Unlocking the Potential Value For Your Business: Building Partnerships Through Understanding Promotional Review

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Allergan

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Print Ads

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“GOALS”

“TARGET”

New Tab

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RALCOY®

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Indicated for lowering blood sugar with diet and exercise in patients diagnosed with type 2 diabetes

Why Ralcoy? | Taking Ralcoy | Resources | About Diabetes | Testimonials

- **Decreases HA_{1C} by up to 3.5%!**
- **Ralcoy® does not cause nausea, unlike Veritas®**
- **Easy to use!**
- **Lose over 7 pounds!**

Important Safety Information

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Data from Clinical Trials

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Hemoglobin A_{1c} (%) Decrease from Baseline	Subjects (%) (n=151)
≤ 0.9	10
1 - ≤ 1.9	35
2 - ≤ 2.9	50
3 - ≤ 3.5	5

Overstatement of Efficacy #1

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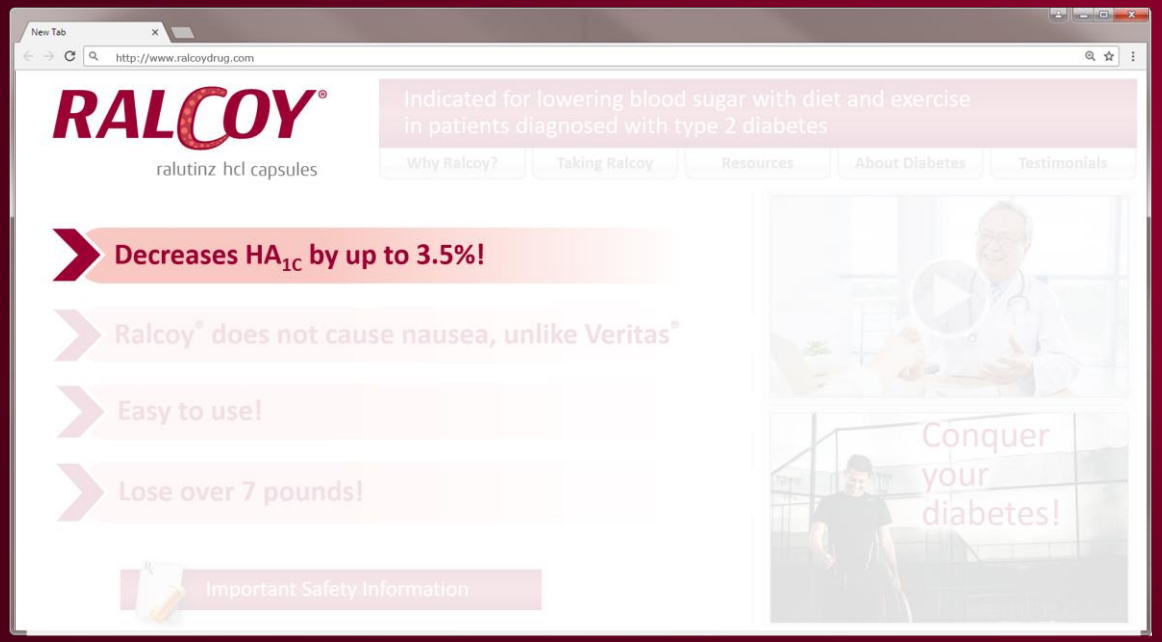

- Alcon Research, Ltd. – PATADAY (Untitled Letter Issued: 2/5/2013)
  - Patient Education Brochure
  - “Zero itch within minutes and up to 16 hours later with just one drop daily”
    - Only 30-60% of patients experienced **complete** relief in clinical trials submitted for approval

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	Ralcoy (n=151)	Placebo (n=151)	p-Value
Hemoglobin A_{1c} (%) Decrease from Baseline	**2.3**	**0.2**	**0.001**

*All patients were on diet and exercise program

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Important Safety Information

Overstatement of Efficacy #2

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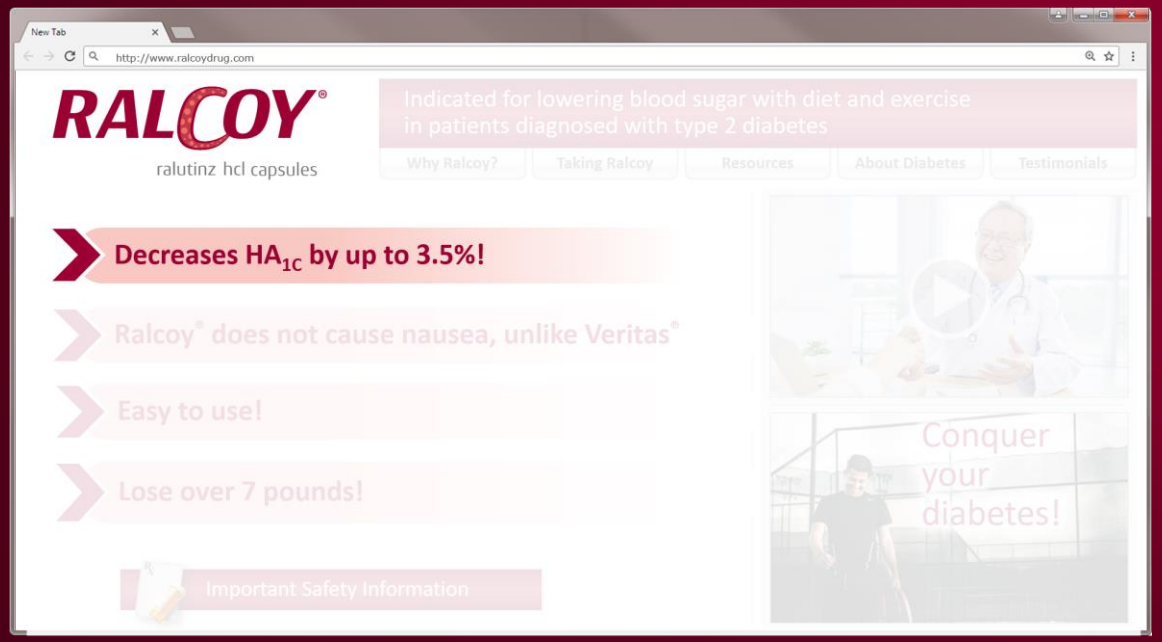

- Watson, Inc. – GELNIQUE (Untitled Letter Issued: 11/30/2010)
  - Restroom stall cling at conference
  - "Significant reduction in incontinence episodes (P<0.0001) 71%"
    - Footnote: "Represents median change from baseline. Reduction with placebo was 55.6%"
    - In pivotal trials:
      GELNIQUE episode reduction was 2.7 per day
      Vs Placebo reduction was 2.0 per day
      -- a difference of <1 episode reduction per day
  - P-value exaggerates significance
  - Overstates magnitude of efficacy by omitting material facts

NOTE: $P \leq 0.05$ is considered conventional level of statistical significance

FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998)

