to evaluate the abuse-deterrence of a proposed generic version of a brand-name Reference Listed Drug (RLD) with labeling that describes properties expected to deter misuse or abuse. Currently, this draft guidance provides testing recommendations for four of the seven categories of abuse-deterrent technologies described in FDA's brand guidance. These include solid oral opioid drug products formulated to incorporate physical or chemical barriers, agonist/antagonists, aversive agents, or combinations of two or more of these technologies. At this time, the Agency believes comparative in-vitro and PK studies typically should be adequate to demonstrate that the proposed ADF generic is no less abuse deterrent than that of the approved RLD. Five key principles described in this guidance include: 1) tier-based approach to testing; 2) evaluation of abuse deterrence such that the proposed generic ADF should be compared to the approved RLD for all routes of abuse using the tier-based approach; 3) a control should be employed and, when possible, it should be a non-abuse version of the approved product; 4) parameters for the discriminatory study conditions should lie within the

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range specified in this guidance for different routes of abuse; and 5) statistical comparisons for each of the different routes of abuse as recommended should be conducted once the in vitro discriminatory study conditions have been identified.

Teva Impact Statement:
Teva Generics R&D now has guidance on how to further develop abuse deterrent generic opioids in our pipeline, efforts that had been on hold in anticipation of this guidance. The discussion of testing and requirements in the draft generic guidance is proving to be a useful tool in preparing our scientific evidence for the upcoming Vantrela ad com.

ADF APPROVED OPIOIDS

2013	Oxycontin (oxycodone HCl), with ADF claims
2014	Targiniq ER (oxycodone and naloxone)
2014	Embeda (morphine sulfate and naltrexone HCl)
2014	Hysingla ER (hydrocodone bitartrate)
2015	MorphaBond (morphine sulfate)

The above table illustrates a significant problem; FDA has been generating guidance and modifying regulations for years, has more than 30 open INDs for abuse deterrent formulation opioids but only has five products approved to date that are allowed to make claims of abuse deterrence. The FDA guidance issued in 2013 created a path forward for branded ADF approvals and the 2016 guidance now provides a similar pathway for ANDAs. The added burden for sponsors to have Ad Coms is resource intensive on both industry and FDA, but if they can help facilitate FDA to more efficient approvals of ADF opioids, this will translate to greater access and adoption of these medicines to our patients.

RELATED RECENT/UPCOMING FDA AD COM MEETINGS AND PUBLIC HEARINGS

March 1	***Science Advisory Board Meeting*** The meeting was focused on understanding the science of pain and the treatment options available. In regard to opioids, the discussion centered on addiction, abuse, and how ADFs could make a positive impact. Teva presented at the open Public Hearing portion of the meeting.
May 3-4,	***Joint Meeting of Drug Safety and Risk Management and the Anesthetic and Analgesic Drug Products Advisory Committee*** As part of Califf's action plan, the expectation is that the LAO REMS program will have more stringent education requirements for physicians prescribing opioids.
May 5	***Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee*** The panels will be discussing KemPharm's benzhydrocodone/acetaminophen oral tablets for the management of acute pain and asked whether the sponsor has demonstrated abuse-deterrent properties for their product that would support labeling and whether the nasal route of abuse is relevant for combination products made up of hydrocodone and acetaminophen. This is the first drug-specific AdCom since FDA announced their Comprehensive Action Plan. This will be important for Teva to attend/observe and see the line of data presented and questioning associated with it regarding demonstration of abuse deterrence.

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June 7	***Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting*** The panels will be discussing Teva's Vantrela data to evaluate whether Teva has adequately demonstrated abuse-deterrence that would support labeling. Teva's data demonstrates that Vantrela deters all three categories of abuse as described in the FDA guidance.
June 8	***Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting*** The panels will be discussing Pfizer's oxycodone HCl and naltrexone HCl extended-release capsules for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The panels will be asked to discuss whether the data are sufficient to support labeling with the properties expected to deter abuse. While this meeting takes place after our Vantrela meeting, it will give us insight into questions the panelists have on this combination product which is analogous to a product in our development pipeline.
Sept 15-16	***Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee Meeting*** The panels will discuss the appropriate development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients, including obtaining PK data and use of extrapolation. To what extent this will impact the pediatric development plan for Vantrela is unclear but the outputs of this meeting will translate to future implications of Teva's other opioid analgesics in development.

