



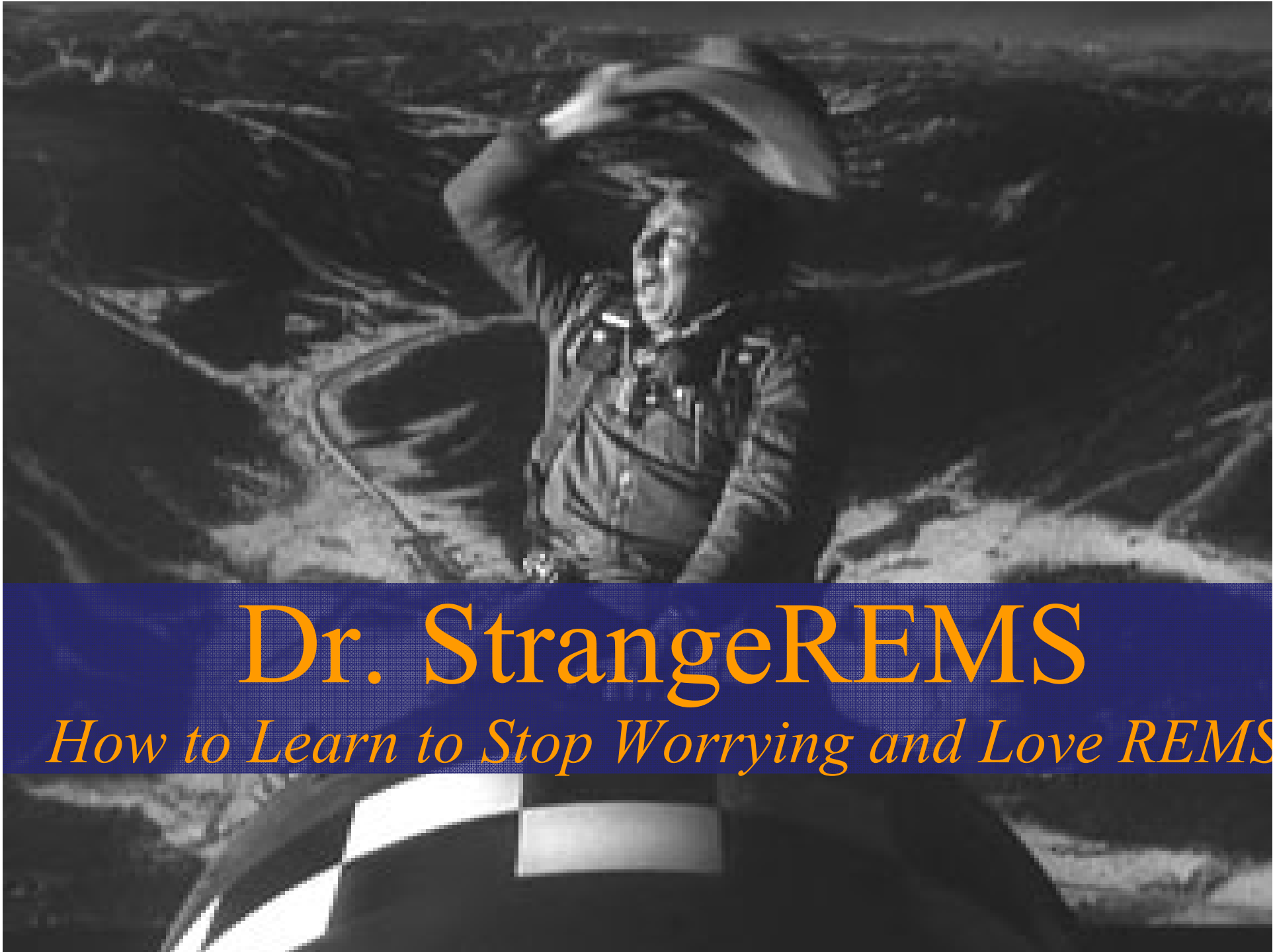
# REMS as a Tool for Profitability

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Or...