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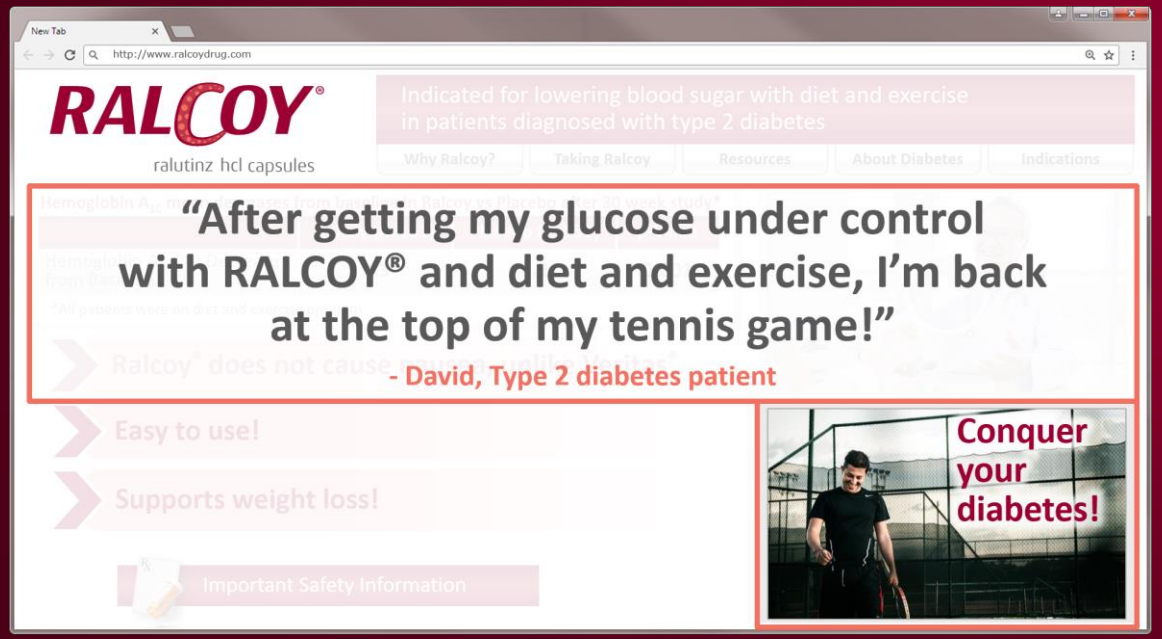
"After getting my glucose under control with RALCOY® and diet and exercise, I'm back at the top of my tennis game!"

- David, Type 2 diabetes patient

Important Safety Information

Overstatement of Efficacy



- Abbott Laboratories – KALETRA (Warning Letter Issued: 7/14/2009)
  - Patient testimonial of Magic Johnson
  - "It **enables me to also be a businessman** once I manage my HIV…. I **still work and have a long day in the office**…"
  - "You're going to have **the same good times**…. It's a **normal life… nothing really changes** other than you're taking medicine…"
  - While this may be accurate for Magic Johnson's own experience, no data supports **disease control** and **preservation of activities of daily living** during treatment for typical patients

Misleading Claims about Efficacy

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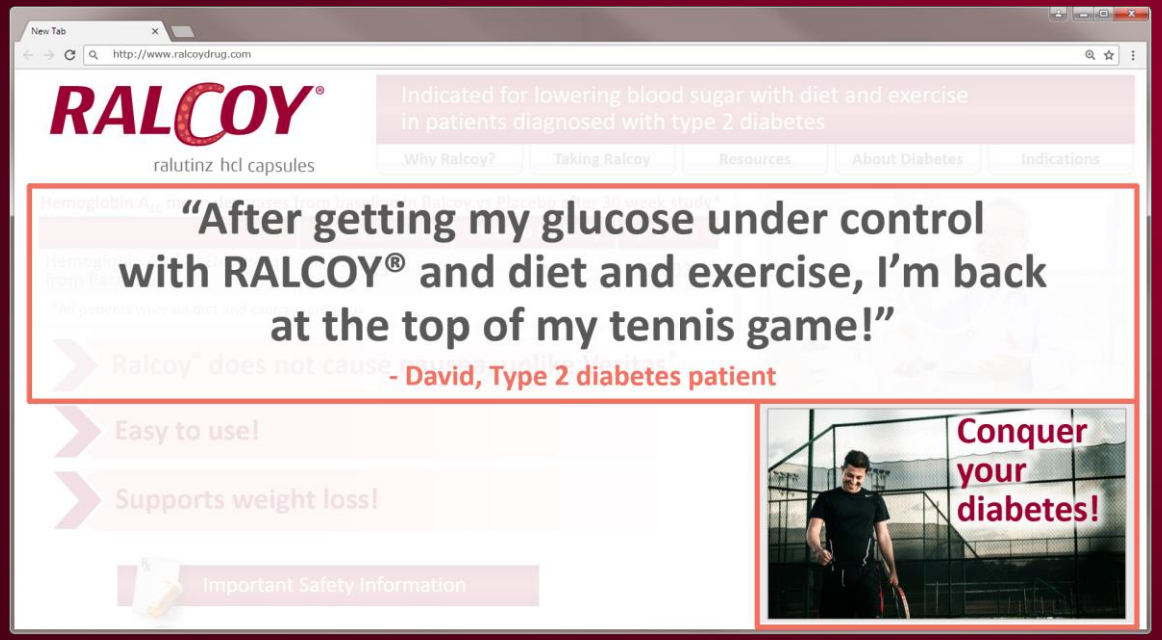

- Pfizer, Inc.– ESTRING (Untitled Letter Issued: 6/19/2018)
  - Video of interview featuring physician and patient
    - Both paid and trained spokespersons
  - Patient: "…Once we came up with the plan and I began using the product it was pretty much an **instant relief**."
    - While this may be accurate for the patient's experience, no data supports instant relief since endpoints were evaluated at **12 weeks**

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Easy to use!

Lose over 7 pounds!

