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REGULATION | POLICY | MARKET ACCESS

FDAAA: Landmark Shift In FDA Authority; Industry Practices

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Prevision Policy, LLC

National Health Policy Forum

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A New Landmark

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Kefauver "Efficacy" Amendments, August 1962

- **Substantial evidence standard**
- **Advent of well-controlled clinical trial as the key to FDA approval**

Thalidomide Prevention Act

FDAAA "Drug Safety" Act, September 2007

- **Post-marketing risk management**
- **Advent of the well-identified patient population**

Thalidomide Control Act

FDA: Public Health Protector

Introductory message to FDA staff (May 2009)

- Praised FDA as the protector of public safety
  - **The agency that kept thalidomide off the market in 1962**
- Should have said:
  - **FDA is the agency that figured out a way to keep thalidomide on the market for 11 years**

FDA Commissioner Margaret Hamburg

Janus Effect

New NDA/BLA priorities

Giving FDA authority in post-market

IND — NDA — REMS — Phase IV

FDA Approval

- Better designed NDAs/BLAs
- Redefines objective of clinical trials: find and identify responders and patient populations
- FDA will look for post-market control plans early in the development cycle

- Mandatory Label Changes
- Look-back safety reviews
- Post-market surveillance

FDA sees its new mandate as the "detection of safety problems…and rapid response"

New Approval Model

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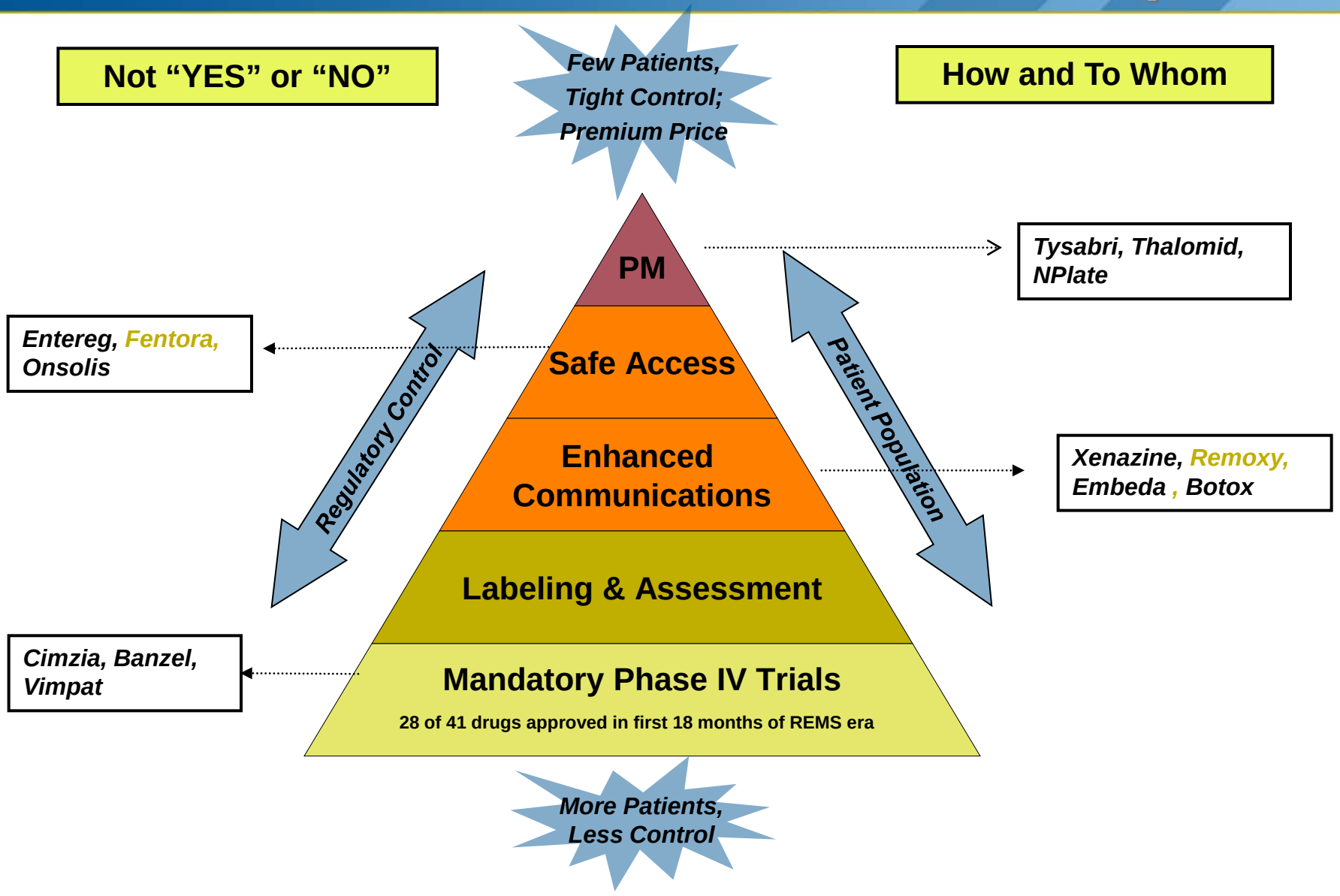