# Dr. StrangeREMS

*How to Learn to Stop Worrying and Love REMS*

# Conventional Wisdom

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REMS are full of oppressively burdensome requirements that will scare away doctors and patients and make it impossible for me to sell my drug.

# How to Avoid a REMS?

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Sorry, you can't...but even so, REMS can provide:

- A product development catalyst
- Closer ties to HCPs through required marketing strategies and multiple marketing tactics
- Lifecycle Management options
- Immunity from prosecution?
- Immunity from liability claims?

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REMS Marketing Strategies and Tactics



**REMS Marketing Requirements:  
The Br'er Rabbit Phenomenon??**

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The REMS Marketing Briar Patch  
*Direct Mail to HCPs*



# Direct Mailings to HCPs

Direct Mailings are a perennial target of DDMAC →



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

## TRANSMITTED BY FACSIMILE

Peter A. Lankau  
President and CEO  
Endo Pharmaceuticals Inc.  
100 Endo Boulevard  
Chadds Ford, PA 19317

RE: NDA 20-612  
Lidoderm® (Lidocaine Patch 5%)  
MACMIS # 13494

## WARNING LETTER

Dear Mr. Lankau:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) in the U.S. Food and Drug Administration (FDA) has reviewed two professional direct mailing pieces (identified as LD-1204F and LD-1316B) for Lidoderm® (Lidocaine Patch 5%) submitted by Endo Pharmaceuticals Inc. (Endo) under cover of Form FDA 2253. The direct mailing pieces are false or misleading for several reasons: first, they contain unsubstantiated effectiveness claims for Lidoderm; second, they omit and minimize serious risk information associated with Lidoderm; and third, they fail to communicate an important limitation in the drug's FDA-approved indication. Thus, the direct mailing pieces misbrand the drug within the meaning of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) and 321(n). These violations are a public health concern because they may encourage use of Lidoderm in circumstances other than those in which the drug has been shown to be safe and effective.

# Direct mail

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## Forteo:

A Dear HCP (DHCP) Letter will be mailed at the time of launch of the GIOP indication. The intended audience for this DHCP letter will be all healthcare professionals who are likely to prescribe FORTEO.

# Forteo Dear HCP Letter

- Forteo direct mail piece has FDA seal of approval and highlights the new indication.

## IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Professional:

Eli Lilly and Company (Lilly) wishes to inform you of important safety information and updates to the Prescribing Information for FORTEO (teriparatide [rDNA origin] injection). FORTEO is indicated for treatment of postmenopausal women with osteoporosis at high risk for fracture and increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture.

The label includes information regarding the new indication for the treatment of men and women with glucocorticoid-induced osteoporosis (GIO) at high risk for fracture and appropriate patient selection. The label has included a boxed warning concerning the potential risk of osteosarcoma since the approval of FORTEO in 2002. Because patients with GIO may be younger than those currently receiving FORTEO, the language in the boxed warning has been updated to reinforce that FORTEO should not be used in pediatric and young adult patients with open epiphyses.

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The REMS Marketing Briar Patch  
*Journal Advertising*

# Journal Advertisements – Multaq

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- Multaq (dronedarone) indicated for heart rhythm disorders, but poses risks for patients with severe heart failure or liver problems.
- REMS requirement:  
Sanofi-aventis will issue REMS Print Advertisements in the following professional society journals, monthly for 24 months, following approval of the REMS:
  - Journal of the American College of Cardiology
  - Circulation
  - Annals of Internal Medicine

# Journal Advertisements – Multaq

sanofi aventis

Because health matters

## Important Information on the Use of MULTAQ® (dronedarone)

**Do not prescribe MULTAQ for patients with NYHA Class IV heart failure (HF) or NYHA Class II–III HF with recent decompensation requiring hospitalization or referral to a specialized HF clinic**

### WARNING: HEART FAILURE

MULTAQ is contraindicated in patients with NYHA Class IV heart failure, or NYHA Class II–III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic.