Important Safety Information

Comparative Claims

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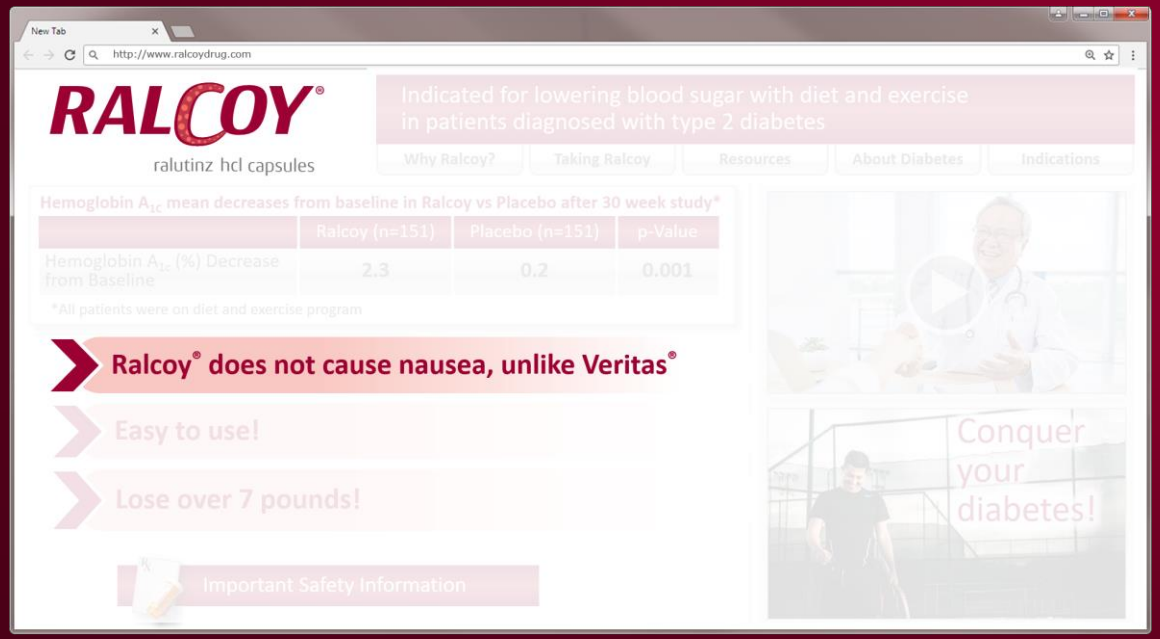
- 21 CFR 214.126 Adequate and well-controlled studies
  - Substantial evidence is needed to support a claim
  - Cannot compare clinical trial data from two separate studies and make a conclusion

- Final Guidance for Industry: Medical Product Communications That Are Consistent with the FDA-Required Labeling – Questions and Answers (June 2018)
  - Comparative safety or efficacy information for approved indications that are not included in the label is permissible, HOWEVER…
    - Requires adequate and well-controlled studies such as a **head-to-head study** within the same indication

NOTE:
Communications **Consistent with Final Label (CFL)** can present data and information for approved indications that are not included in the label, but must not change safety/risk profile of product

Unsubstantiated Superiority Claims



- Mission Pharmacal – TINDAMAX (Untitled Letter Issued: 1/23/2014)
  - Sales sheet
  - "TINDAMAX (tinidazole tablets) is the one and only treatment for BV that gives your patients… **better tolerability** – than **metronidazole**… **shorter dosing**… vs 7-day **metronidazole"**
    - References cited to support claims were from studies in incorrect patient population and doses
  - Must be supported by head-to-head clinical trials

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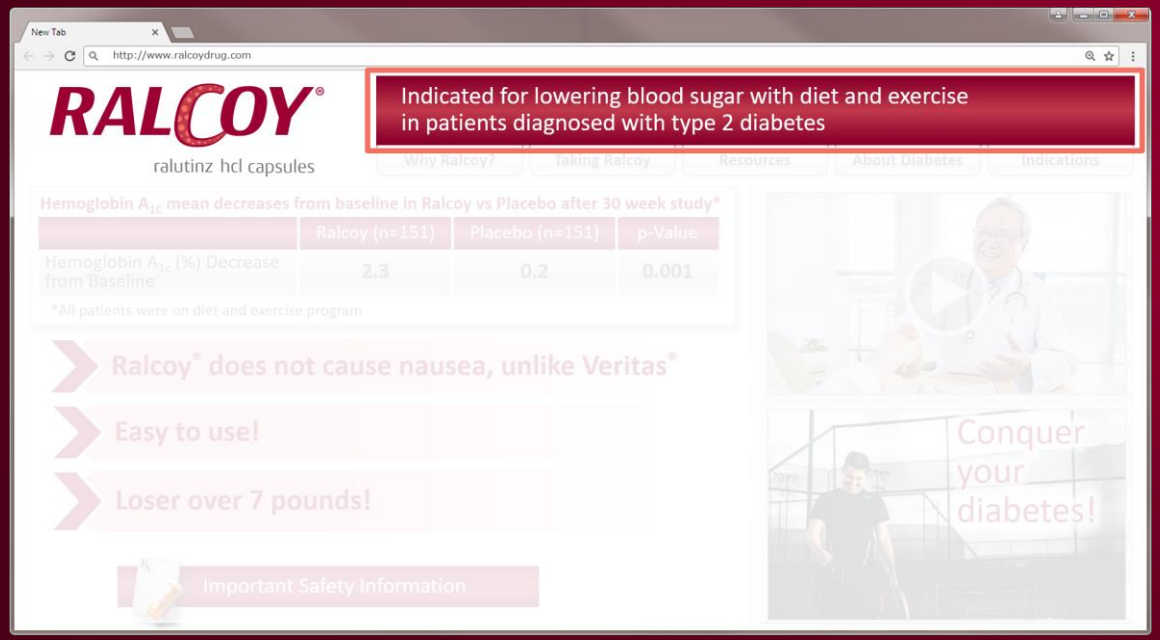
- Easy to use!
- Loser over 7 pounds!

Important Safety Information

Inadequate Communication of Indication



- Spriaso, LLC – TUXARIN ER tablets (Warning Letter Issued: 12/13/2016)
  - Product webpage
  - Label states it is not to be used in patients under 18 years of age
    - Not communicated on webpage
  - Does not communicate the full indication of drug

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- **RALCOY® can significantly decrease the bone mineral density in patients, which can result in an increased rate of bone fractures. Bone loss is greater with increasing duration of use and may not be completely reversible.**
- Other side effects of RALCOY® include blurred vision, dry mouth, drowsiness, dizziness, abdominal pain, weakness, and low blood sugar.

Important Safety Information

Prominent Text

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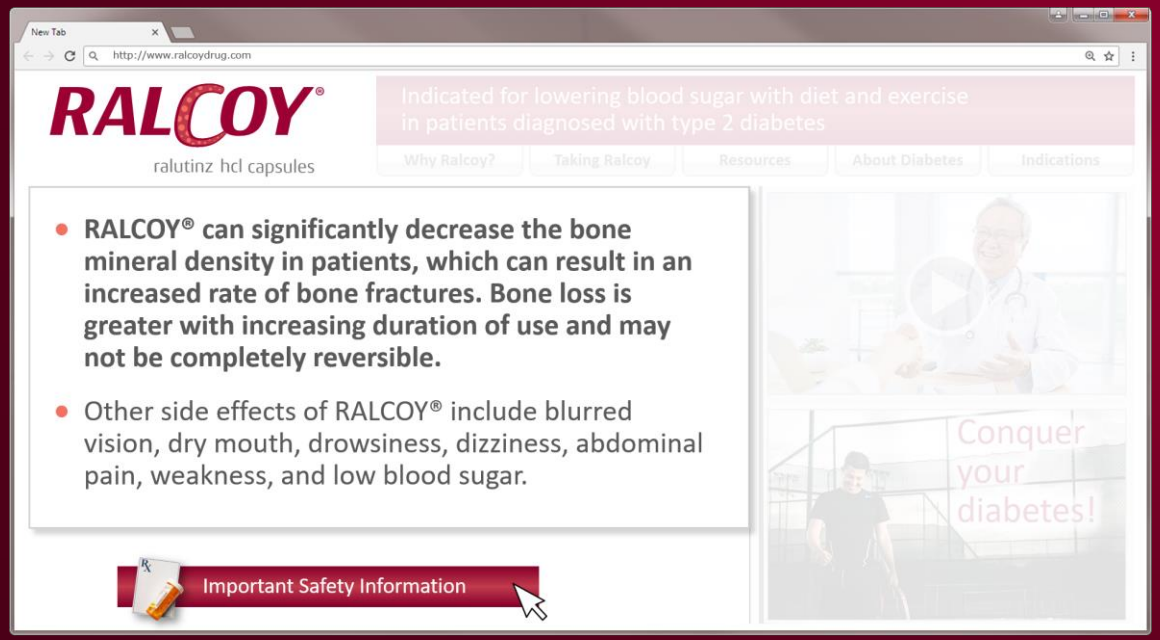
- Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion (May 2009)
  - Risk is inconspicuous compared to benefits
    - Small font size, not bolded
  - Risk information should be comparably noticeable and accessible to audiences in terms of language, formatting, and location
    - must appear with or near benefits as an integral part of the piece and not only through a brief summary page
  - Most serious risks are generally material to ***any*** presentation of efficacy