KEY REGULATORY HISTORY

1995	Oyxcontin (oxycontin controlled-release) approved; first formulation of oxycodone that allowed for dosing every 12 hours instead of every 4-6 hours.
1998	Actiq (fentanyl citrate) approved; first pain medicine approved to treat breakthrough pain in patients with cancer. Approved under subpart H (limited distribution and prior clearance for all promotional activities) Also included a risk management plan. This formulation created concerns in pediatrics as it was referred to as a 'lollipop'. FDA requested Cephalon to explore new formulations.
2001	Oxycontin label was changed to add and strengthen warnings about the drug's potential for misuse and abuse.
2003	Controlled Substance Staff (CSS) created within FDA to oversee the evaluation of abuse liability, drug dependence and risk management, and make recommendations on drug scheduling of new compounds.
2006	Formation of Cross Company Abuse Liability Consortium (now Counsel) – a 'grass roots' collaboration of colleagues from several pharmaceutical companies that came together to advance the science and regulatory environment of abuse potential assessment.
September 2006	Fentora (fentanyl citrate) is a buccal tablet approved for breakthrough pain in patients with cancer. Fentora was the first opioid approved under the then FDA Risk MAP Guidance.
2006	Cephalon joins CCALC and has been an active participant since.

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Spring 2007	Cephalon learns of serious adverse events (SAEs) of misuse and abuse of Fentora. Begins data review to support labeling change intended to improve dosing instruction language to mitigate future SAEs associated with misuse or abuse.
Late Summer 2007	Cephalon learns of death associated with misuse and abuse of Fentora and notifies FDA. Cephalon and FDA begin process to modify labeling and Risk MAP.
September 2007	***Food and Drug Administration Amendments Act*** established requirement of Risk Evaluation and Mitigation Strategies (REMS) for drugs requiring additional steps beyond labeling to ensure the safe use of a product. The timing of this significantly impacted Fentora as the changes in legislation regarding the enhanced risk management requirements came at the same time that the Fentora team was evaluating SAEs associated with the product and preparing the sNDA for use in non-cancer related breakthrough pain. In parallel to this, FDA was not in agreement among themselves with their interpretation of the new law, making their lack of concurrence difficult for negotiations and implementation of REMS.
November 2007	Cephalon submits sNDA for use of Fentora in patients with non-cancer related breakthrough pain and is notified they will go to FDA Advisory Committee Meeting. Key issues of concern – was the REMS that was submitted with sNDA adequate to address the risks associated with use of Fentora for non-cancer related breakthrough pain and was there a medical need for chronic use of opioids in patients that did not have cancer given the risk/benefit ratio?
May 2008	Fentora goes to FDA Advisory Committee to assess the risk/benefit of use of it in patients with non-cancer related breakthrough pain.
2009	FDA launched the ***Safe Use Initiative*** to reduce preventable harm by medicines, including opioids. FDA began collaborating with DEA and others to educate the public on the safe disposal of opioids.
2010	FDA approved first abuse deterrent formulation – a new formulation of OxyContin.
2011	FDA approved REMS for transmucosal immediate – release fentanyl (TIRF) products. Teva's Actiq and Fentora impacted by this REMS.
2012	**FDA approved ER/LA opioids class-wide REMS.**
2013	FDA issued draft guidance entitled '***Guidance for Industry – Abuse-Deterrent Opioids – Evaluation and Labeling'.*** Teva provided significant comments on this guidance to the docket.
2013	FDA held public hearing - **Impact of Approved Drug Labeling on Chronic Opioid Therapy: Part 15 Hearings.** FDA issued a letter to opioid prescribers in which significant safety information was updated in all LAO products.
October 2014	**FDA held Public Hearing of Branded and Generic Manufacturers of Opioids to Discuss the Regulatory Policy to Develop ADF Opioids.** Teva had an active leadership role in this meeting, leading the Generic Industry Working Group (GIWG) and actively participating on the Branded Industry Working Group (BIWG). This resulted in FDA seeing Teva as a thoughtful sponsor seeking regulatory policy to ensure there was a path forward for the development and approval of abuse deterrent opioids for patients with pain, such that policy rewarded innovation while also facilitated development and approval of affordable generic opioids. Teva helped to shape the regulatory environment as demonstrated by much of their comments incorporated into FDA guidance documents.
Sept 2015	CDC had webinar describing opioid prescribing guidelines in development for the general

	practitioner. Teva submitted comments to the docket.
Dec 2015	CDC Guideline for Prescribing Opioids for Chronic Pain – draft published.
February 2016	**FDA announces Comprehensive Action Plan to address misuse and abuse of opioids.**
March 2016	**CDC published Final CDC Guideline for Prescribing Opioids for Chronic Pain.** CDC received more than 4,000 comments in three months. Teva provided comments on the initial announcement in September 2015.
March 2016	**FDA announced enhanced warning for immediate-release (IR) opioid pain medications related to risks of misuse, abuse, addiction, overdose and death.**
March 2016	**FDA published draft guidance entitled '*General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*'.** Teva staff reviewing guidance now to ensure one Teva interpretation and will be submitting comments to the docket.

REFERENCES

1. Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse
2. Guidance for Industry: Abuse-Deterrent Opioids- Evaluation and Labeling
3. General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products
4. Development and Regulation of Abuse-Deterrent Opioid Medications; Public Meeting
5. FDA Advisory Committee Calendar Page
6. FDA Opioid Letter 2013