In a placebo-controlled study in patients with severe heart failure requiring recent hospitalization or referral to a specialized heart failure clinic for worsening symptoms (the ANDROMEDA Study), patients given dronedarone had a greater than two-fold increase in mortality. Such patients should not be given dronedarone.

### Prescribers should also be aware of other important contraindications, including:

- Coadministration of strong CYP3A4 inhibitors, medicinal products including Torsade de Pointes, or Class I or III antiarrhythmic agents
- Second- or third-degree atrioventricular block, sick sinus syndrome (except when used in conjunction with a functioning pacemaker), or bradycardia of <50 bpm
- QTc Bazett ≥500 ms or PR interval >280 ms
- Severe hepatic impairment
- Pregnancy or nursing mothers

### MULTAQ is an antiarrhythmic drug indicated to:

- Reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AFib) or atrial flutter (AFL) with a recent episode of AFib/AFL and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or left ventricular ejection fraction [LVEF] <40%), who are in sinus rhythm or who will be cardioverted

### Sanofi-aventis is committed to appropriate patient care and treatment

The mPACT Program has been developed for health care professionals who will prescribe MULTAQ, in an effort to help ensure appropriate patient selection.

Visit [www.MULTAQ.com](http://www.MULTAQ.com) for more information.

Please see accompanying Brief Summary before prescribing MULTAQ.

RISK MITIGATION PROGRAM  
**mPACT**  
MULTAQ® Partnership  
for Appropriate Care and Treatment

US, 090, 03, 03, 0716 June 2009 © 2009 Sanofi-aventis U.S. LLC

Wiley  
Rein  
LLP

# Journal Advertisements – Multaq

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## **MULTAQ is an antiarrhythmic drug indicated to:**

- Reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AFib) or atrial flutter (AFL), with a recent episode of AFib/AFL and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter  $\geq 50$  mm or left ventricular ejection fraction [LVEF] <40%), who are in sinus rhythm or who will be cardioverted

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The REMS Marketing Briar Patch  
*Targeting and Using Key Opinion Leaders*



# Key Opinion Leaders/Speaker Bureaus

DEPARTMENT OF HEALTH AND  
HUMAN SERVICES

Office of Inspector General

Draft OIG Compliance Program  
Guidance for Pharmaceutical  
Manufacturers

AGENCY: Office of Inspector General  
(OIG), HHS.

activities. For instance, pharmaceutical manufacturers may engage physicians to perform research, data collection, and consulting services, to serve on advisory boards, to participate in focus groups, or to speak at meetings. While there may be legitimate purposes to these arrangements, they pose a substantial risk of fraud and abuse; without appropriate safeguards, they can result in payments for referrals.

# Opinion Leaders – Cimzia REMS

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## *2.2.3 Medical Scientific Liaison Slide Decks (Safety-related)*

A specific dedicated slide deck to inform healthcare providers about the occurrence of unrecognized histoplasmosis and other invasive fungal infections in patients at risk will be presented to all Gastroenterology Key Opinion Leaders (approximately 500) and Rheumatology Key Opinion Leaders (approximately 600).

Please see appended slide deck.