Minimization of Risk Information



- Bracco Diagnostics, Inc. – ISOVUE inj. (Untitled Letter Issued: 1/7/2010)
  - Product webpage
  - Incomplete safety information
  - "Please click on the 'downloads and PI' tab for full prescribing information"
    - This statement does not mitigate the omission of certain risks and fails to present risk information with comparable prominence to benefits

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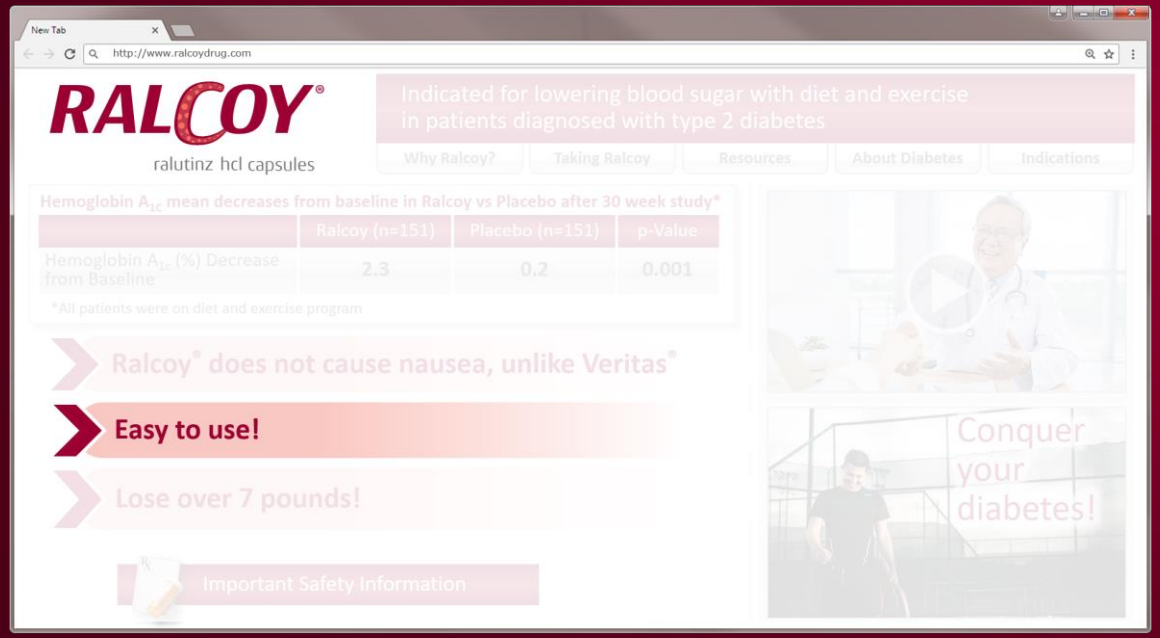
Important Safety Information

False or Misleading Benefit Presentation



- United-Guardian Inc – RENACIDIN (Warning Letter Issued: 12/13/2016)
  - Professional e-mail
  - “Simplifies long-term care”
    “Easy 30mL dosing and delivery”
    - No references cited to support the product convenience
    - Omits material information from the PI regarding dosage and administration

Convenience Data

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- Final Guidance for Industry: Medical Product Communications That Are Consistent with the FDA-Required Labeling – Questions and Answers (June 2018)
  - **Product convenience** information is permissible if presented with substantial evidence in a truthful, non-misleading way
    - Requires close collaboration with clinical development to design appropriate study
  - Other information, such as long-term safety/efficacy data and patient-reported outcomes, could be considered consistent with the label
    - *See additional slides in appendix*

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Clinical Trial Information

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End points and assessments

The primary efficacy end point was change from baseline in A1C at week 30 in the main patient cohort. Secondary efficacy measures included change from baseline at week 30 in body weight FPG. Safety assessments included vital signs, lab measurements, and adverse events as observed or

Statistical analysis

Analyses of change from baseline in A1C, FPG, and body weight were performed by ANCOVA with the treatment group as effect and baseline value as covariate. Point estimates and 95% CI were calculated for the mean change from baseline between treatment groups. Per study design, no *P*-values were generated for end points in exploratory cohorts.

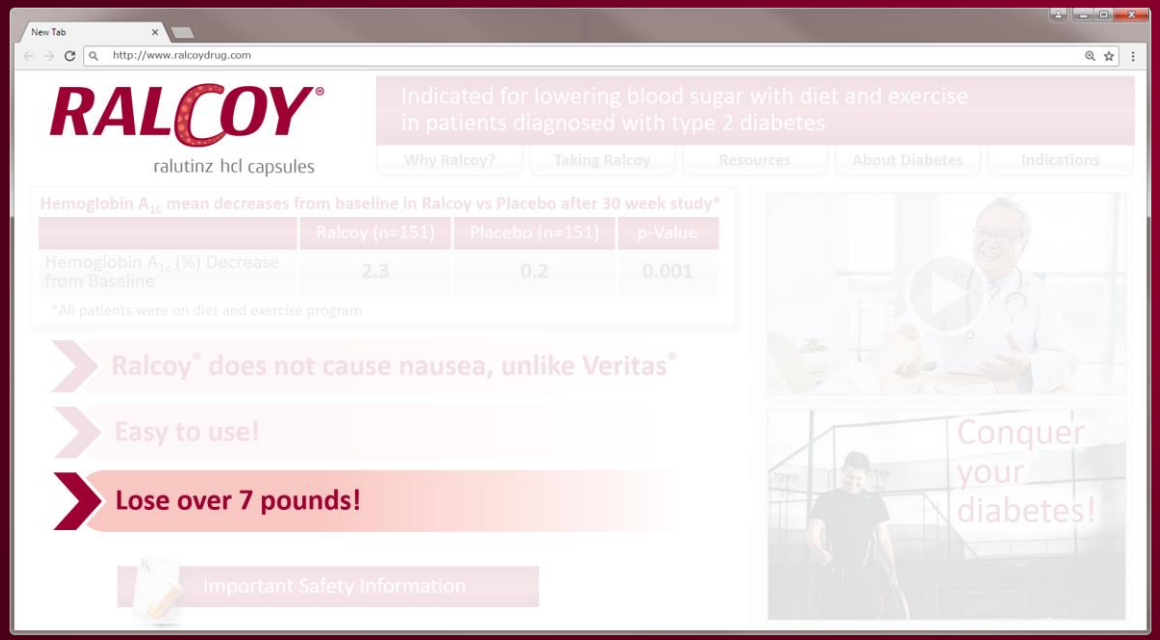
Table 2: Results at Week 30 in a Placebo-Controlled Study of Ralcoy vs Placebo

