The Do's and Don'ts of Patient Communications

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Do's and Don'ts of Patient Communications in the Pre-Approval Space

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The views expressed are my own and may not reflect those of my employer, Spark Therapeutics.

This presentation is not intended to substitute for legal advice and guidance from your own counsel.

Why talk to patents or patient groups prior to product approval?

- Gather patient and caregiver perspectives on product development
- Support disease state education
- Encourage their communication with FDA on the potential value of investigational products and the impact of a disease on their lives *(as FDA has invited)*
- Respond to unsolicited requests for information and be a trusted source of information

  Patients and caregivers are increasingly sophisticated and organized
- Gather valuable insights on what information or programs would be meaningful to patients and caregivers if product were approved

FDA is increasingly engaging patients and patient advocacy groups in a variety of programs and regulatory processes

How are communications about unapproved products regulated?

- Under section 502(f)(1)the FFDCA, a drug is misbranded if it fails to provide ‘adequate directions for use’

- Adequate directions for use are those by which a layperson may safely use the product for its intended purposes (21 CFR §201.5)

- Because such adequate directions cannot be provided for a prescription drugs or device, the Act provides an exemption from the requirement if the drug complies with certain requirements (21 CFR §201.115(b))

- One such requirement is 21 CFR §312.7:

Promotion of unapproved products is forbidden under the FFDCA

- 21 C.F.R. § 312.7 Promotion of investigational drugs. (a) Promotion of an investigational new drug. **A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.** 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. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

Recent enforcement letters on pre-approval promotion to consumers

- Crenolanib besylate - June 28, 2018 (Arog)
  - On Crenolanib website:

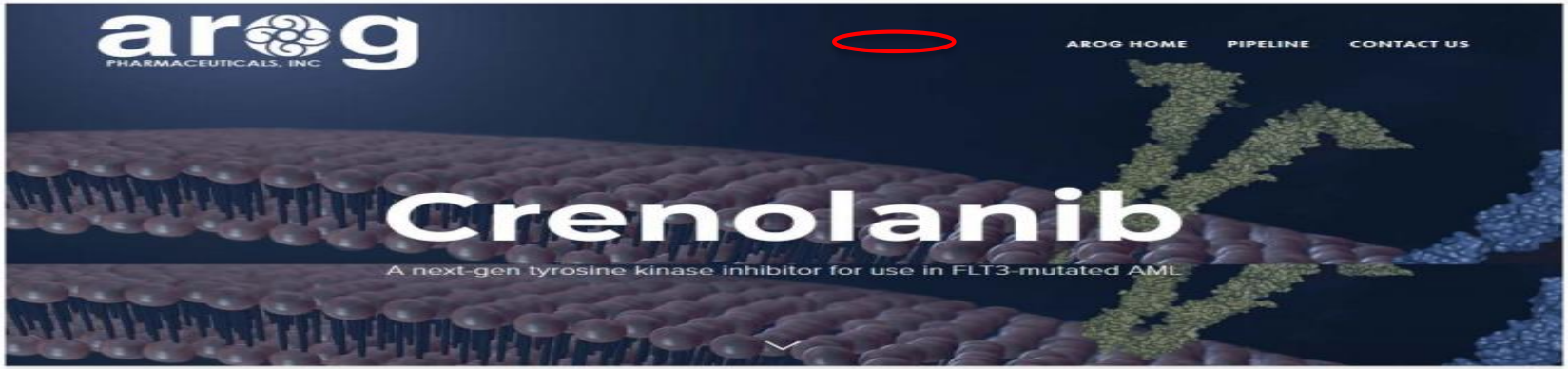
Claims:

Combination Therapy—Future of AML Treatment
CRENOLANIB: Combinable with chemotherapy at full doses

Eradicating Activating Mutations
CRENOLANIB: Potent inhibitor of FLT3, PDGFRα, PDGFRβ

The above claims make numerous conclusory statements about the safety and effectiveness of Crenolanib. For example, the webpage states that Crenolanib is "for use" in FLT3-mutated ALM without including information that Crenolanib is an investigational new drug that has not been approved for any use and states that Crenolanib is a "potent inhibitor for FLT3-ITD and secondary KD mutants," an efficacy claim of clinical benefit that has not been established. Moreover, these claims suggest in a promotional context that Crenolanib, an investigational new drug, has been shown to be different from or superior to other approved therapies for treating AML, and is safe or effective for such uses.

Who's the audience?



THE ROLE OF FLT3 MUTATIONS IN AML

Roughly one-third of AML patients harbor an internal tandem duplication (ITD) in FLT3, a receptor tyrosine kinase. Mutations of FLT3 at D835, a point mutation in the tyrosine kinase domain (TKD), have also been observed in AML patients. Both ITD and TKD mutations lead to constitutive activation of the tyrosine kinase function, making FLT3 an attractive drug target in AML patients. Both ITD and TKD mutations render FLT3 resistant to currently approved inhibitors. Moreover, novel activating FLT3 mutations are being identified in patients with AML. As the clinical development of FLT3 inhibitors proceeds into advanced phase trials, FLT3 mutations will represent a new obstacle in the care of FLT3-mutated AML patients.