# Opinion Leaders – Xenazine

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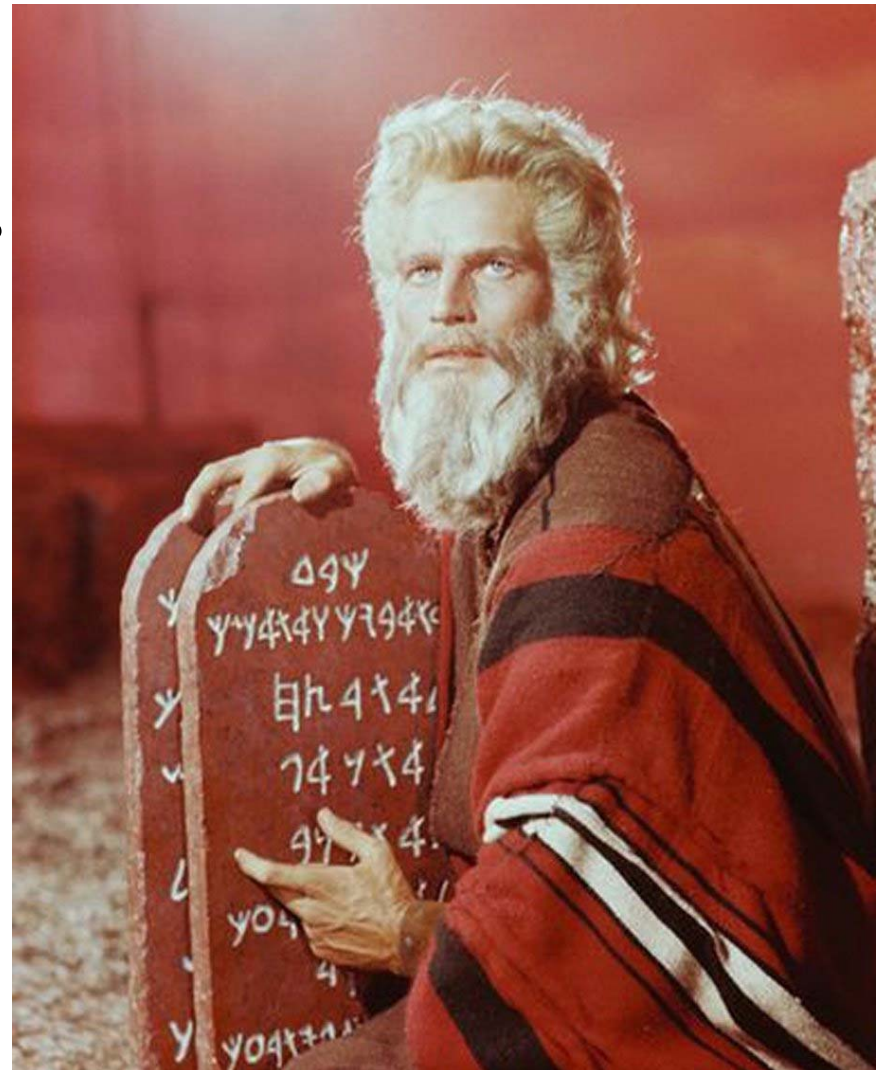
- Ongoing Healthcare Professional Education - The Sponsor will also use several educational vehicles to continue educating and updating Healthcare Professionals about tetrabenazine and the REMS. These include a trained Speaker's Bureau which will schedule local and regional thought leader symposia.

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The REMS Marketing Briar Patch  
*Collaboration of Marketing With  
Medical Science Liaisons*

# Collaboration of Marketing With Medical Science Liaisons

*“Thou shalt clearly separate the functions of your Marketing and Medical Affairs departments.”*



# Marketing/MSL Collaboration – Xenazine REMS

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minimization messages after launch. The Sponsor's clinical team and sales professionals will be present at annual meetings of the major professional societies of neurologists and movement disorder specialists (e.g., American Academy of Neurology, American Neurological Association, Movement Disorder Society) and will use these opportunities to reinforce the REMS messages. Continuing education formats will also be available for physicians and pharmacists on the product web site.

# Marketing/MSL Collaboration – Cimzia REMS

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If a CIMZIA<sup>®</sup> kit containing the lyophilized powder for reconstitution with diluent, needles, and swabs, is distributed to be administered by a healthcare professional, the MG will be provided by the healthcare professional, and additional MGs will be provided by UCB Medical Science Liaisons (MSLs) and sales representatives to healthcare providers if necessary.

# Marketing/MSL Collaboration – Samsca REMS

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The Prescriber Brochure will be included with the Dear Healthcare Provider Letter, and will be distributed as indicated above. In addition, both documents will be posted on the website, [samsca.com](http://samsca.com). The brochure will also be presented and distributed by Otsuka sales representatives. This effort will be supplemented by education by Medical Science Liaisons.