Efficacy Parameter	Ralcoy (n= 151)	Placebo (n=151)	P-Value
Hemoglobin A_{1c} (%) Decrease from Baseline *(adjusted mean)*	2.3	0.2	P < 0.001
Body Weight (kg) Change from Baseline *(adjusted mean)*	-3.4	-1.8	**P < 0.08**

NOTE: $P \leq 0.05$ is considered conventional level of statistical significance

FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998)

Omission of Material Fact



- Spectrum Pharmaceuticals, Inc.– ZEVALIN (Warning Letter Issued: 7/23/2013)
  - Sales aid for Zevalin
  - "ZEVALIN patients experienced a median time to [cancer] progression of 12.1 months vs 10.1 months for rituximab patients"
    - HOWEVER, label says, "Time-to-disease-progression was **not significantly different** between study arms"
  - Omitting statistical significance makes a misleading efficacy claim

Communicating Other Endpoints

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- Final Guidance for Industry: Medical Product Communications That Are Consistent with the FDA-Required Labeling – Questions and Answers (June 2018)
  - Communications that are consistent with the label can include information that does not necessarily meet the evidentiary standard required for approval or clearance
  - Can present descriptive analyses of individual components of a **composite endpoint**, **without p-values and without additional claims based on these components**
  - Cannot use inadequately powered or post-hoc analysis data to support efficacy conclusions either directly (e.g., efficacy claims) or indirectly (e.g., presenting p-values to imply statistical significance)

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-

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- Easy to use!
- Supports weight loss!

Important Safety Information

Video	Physician Voiceover	SUPER
	“RALCOY® is a medication I use to decrease the blood sugar in my patients, and in turn may help prevent potential cardiovascular disease, kidney damage, and cataracts or blindness.”	
	“I especially like to use RALCOY® if my patient’s blood sugar is uncontrolled. I have noticed my patients seem to feel better as they take this medication.”	
	(Upbeat music playing)	• RALCOY® can significantly decrease the bone mineral density in patients, which can result in an increased rate of bone fractures. Bone loss is greater with increasing duration of use and may not be completely reversible. • Other side effects of RALCOY® include blurred vision, dry mouth, drowsiness, dizziness, abdominal pain, weakness, and low blood sugar

Post Hoc Analysis

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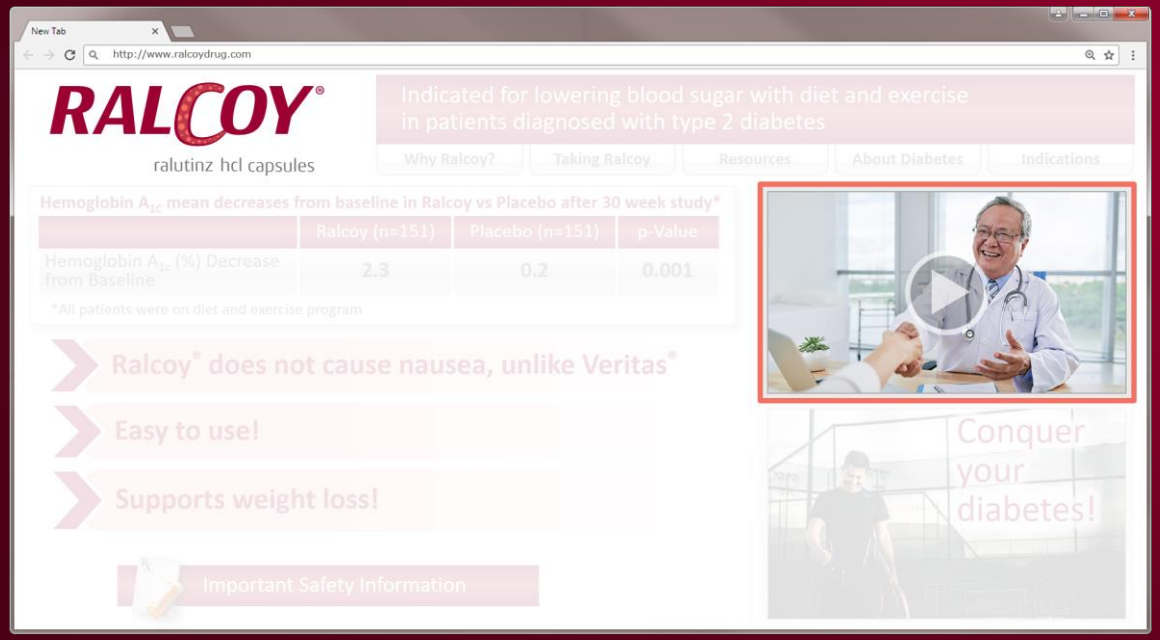
- Guidance for Industry: Multiple Endpoints in Clinical Trials (January 2017)
  - Post hoc analyses of trials can be used to generate hypotheses for future testing, but they do not yield definitive results
  - Biased analysis and results influenced by desire for trial success
  - No credible way to correct for multiplicity of statistical analyses or control Type I error rate
  - Post hoc analyses on their own cannot establish effectiveness

Misleading Risk Presentation



- Pfizer, Inc.– ESTRING (Untitled Letter Issued: 6/19/2018)
  - DTC video of interview featuring physician and patient
  - Patient: "I do not experience any side effects. I'm, for me, I was able to just feel relief."
    - Misleadingly suggests that typical patient will not experience side effects
  - Additionally, video fails to disclose ***any*** safety information

Delivery of Risk Information

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- Guidance for Industry: Consumer-Directed Broadcast Advertisements (August 1999)
  - "Advertisements broadcast through media such as television, radio, or telephone communications systems must disclose the product's major risks in either the **audio** or **audio and visual** parts of the presentation."