CRENOLANIB IS A SELECTIVE TYPE I PAN-FLT3 INHIBITOR

Crenolanib, a type I TKI, is a potent inhibitor of FLT3-ITD and secondary KD mutants. Crenolanib represents the first TKI to exhibit both kinase selectivity and invulnerability to resistance-conferring KD mutations. Crenolanib , which spares cKIT, represents a promising therapy for achieving deep and durable responses in FLT3-mutant AML.

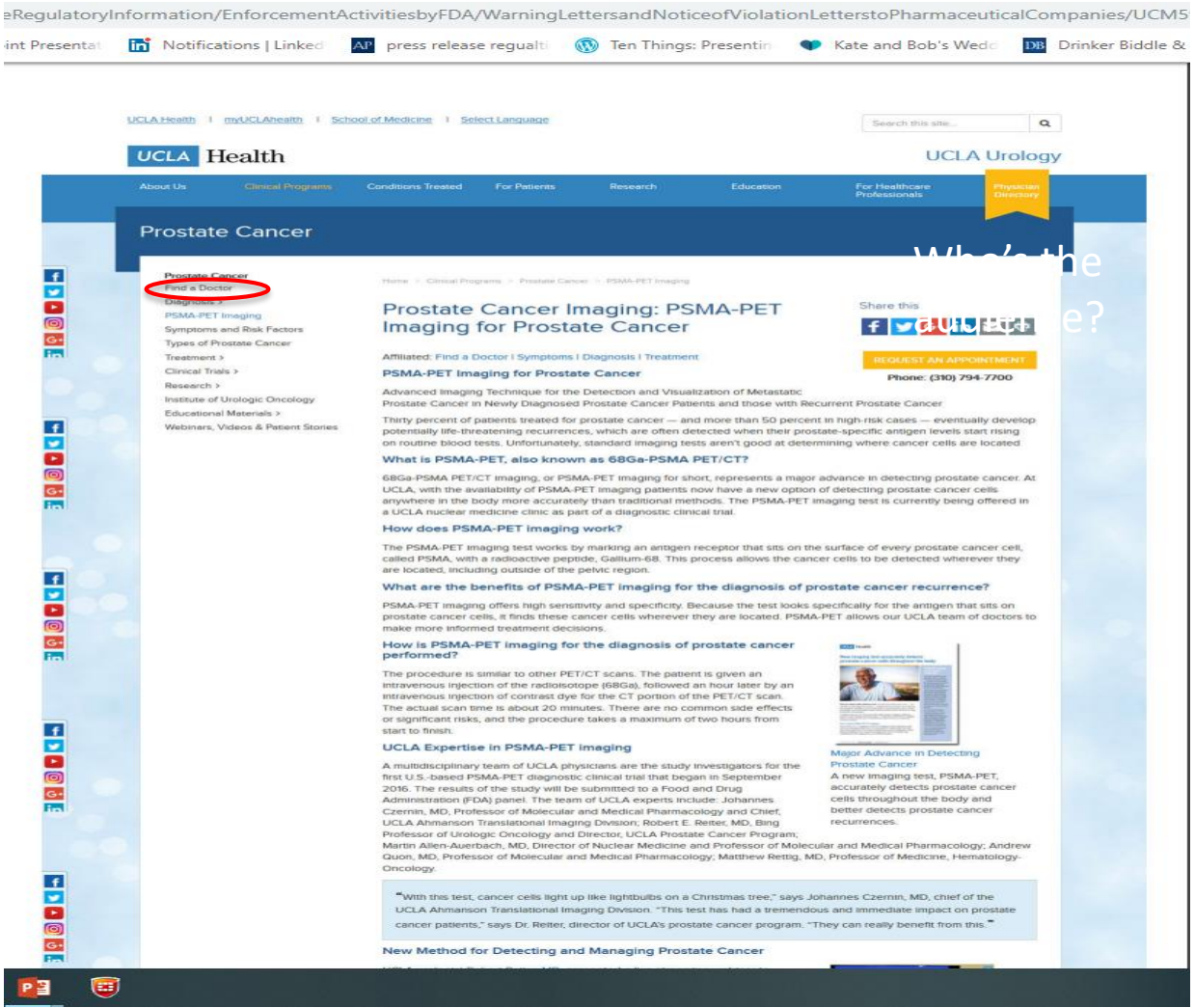
Recent enforcement letters on pre-approval promotion to consumers

- 68GA PSMA – December 28, 2017 (UCLA)
  - On UCLA Health Website:

The webpage and brochure contain claims that promote Ga68-PSMA as safe and effective for the purpose for which it is being investigated or otherwise promote the drug, including the following:

  - New imaging test accurately detects prostate-cancer cells throughout the body
  - 68Ga-PSMA PET/CT imaging, or PSMA-PET imaging for short, represents a major advance in detecting prostate cancer. At UCLA, with the availability of PSMA-PET imaging patients now have a new option of detecting prostate cancer cells anywhere in the body more accurately than traditional methods.
  - Since PSMA-PET imaging became available at UCLA in September, patients now have a new option that's better at detecting the location of prostate-cancer recurrences.
  - This test has had a tremendous and immediate impact on prostate-cancer patients . . .. They can really benefit from this.
  - There are no common side effects or significant risks . . .
  - In contrast to the traditional studies, PSMA-PET imaging offers high sensitivity and specificity.