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The REMS Marketing Briar Patch  
*Medical Conferences*

# Attendance at Medical Conferences

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## FDA Guidance:

“The communication plan may include...disseminating information about REMS elements to health care providers through professional societies....”

## Xenazine REMS:

minimization messages after launch. The Sponsor’s clinical team and sales professionals will be present at annual meetings of the major professional societies of neurologists and movement disorder specialists (e.g., American Academy of Neurology, American Neurological Association, Movement Disorder Society) and will use these opportunities to reinforce the REMS messages. Continuing education formats will also be available for physicians and pharmacists on the product web site.

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The REMS Marketing Briar Patch  
*Targeting and Tracking Prescribers*

# Targeting and Tracking Prescribers

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Tasigna:

Within 3 months of approval of the REMS and quarterly thereafter, Novartis will hand deliver and discuss educational materials with likely Tasigna prescribers; that is, the approximately 6,000 US prescribers who treat patients for chronic myelogenous leukemia (CML).

# Targeting and Tracking Prescribers

Exalgo:

- Covidien will ensure that training will be provided to healthcare providers who prescribe EXALGO. To become trained, each prescriber will be provided with the materials in the EXALGO REMS Healthcare Professional Education Program Kit.
- Prescribers will be re-trained...every two years or following substantial changes to the EXALGO REMS. Substantial changes may include, changes in the EXALGO Full Prescribing Information, EXALGO Medication Guide, or EXALGO REMS that require substantial modification of the educational materials.

# Targeting and Tracking Prescribers

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Forteo:

A Dear HCP (DHCP) Letter will be mailed at the time of launch of the GIOP indication. The intended audience for this DHCP letter will be all healthcare professionals who are likely to prescribe FORTEO. Lilly has identified these providers as any HCP who has prescribed FORTEO in the last 12 months. These include physicians, nurse practitioners, and physicians' assistants, predominantly in the specialties of Rheumatology, Endocrinology, Internal Medicine, and Family Practice.

# Targeting and Tracking Prescribers

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Multaq required print advertisements to target:

- Key stakeholders: Health care professionals, including cardiologists, electrophysiologists, hospitalists, internal medicine and family practice physicians who regularly prescribe antiarrhythmic agents will be targeted. Members of relevant professional societies will also be targeted.
- Secondary stakeholders: Nurse practitioners and physician assistants who work in offices of the above-mentioned physicians will also be targeted as secondary stakeholders for education.

# The Big Picture Marketing Perspective

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REMS are a burden and an opportunity –

- Accentuating the negative vs. deeper HCP relationships
- Key is how will HCPs come to view the barrage of REMS requirements and how their behavior changes:
  - Retention through repetition, or information overload?
  - Will the “right” behavior follow the “right” information?
  - Discounting/dilution/paternalistic bias effects?
  - Common enemy effect?
  - Complacency effect?
- Assessment requirements reflect fundamental uncertainty about REMS writ large.



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# Competitive Impacts of REMS

# Competitive Impacts – Generics' Views

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- REMS “is on the fast track of becoming another powerful lifecycle management tool.”  
– *GPhA Comments on FDA REMS Guidance, Dec. 23, 2009.*

# Competitive Impacts – Generics’ Views

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- “[U]nless FDA takes swift action now...to prevent REMS gaming, consumers will be prevented from having timely access to generic versions of an increasing number of important drugs.”

– *Dr. Reddy’s Citizen Petition (June 10, 2009).*

# Competitive Impacts – Generics’ Views

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- “the REMS mechanism could conceivably create economic incentives for brand companies to increase distribution costs in order to protect market position. This is certainly not the result that Congress intended...and it is bad public policy.”