Risk Information in Media Ads

- Celgene Corporation – OTEZLA (Warning Letter Issued: 12/12/2016)
  - TV advertisements
  - Song is played loudly during the risk information statement
- Supernus Pharmaceuticals – OXTELLAR ER (Warning Letter Issued: 10/31/2016)
  - Video featuring Key Opinion Leader
  - Physicians states benefits without risk information.
  - Risk information is displayed at end of video, which is not likely to catch viewer's attention

Conference Booth

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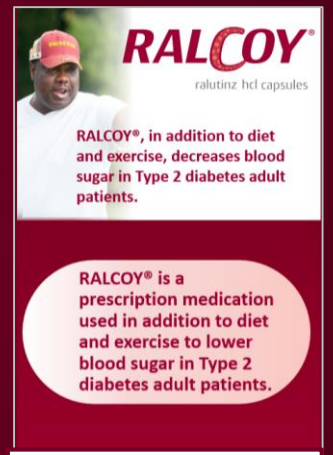
1

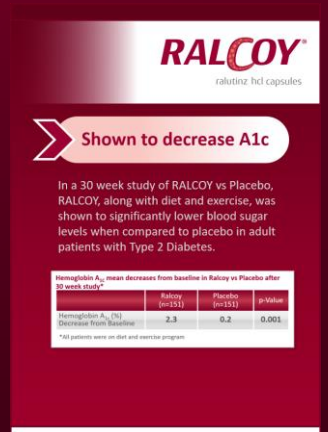
SIDE EFFECTS, RISKS

2



LIMITATIONS OF USE

3



BOX WARNING

4

Misleading Risk Presentation

- Collegium Pharmaceutical, Inc. – XTAMPZA ER capsules (Warning Letter Issued: 2/9/2018)
  - Exhibit booth at 2017 ASHP* Summer Exhibition
  - Risk statements displayed near the floor, often behind table or chair, as observed by OPDP representative at the meetings
  - Safety and risk information displayed in side panel of principal display
    - Small font, no associated visual elements

* ASHP = American Society of Health-System Pharmacists

VP of Marketing is struggling to understand why the Advertising and Promotional Review Committee is requiring so many changes.

What is the risk?

Corporate Penalties

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Company	Fine ($)	Reason	Date
Pfizer	2.3 Billion	Off-Label Promotion	January 2009
Eli Lilly	1.42 Billion	Off-Label Promotion	January 2009
AstraZeneca	520 Million	Off-Label Promotion	April 2010
GalaxoSmithKline	3 Billion	Promotion for Unapproved Age	July 2012
Johnson & Johnson	2.2 Billion	Off-Label Promotion	November 2013
Endo	192.7 Million	Off-Label Promotion	February 2014

Individual Liability

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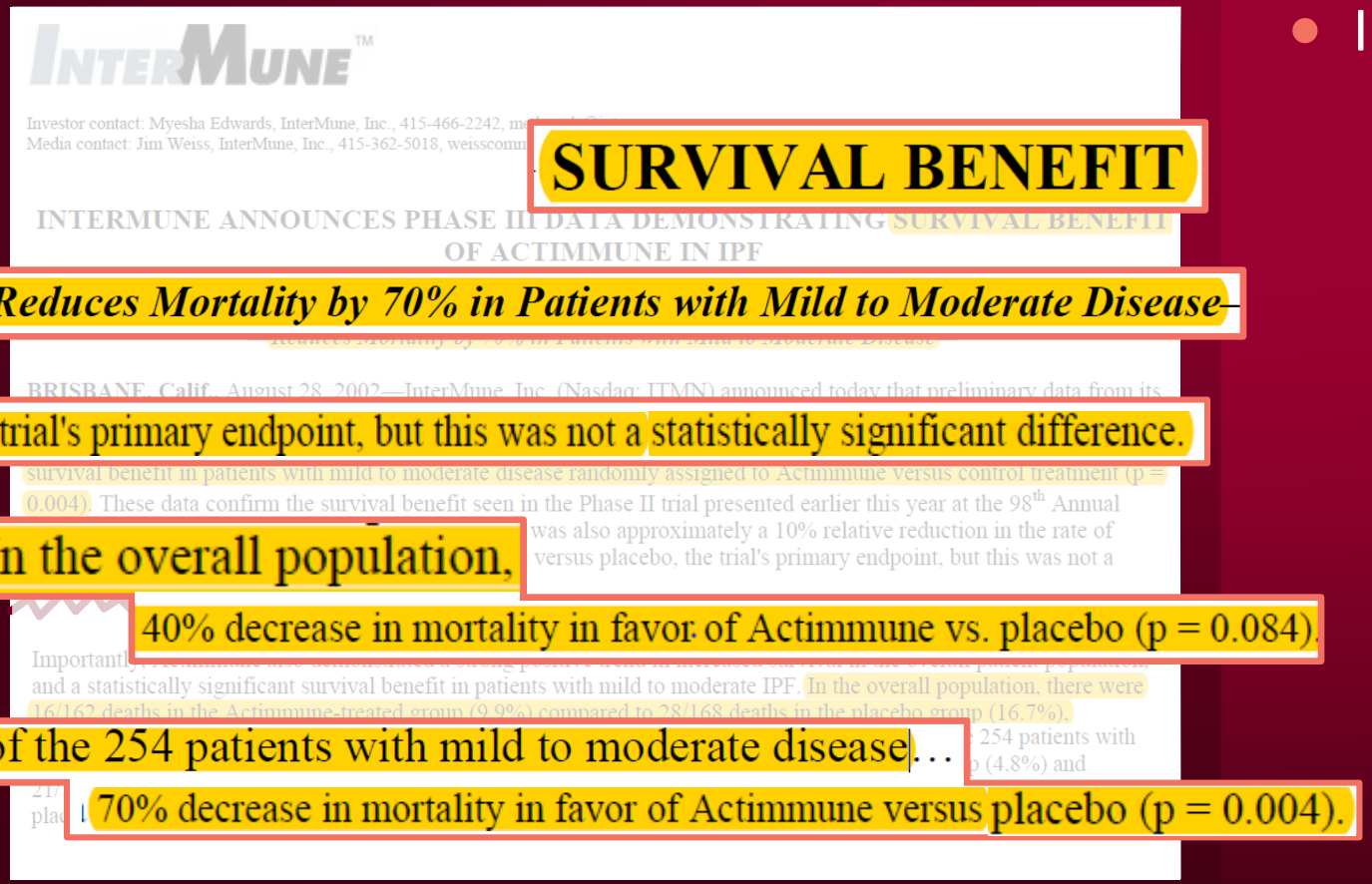
- *United States v. Park* (1975) – **"Park Doctrine"**
  - US Supreme Court rules FDA can seek conviction against responsible corporate officers (RCO) for corporate misdemeanors
  - **Anyone with authority to prevent or detect and correct violation** is a responsible corporate officer
- FDA Regulatory Procedures Manual (2011)
  - FDA outlines criteria and intentions for referral to Department of Justice for prosecution under Park Doctrine
- Memorandum from Deputy Attorney General Sally Q. Yates, US Department of Justice -- Individual Liability for Corporate Wrongdoing. (2015) – **"Yates Memo"**
  - Department of Justice approach to seek **individual accountability** in corporate misconduct

Criminal and Civil Charges: Wire Fraud



INTERMUNE™

Investor contact: Myesha Edwards, InterMune, Inc., 415-466-2242, ma
Media contact: Jim Weiss, InterMune, Inc., 415-362-5018, weisscomm

SURVIVAL BENEFIT

INTERMUNE ANNOUNCES PHASE III DATA DEMONSTRATING SURVIVAL BENEFIT OF ACTIMMUNE IN IPF

-Reduces Mortality by 70% in Patients with Mild to Moderate Disease-

BRISBANE, Calif., August 28, 2002—InterMune, Inc. (Nasdaq: ITMN) announced today that preliminary data from its

trial's primary endpoint, but this was not a statistically significant difference.

survival benefit in patients with mild to moderate disease randomly assigned to Actimmune versus control treatment (p = 0.004). These data confirm the survival benefit seen in the Phase II trial presented earlier this year at the 98th Annual

In the overall population,

was also approximately a 10% relative reduction in the rate of versus placebo, the trial's primary endpoint, but this was not a

40% decrease in mortality in favor of Actimmune vs. placebo (p = 0.084).