The UCLA Health page is aimed at patients and caregivers



UCM593221.pdf | DOCUMENT INFORMATION PAG

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCcompanies/UCM593221.pdf

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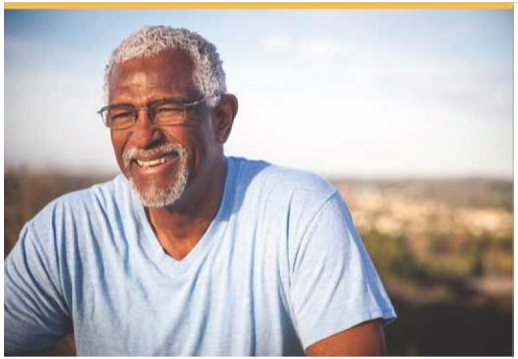
UCLA Health

New imaging test accurately detects prostate-cancer cells throughout the body



There are about 3 million American men currently living with prostate cancer — and 220,000 new cases diagnosed each year — making it the most common cancer affecting this population. Although cure rates are generally very good, detecting cancer cells that have spread or recurred outside the pelvic region has been an area of weakness in caring for prostate-cancer patients.

To address this issue, UCLA is now the first medical center in Southern California — and one of only a handful across the country — to offer 68Ga-PSMA PET/CT imaging, which can detect prostate-cancer cells anywhere in the body more accurately than traditional methods.

About 68Ga-PSMA PET/CT imaging

68Ga-PSMA PET/CT imaging, or PSMA-PET imaging for short, represents a major advance in detecting prostate cancer. First developed in Germany about three years ago, it's been offered in a UCLA nuclear medicine clinic as part of a diagnostic clinical trial since September 2016. Because it isn't approved by the U.S. Food and Drug Administration, this imaging test is not covered by insurance.

PSMA-PET imaging better detects recurrences

Thirty percent of patients treated for prostate cancer — and more than 50 percent in high-risk cases — eventually develop potentially life-threatening recurrences, which are often detected when their prostate-specific antigen levels start rising on routine blood tests.

Unfortunately, standard imaging tests aren't good at determining where cancer cells are located, says Robert E. Reiter, MD, Bing Professor of Urologic Oncology and director of UCLA's prostate cancer program. "For the past 20 years, I've had to tell patients with recurrences that I don't know where the cancer is located," Dr. Reiter says. "We've been blind, basically."

Since PSMA-PET imaging became available at UCLA in September, patients now have a new option that's better at detecting the location of prostate-cancer recurrences. "With this test, cancer cells light up like lightbulbs on a Christmas tree," says Johannes Czernin, MD, chief of the UCLA Ahmanson Translational Imaging Division.

"This test has had a tremendous and immediate impact on prostate-cancer patients," Dr. Reiter adds. "They can really benefit from this."

"68Ga-PSMA PET/CT represents a major advance in detecting prostate cancer. Because it isn't approved by the US Food and Drug Administration, this imaging test is not covered by insurance."

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Recent enforcement letters on pre-approval promotion to consumers