– *Roxane Labs Citizen Petition (Feb. 3, 2010)*

# Competitive Impacts – FDAAA

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## FDAAA:

“No holder of an approved covered application shall use any element to assure safe use...to block or delay approval of an application under section 505(b)(2) or (j) or to prevent application of such [ETASU] ...to a drug that is the subject of an [ANDA].” 21 U.S.C. § 355-1(f)(8)

- *What does this mean?*
- *Who does it apply to?*
- *How can it be enforced?*
- *What are the generics' concerns?*

# Competitive Impacts – Revlimid

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- Revlimid subject to closed distribution REMS.
- Generics cannot purchase the brand product on the market for bioequivalence testing necessary for ANDA filing and approval
- Dr. Reddy's requested that Celgene sell it samples directly, but Celgene refused.
- Dr. Reddy's requests mechanisms for FDA to allow generics to buy samples and/or to require NDA holders to provide samples for purposes of bioequivalence testing.

## Competitive Impacts – 505-1(f)(8)

- “**No holder** of an approved covered application **shall use** any element to assure safe use...to block or delay approval of an application under section 505(b)(2) or (j) or to prevent application of such [ETASU] ...to a drug that is the subject of an [ANDA].” 21 U.S.C. § 355-1(f)(8)
  - If sponsor proposes a blocking REMS, is that a prohibited “use” even if FDA approves it?
  - If the ETASU requires third parties to act in a way that blocks generics, is the NDA “holder” unlawfully “using” the ETASU?
  - Only potential enforcement mechanism is to prohibit the branded drug from being sold (21 U.S.C. 355-1(p)). FDA unlikely to use this nuclear option

# Competitive Impacts – Conundrum

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“A person may not introduce or deliver for introduction into interstate commerce a new drug if...the person fails to maintain compliance with the requirements of the approved [REMS] or with other requirements of section 505-1.” 21 U.S.C. § 355(p).

- Thus, if the approved REMS requires that only registered entities and persons receive the drug, the innovator cannot lawfully provide the drug to non-registrants.
- But, what about the “other requirement” of 505-1 that a company cannot “use” an ETASU to block generics?



# Competitive Impacts – Conundrum

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- If an approved closed distribution REMS had a carve-out allowing sales of samples for testing, would refusal to sell be a “use” of the REMS to delay generics?
  - Historically, generics obtain samples from the supply chain, not directly from manufacturer. Would refusal to sell now, or contractual restrictions on pharmacy resale for testing, violate 355-1(f)(8)? I.e., does FDAAA, *sub silentio*, create a new obligation to engage in a commercial transaction?

# Cost-Sharing for ETASUs – CellCept

- Roxane Citizen Petition (Feb. 2010).
- Roche/FDA developed REMS without input from already-approved generics.
- Roche demands cost sharing based on market share and number of companies.
- Roxane argues that generic price structure creates unfair burden – generic market share 57% by volume, but only 16% by sales \$\$.

# Cost-Sharing for ETASUs – CellCept

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- Roxane requests FDA allow existing approved generic competitors to participate in development of a new REMS or not have to share in the costs of implementing the ETASUs.
- FDAAA allows generic opt-out if
  - Burden of shared system outweighs benefit, considering impact of HCPs, patients, and applicants, or
  - ETASU is patented and generic was unable to obtain a license to use the system.
- Roxane not likely interested in running its own system – just a better bargaining position via FDA intervention.

# Competitive Issues – Patents

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- FDAAA acknowledges the right to patent REMS elements 21 U.S.C. § 355-1(i)(1)(B)(ii):
  - Single shared (innovator/generic) ETASU required, unless “an aspect of the [ETASU] for the applicable listed drug is claimed by a patent...and the [ANDA] applicant...certifies that it has sought a license...and that it was unable to obtain a license.”
- Thus, FDAAA recognizes that patented ETASUs do not need to be licensed, even though this could delay a generic entrant.

# Competitive Impacts – FOBs

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- REMS involving change to established name (e.g., botulinum toxin)
- Interchangeability requires that a follow-on biologic have the same or highly similar active ingredient
- On top of the challenges for FOB interchangeability generally, if safety requires differentiating established names the barrier gets higher.

# The Big Picture

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- REMS are a burden and an opportunity...
  - Cost and delay vs. new opportunities
  - Accentuating the negative vs. deeper HCP relationships
  - Greater safety vs. less savings from generics
- ...but where will the balance points settle?

Stay Tuned!