Importantly, InterMune also demonstrated a strong positive trend in increased survival in the overall patient population and a statistically significant survival benefit in patients with mild to moderate IPF. In the overall population, there were 16/162 deaths in the Actimmune-treated group (9.9%) compared to 28/168 deaths in the placebo group (16.7%).

of the 254 patients with mild to moderate disease…

254 patients with

(4.8%) and

70% decrease in mortality in favor of Actimmune versus placebo (p = 0.004).

- InterMune Inc. – ACTIMMUNE
  - CEO wrote headline and approved press release claiming survival benefit data from Phase III clinical trial
  - Primary endpoint: Progression-free survival in patients with IPF vs. placebo
    - **p = 0.084** in overall population
  - In post-hoc analysis of subpopulation:
    - **p = 0.004** in mild to moderate IPF
- *United States v. Harkonen* (2009)
  - Court pursues $200,000 fine and 20 years in prison for CEO

* IPF = Idiopathic Pulmonary Fibrosis

Individual Prosecution

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Executive	Penalty	Reason	Date
CEO (InterMune)	6 months house arrest $20,000	Approval of Press Release of False and Misleading Efficacy Claims	September 2009
2 Sales Managers (Pfizer)	6 months house arrest 2 years probation $75,000	Off-label Promotion	December 2009
Lawyer Medical Director President (Purdue Pharma)	$34.5 Million Total ($600 M Corporate Fine)	Understating Risk Information	May 2007

Appendix

Includes:

Guidance for Industry: Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers (Jun 2018)

Educational Standards of Pharma Communications

Additional Cases of Individual Prosecutions

Consistent with Final Label (CFL)

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- Final Guidance for Industry: Medical Product Communications That Are Consistent with the FDA-Required Labeling – Questions and Answers (January 2019)
  - Communicating data and information about approved/cleared uses of products that are not contained in the label but consistent with the final label (CFL)
  - Three factors considered in determining CFL:
    1. Consistent with label in:
       i. Indication
       ii. Patient population
       iii. Limitations and directions for use, handling, or preparing product
       iv. Dosing and administration
    2. Communication's potential to increase patient risk relative to label
    3. Communication must not represent or suggest conditions under which the directions for use in the label may not allow for the safe and effective use of the product
  - Requires scientifically appropriate and statistically sound evidence, including appropriate context information and disclosure of limitations

Consistent with Final Label (CFL) - Continued

RALCOY®
ralutinz hcl capsules

- Examples provided in FDA Guidance:

Information that COULD be CFL:

- Long-term safety/efficacy if approved for chronic use
- Effect or use in patient subgroups within approved population
- Onset or duration of action for approved indication
- Safety/efficacy comparison to another product approved for the same indication
- Additional context about adverse reactions
- Patient-reported outcomes
- Product convenience
- Additional context about mechanism of action

Information that is NOT CFL:

- Use of product in unapproved disease or condition
- Use of product in unapproved population
- Use of product in an unapproved stage, severity, or manifestation of disease
  - E.g., Mild vs severe asthma
- Use of product as monotherapy when only approved for use in conjunction with other products or therapies
- Use of product through unapproved route of administration, strength, dosage, or regimen
- Use of product in unapproved dosage form

Educational Standards of Communications

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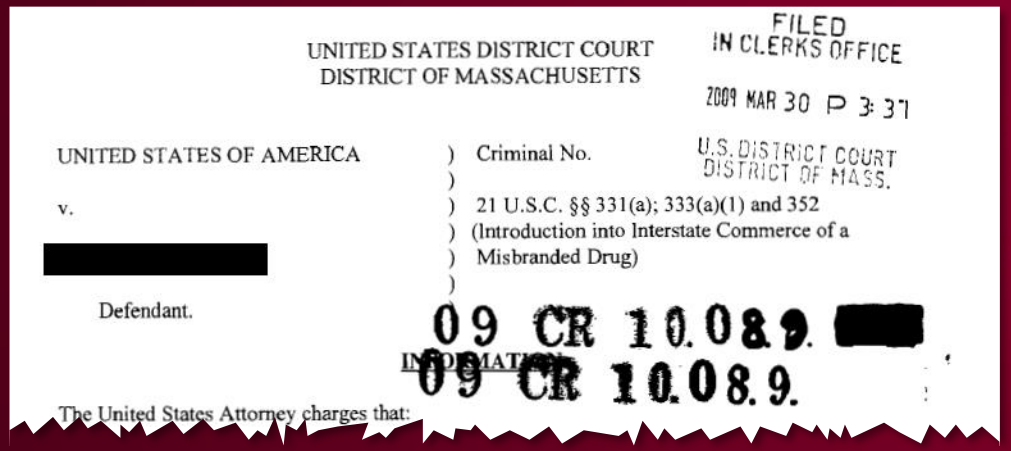
- "Pharma ads are sunnier than they used to be. But are they better?" – *FiercePharma* (May 2018)
  - Study compared pharmaceutical advertisements in 2016 to those from 2004
  - More lacking in health condition and drug education
  - More likely to focus only on post-medication mood, health, and social benefits
  - Ads fulfill public health function in addition to marketing function

- "DTC Broadcast Advertisements for Pharmaceuticals: Off-label Promotion and Adherence to FDA Guidelines'" – *Journal of General Internal Medicine* (February 2018)
  - Few ads fully compliant to FDA guidelines for DTC advertising
  - Data rarely provided, risks are not quantified, suggestive off-label promotion