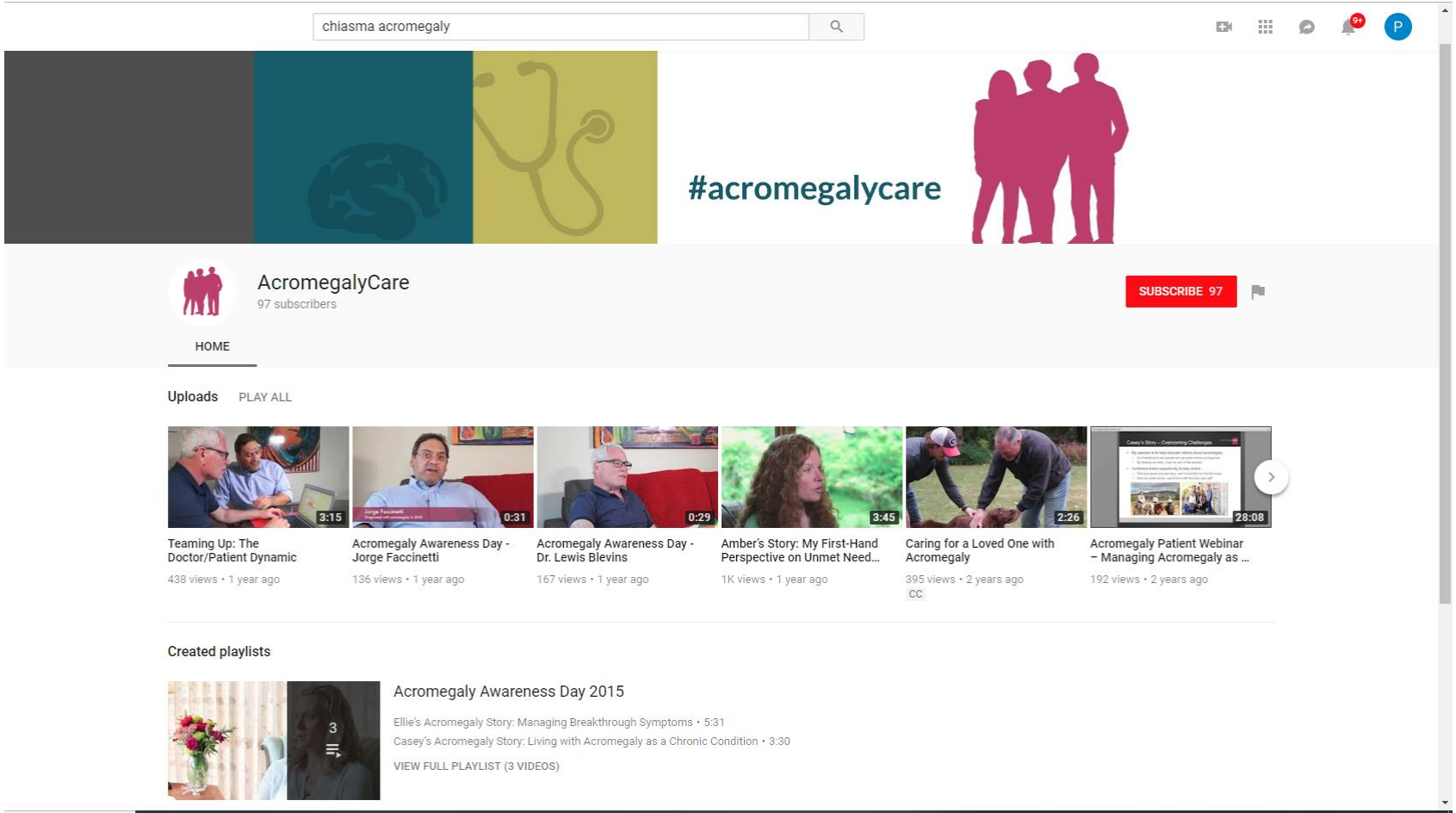
- Octreotide capsules – December 21, 2016 (Chiasma)

Video posted on YouTube presents claims that promote octreotide as safe and effective for the purpose for which it is being investigated or otherwise promote the drug, including the following:

> (1:43) Dr. Shlomo Melmed: *"I think the most important result of the trial was that the drug is safe and safety is a paramount concern for any new drug being used and the physician using the new drug should be assured and be able to reassure his or her patients that in fact the drug is safe. Secondly that the drug is efficacious and the effectiveness of the drug was proven in the clinical trials in that about 62% of patients who were known to respond to octreotide were shown to achieve the primary endpoint which was a maintenance of normal IGF 1 levels. Oral octreotide is a capsule of octreotide, the same octreotide which you use in your injections and which is available to be swallowed and absorbed in the gastrointestinal system and exert its effects on the body similarly to the injectable octreotide."*
>
> (2:51) Jill Sisco: *"I think that what matters most **to patients** is a) that it will work for them or that if it doesn't work for them they can go to a different therapy and there is no harm no foul by trying a new oral alternative."*

FDA: "We acknowledge that the statement 'Product is an investigational new drug and not available for commercial distribution,' is included as a SUPER on the screen for eight seconds at the end of the video. However, there is no disclaimer that would sufficiently mitigate the extensive claims and presentations throughout the majority of this video that suggest in a promotional context that octreotide capsules, an investigational new drug, is safe or effective for such uses, when FDA has not approved octreotide capsules for any use."

Chiasma's current disease awareness YouTube site for patients and caregivers



Recent enforcement letters on pre-approval promotion to consumers

- NDA 022324 Remoxy (oxycodone) Extended-Release Capsules MA5 – September 8, 2016 (Durect)

Durect website and Remoxy ER website include inappropriate claims for an investigational product:

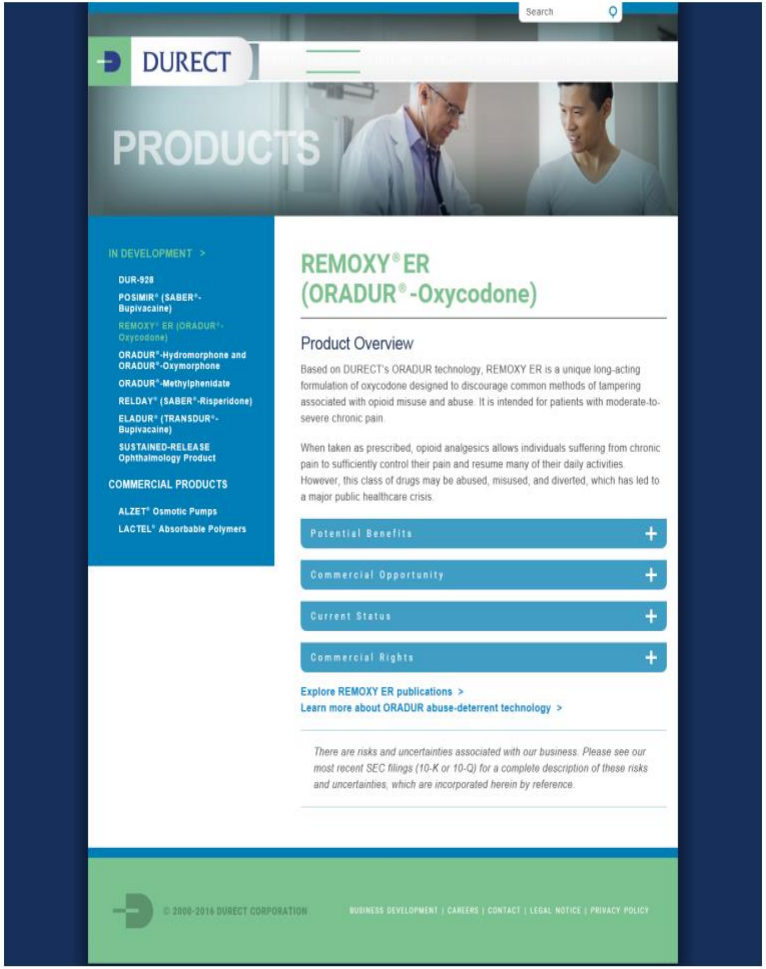
"Long-lasting" and "Tamper-resistant" are phrased as established facts

> *"Nothing in this presentation, which identifies the product by its trade name under which the NDA indicates Pain Therapeutics intends to commercially market the product, discloses that this product is an investigational new drug…and the presentation is thereby misleading."*

Under 'Potential Benefits':

"Effective long-term pain control and convenience of twice-daily dosing."
"Proprietary formulations with several properties designed to deter abuse by the most common methods."

> *"The prominent claims under the Product Overview and Potential Benefits headings …suggest that Remoxy ER is safe and effective for the purpose for which it is being investigated or otherwise promote the drug as having several properties to deter abuse …and as providing 'long-term pain control' …"*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COMMERCIAL PRODUCTS
ALZET® Osmotic Pumps
LACTEL® Absorbable Polymers
REMOXY® ER (ORADUR®-Oxycodone)
Product Overview
Based on DURECT's ORADUR technology, REMOXY ER is a unique long-acting formulation of oxycodone designed to discourage common methods of tampering associated with opioid misuse and abuse. It is intended for patients with moderate-to-severe chronic pain.
When taken as prescribed, opioid analgesics allows individuals suffering from chronic pain to sufficiently control their pain and resume many of their daily activities. However, this class of drugs may be abused, misused, and diverted, which has led to a major public healthcare crisis.
Potential Benefits +
Commercial Opportunity +
Current Status +
Commercial Rights +
Explore REMOXY ER publications >
Learn more about ORADUR abuse-deterrent technology >
There are risks and uncertainties associated with our business. Please see our most recent SEC filings (10-K or 10-Q) for a complete description of these risks and uncertainties, which are incorporated herein by reference.
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Examples from Spark Therapeutics

Disease Awareness

aShared Vision℠ | Understanding IRDs | Gene Therapy Research | Genetic Testing | Community Stories | Resources | For Health Care Professionals

Get Our Newsletter

We're now on Facebook. See what we're talking about. **Join us on Facebook**

Inherited retinal diseases (IRDs).

The conditions vary, but those with IRDs may face many similar challenges, including night blindness (nyctalopia), declining vision, or blindness at birth.

See the conditions

Cutting edge science.

Are you following the always evolving field of gene therapy research? Deepen your understanding of how researchers are approaching IRDs in this fascinating field.