Criminal and Civil Charges: Off-Label Promotion



UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

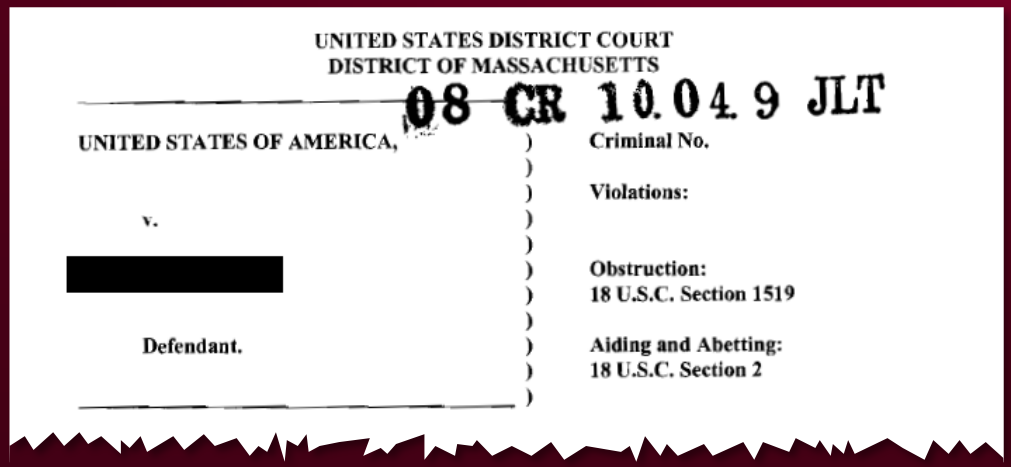
FILED
IN CLERKS OFFICE
2009 MAR 30 P 3:37
U.S. DISTRICT COURT
DISTRICT OF MASS.

UNITED STATES OF AMERICA) Criminal No.
)
v.) 21 U.S.C. §§ 331(a); 333(a)(1) and 352
) (Introduction into Interstate Commerce of a
) Misbranded Drug)
)
Defendant.)

09 CR 10089 [redacted]
09 CR 10089.

INFORMATION

The United States Attorney charges that:



UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

08 CR 10049 JLT

UNITED STATES OF AMERICA,) Criminal No.
)
v.) Violations:
)
[redacted]) Obstruction:
) 18 U.S.C. Section 1519
)
Defendant.) Aiding and Abetting:
) 18 U.S.C. Section 2

- Pharmacia & Upjohn (Pfizer) – BEXTRA
  - Bextra gains FDA approval in 2001 for treatment of arthritis and menstrual discomfort
  - Regional manager charged with directing sales team to promote **off-label** uses of Bextra in the prevention of deep vein thrombosis in joint replacements
  - Sales manager charged with obstruction of justice for instructing sales representatives to delete evidence of off-label communications from computers

Criminal and Civil Charges: Misbranding

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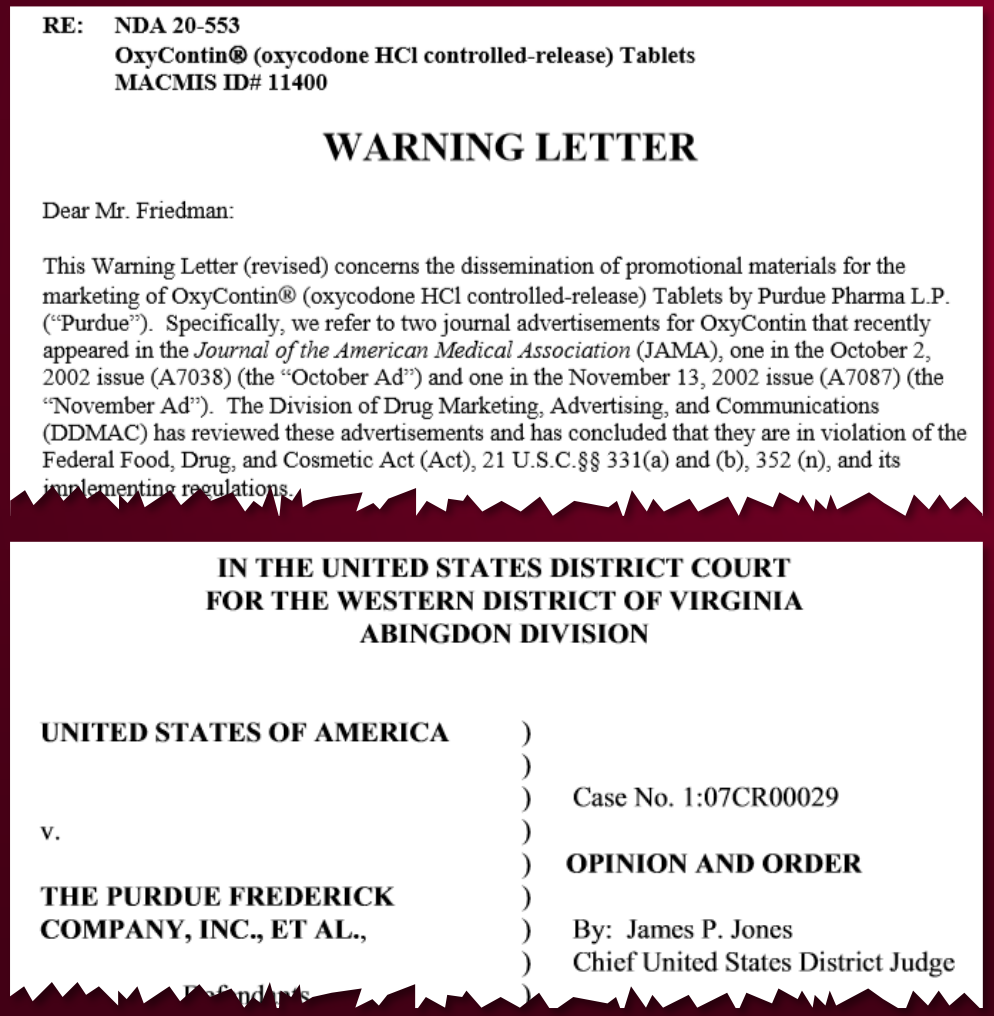

RE: NDA 20-553
OxyContin® (oxycodone HCl controlled-release) Tablets
MACMIS ID# 11400

WARNING LETTER

Dear Mr. Friedman:

This Warning Letter (revised) concerns the dissemination of promotional materials for the marketing of OxyContin® (oxycodone HCl controlled-release) Tablets by Purdue Pharma L.P. ("Purdue"). Specifically, we refer to two journal advertisements for OxyContin that recently appeared in the *Journal of the American Medical Association* (JAMA), one in the October 2, 2002 issue (A7038) (the "October Ad") and one in the November 13, 2002 issue (A7087) (the "November Ad"). The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these advertisements and has concluded that they are in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C.§§ 331(a) and (b), 352 (n), and its implementing regulations.

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
ABINGDON DIVISION

UNITED STATES OF AMERICA)
)
) Case No. 1:07CR00029
v.)
) **OPINION AND ORDER**
THE PURDUE FREDERICK)
COMPANY, INC., ET AL.,) By: James P. Jones
) Chief United States District Judge
Defendants)

- Purdue Pharma L.P. – OXYCONTIN
  - Warning letter issued in 2003 for print ads in *JAMA*
    - Omits safety information regarding formulation
  - *United States v. The Purdue Frederick Co., Inc., et. al*
    - Guilty plea in 2007
    - Sales representatives misled physicians on abuse potential and associated risks, among other charges