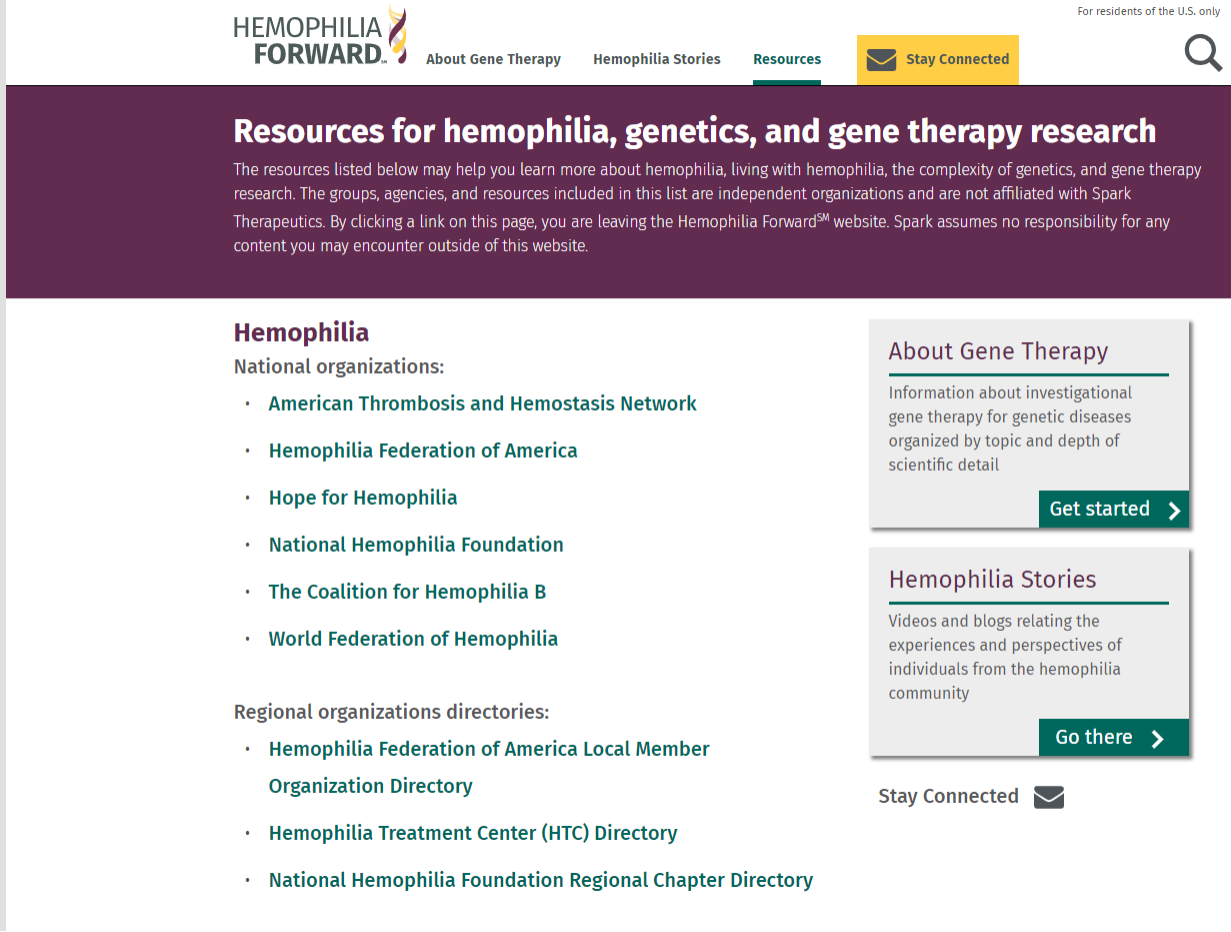
See how the science works

Pinpoint your mutation location.

Science can now decipher which gene is responsible for causing a number of IRDs. Here's a simple overview to help you understand the basics of the genetic testing process.

Learn about genetic testing

Disease Awareness



Pre-Approval Do's and Don'ts

Do's	Don'ts
Listen: Engage patients and patient advocacy groups as valuable sources of insights for product development.	Promote or otherwise suggest that an investigational product is safe or effective
Support disease educational activities that meet the needs of patients.	Patronize patient advocacy groups by expecting them to adopt or champion company positions or interests
Encourage patients and patient advocacy groups to engage with FDA to voice their opinions on risks and benefits of therapies and the impact of disease on their lives.	Deploy patient advocacy employees without appropriate training on pre-approval restrictions or without clear and appropriate roles and responsibilities.
Be a dependable, objective information resource	Give medical advice

Arnold & Porter

The Do's and Don'ts of Patient Communication

Abraham Gitterman, Associate, Arnold & Porter LLP

FDA Advertising & Promotion General Principles

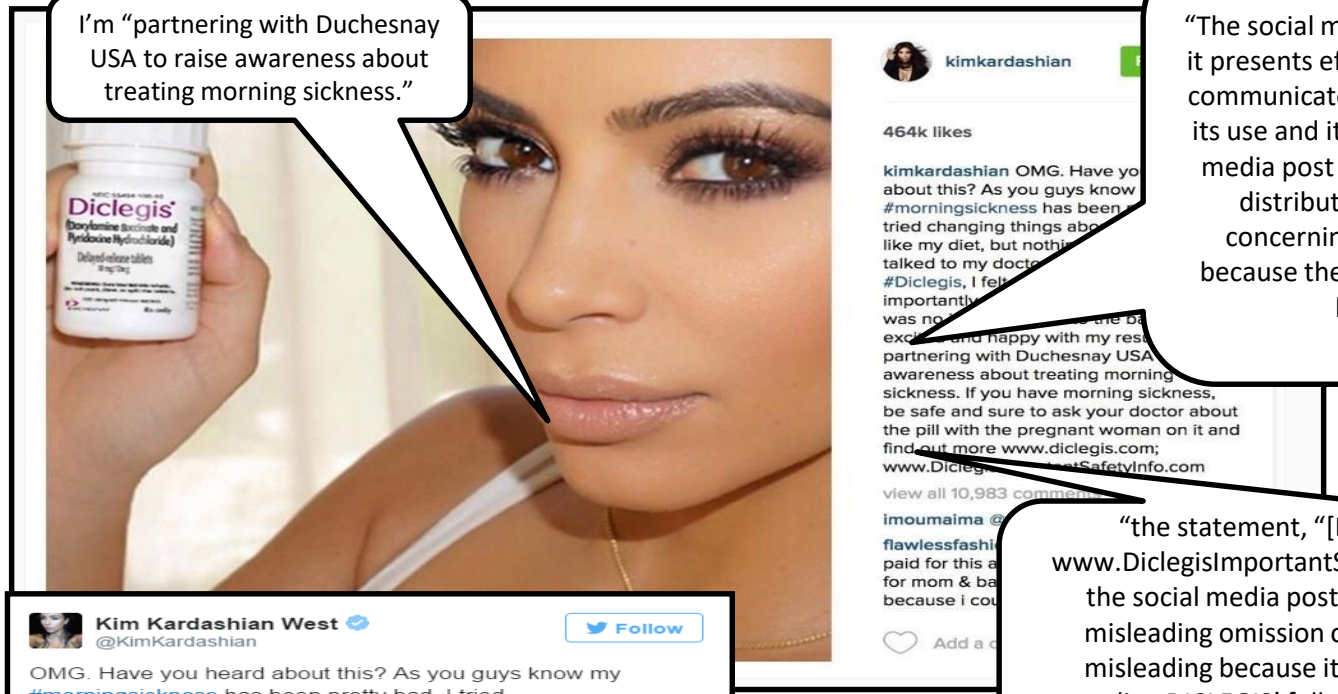
- Promotional materials and communications should:
  - Not include false or misleading information
  - Be supported by “substantial evidence”
  - Not lack in “fair balance”
  - Not discuss off-label uses or broaden indication/population
  - Not overstate efficacy or safety
  - Not make unsubstantiated comparative/superiority claims
- Violative promotional materials could result it civil, criminal, and administrative actions under FDCA
  - “Prohibited acts”
  - Misbranding, adulteration
  - OPDP Warning/Untitled Letter
  - Also *qui tams* under federal/state False Claims Act (FCA)

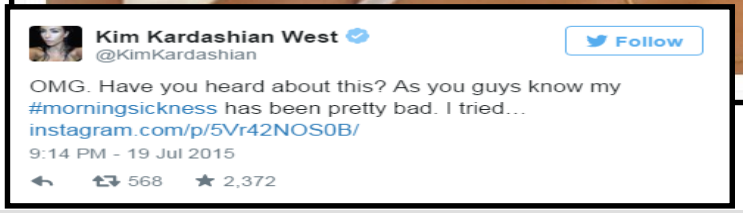
OPDP Priority Areas

- Regardless of promotional medium, OPDP has historically focused on:
  - Newly approved products
  - Products with significant risks
  - Products cited for violations in the past
  - Products cited in complaints
  - Products promoted with far reaching campaigns
- FDA will consider
  - Nature of the violation and how egregious
  - Magnitude of impact on public health
  - Need for corrective action
  - Repetitive violations

“Kardashian” Warning Letter

I’m “partnering with Duchesnay USA to raise awareness about treating morning sickness.”





“The social media post is false or misleading in that it presents efficacy claims for DICLEGIS, but fails to communicate any risk information associated with its use and it omits material facts. Thus, the social media post misbrands DICLEGIS … and makes its distribution violative. These violations are concerning from a public health perspective because they suggest that DICLEGIS is safer than has been demonstrated.”

“the statement, “[F]ind out more www.diclegis.com; www.DiclegisImportantSafetyInfo.com[,]” appears at the end of the social media post; however, this does not mitigate the misleading omission of risk information.” The post also “is misleading because it fails to provide material information regarding DICLEGIS’ full approved indication, including important limitations of use.”

“Ty Pennington” Warning Letter

“Now once I got on medication it’s just **amazing** the transformation I made. I - It **literally changed my life**, and **gave me the confidence to achieve my goals**, like being an artist. ... But with the medicines like **Adderall XR, it’s truly a transformation**. I mean talk about an Extreme Makeover, I’m like living it. ... It’s **not easy to communicate with people**, including your own family. …. So as someone who has had ADHD, and is overcoming it, **proper treatment has truly changed my life and made an amazing difference**.”

“This video overstates the efficacy of Adderall XR by implying that this product will “transform” patients’ lives and improve their “confidence.” … “Furthermore, the video overstates the efficacy of Adderall XR by implying that Adderall XR will help patients overcome communication difficulties and help them to “fit in” and not feel “different” or “alienated.”

Copaxone Warning Letter

Before Treatment

- "It's hard to believe that just a few years ago [David] had to use a cane for mobility and often could barely muster enough energy to work half a day. This was the case for David, who was diagnosed with multiple sclerosis (MS) in 2002. David awoke one morning experiencing numbness in his toes."
- "Over the course of a few weeks, the numbness moved up his body and he eventually became partially paralyzed from the chest down."

After Treatment

- "With the help of his doctor, David began COPAXONE® (glatiramer acetate injection) therapy in 2003"
- "After a year and a half of hard work and determination, David was the USA Triathlon National Champion in the physically challenged category."
- David went on to compete and win numerous national and international triathlons from 2005-2008.

FDCA & Social Media: Owned or Controlled Sites

- FDA also regulates social or interactive promotional media (e.g., blogs, Facebook, Twitter, YouTube, etc.)
  - "Draft Guidance for Industry: Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics" (2014)
- A firm **is** responsible for promotional communications on sites that are:
  - Owned, controlled, created, influenced or operated by, or on behalf of, the firm (e.g., Twitter, Facebook, blogs, etc.)
- FDA looks at whether firm *or* "anyone acting on its behalf," influences or controls promotional activity or communication, *in whole or in part*
- Firm's are responsible for content if they:
  - Exert influence over a site "in *any* particular, even if influence is limited in scope"
  - "collaborate[] on or ha[ve] **editorial, preview, or review privilege**" over content
- **Not** responsible if *only* financial support (e.g., unrestricted educational grant) *and* no other control or influence

FDA & Social Media: UGC

- Introduces concept of user generated content (UGC)
  - Anything people write, say, post on social media platforms
- A firm is *not* responsible for UGC that is "truly independent of the firm"
  - *e.g.*, not produced by or on behalf of, or prompted by the firm in any particular. *Cf*. 47 U.S.C. 230(c)(1)
- FDA will not ordinarily view UGC on firm-owned or firm-controlled venues (e.g., blogs, message boards, and chat rooms) as promotional content on behalf of the firm as long as:
  - The user has no affiliation with the firm **and**
  - The firm had no influence on the UGC

FDA & Social Media: Third-Party Sites

- Firm's are responsible for promotion on third-party sites if they have *any* control or influence, *even* if limited in scope
  - *E.g.*, the firm collaborates or has editorial, preview, or review privilege" over content.
- **Not** responsible if *only* financial support (e.g., unrestricted educational grant) *and* no other control or influence
- Providing promotional materials (e.g., banner ads)
  - A firm is only responsible if it *directs* the placement of the promotion within the site
  - Otherwise, firm is only responsible for promotional materials disseminated on site (e.g., comply with FDA regulations), not the third-party site itself

Patient Communications: Other Considerations

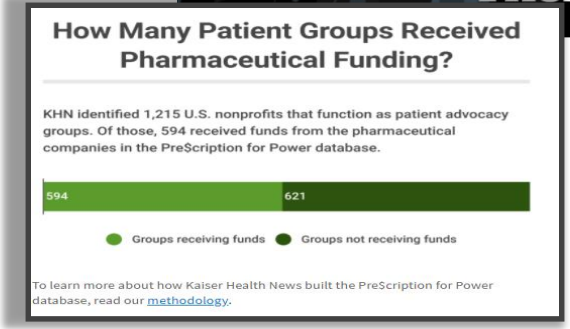
- FDA 2004 Disease Awareness Guidance (2015 withdrawn)
- Correcting Independent Third-Party Misinformation (FDA draft guidance)
- HIPAA, COPPA, other privacy laws
- Compassionate Use / Right to Try / Expanded Access
- Adverse event reporting, monitoring
- Transparency, endorsements (FTC) and use of patient consultants
- Fraud & Abuse / Healthcare compliance (e.g., Anti-Kickback Statute)
  - Discussion of reimbursement, coverage, patient assistance programs (PAPs), etc.
  - Interactions with patient advocacy groups, guidelines committees, professional medical associations

Patient Advocacy Groups

KHN launches "Pre$cription for Power," a groundbreaking database to expose Big Pharma's ties to patient groups.

Pharmaceutical companies gave at least $116 million to patient advocacy groups in a single year, reveals a new database logging 12,000 donations from large publicly traded drugmakers to such organizations.

Pharmaceutical Company	Tracked Donations to Patient Advocacy Groups 2015	Number of Patient Advocacy Groups 2015
Pfizer Inc.	$28,860,052	390
AbbVie Inc.	$24,681,287	59
Bristol-Myers Squibb Co.	$20,528,919	84
Eli Lilly and Co.	$14,939,403	70
Merck & Co. Inc.	$8,634,706	62
Johnson & Johnson	$6,063,579	278
Amgen Inc.	$3,165,159	28
Abbott Laboratories	$2,788,737	71
Gilead Sciences Inc.	$2,576,404	8
Alexion Pharmaceuticals Inc.	$2,574,555	12
		30
		18
		123
Biogen Inc.	$152,827	67



spent on federal lobbying. The 14 companies that contributed $116 million to patient advocacy groups reported only about $63 million in lobbying activities that same year.

Patient Communications: Considerations

- Comply with applicable FDA regulations, guidance (e.g., branded, unbranded, social media, transparency, etc.)
  - Fair balance; on-label, no overstatement of efficacy, superiority, QOL
  - Address unique aspects of social media (e.g., “like,” “share,” commenting, personal blogs)
- Appropriate patients/caregivers, objective criteria (e.g., on-label, representative)
- Not intended to interfere with clinical decision-making; not medical advice
- Not a reward to patient or their HCP for using product now/future
- Respect patient privacy, comply with HIPAA/privacy laws
- Contracts for services (written agreement, FMV); require company training
- Limited role access, coverage, reimbursement, lobbying
- Comply with patient advocacy group rules
- Consider policies, SOPs, centralized function to handle patient engagement