A Tiered Approval System

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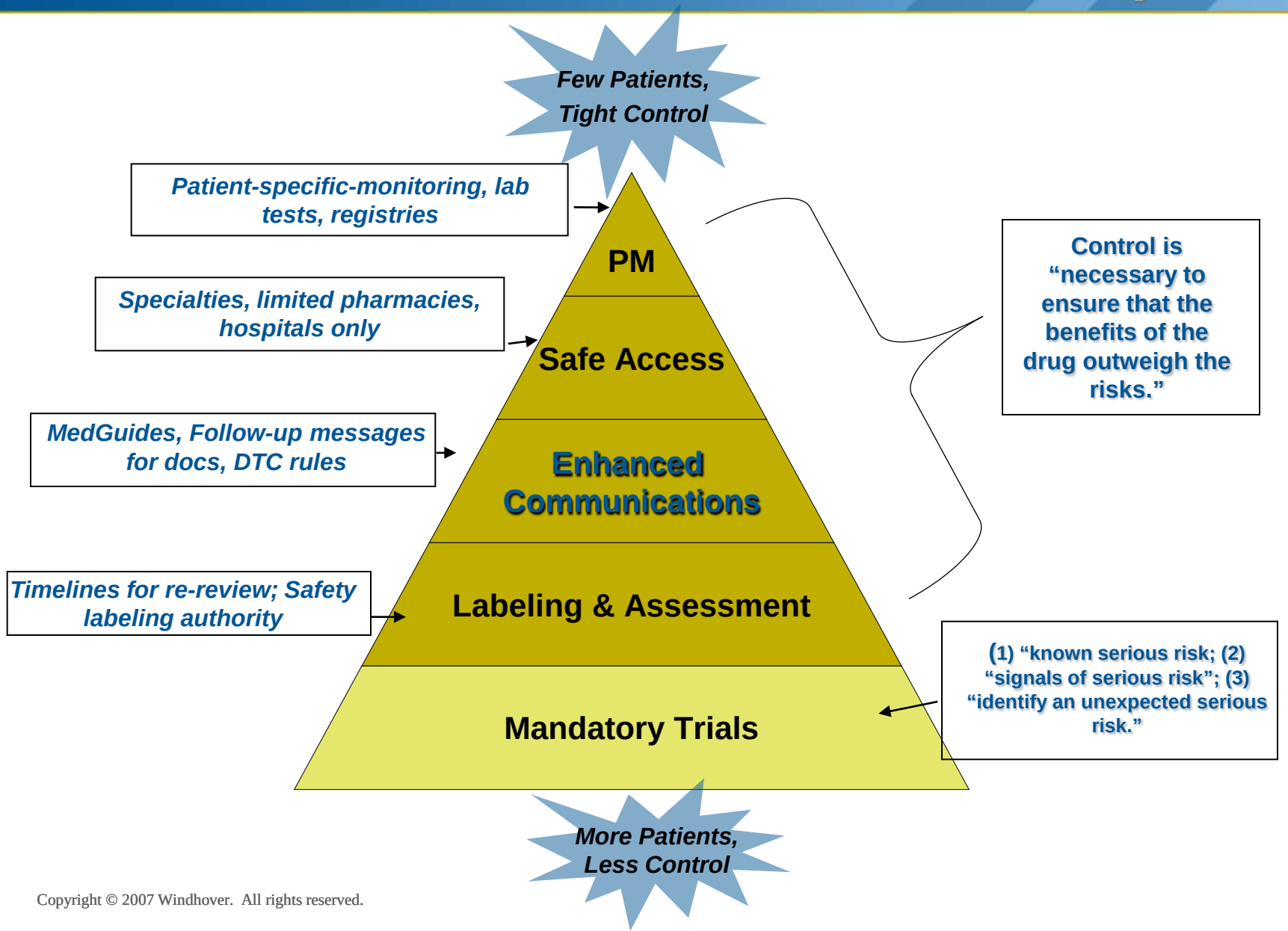

How Big Are The Changes?

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FDA

✓ The Search for Responders:

Even if a drug has only a 10% effect, “it might have a rather large effect in a fraction of the population.” There are plenty of opportunities in early studies to identify the responders and incorporate that information into the design of later-phase trials.

-- FDA CDER Deputy Director Robert Temple

✓ FDA’s Role In Health Delivery

FDA plans to be "a much more active player as part of the health care delivery system." The agency will be involved in "assuring that drugs are not only safe and effective if they're used as labeled, but that they are safe and effective in real use and in the real world…”

-- CDER Director of Executive Programs Deborah Henderson

Industry

✓ A New REMS Process

BIO is already asking FDA for a schedule of REMS topics and meetings during IND/NDA phases: e.g. discuss patient inclusion and exclusion in relation to REMS at time of IND submission.

-- Comments on FDA REMS Guidance

PDUFA V warm-up

✓ Free Speech Challenge

Allergan is challenging the authority of FDA to require warnings about off-label uses of *Botox*. FDA’s warnings “do not give physicians using *Botox* for spasticity specific guidance about how to further minimize that risk.”

-- Allergan comments on October 1, 2009 suit filed in DC federal court

Far-reaching REMSifications

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1. **FDA and health economics data**

   One of six mandatory post-market studies for *Prevnar-13* calls for Pfizer to conduct an "ecologic study to assess national trends in health care visits for otitis media in children younger than five years of age." FDA requiring sponsors to collect general data about the impact of their products on health care system.

2. **Follow-on Biologics**

   Class REMS for botulinum products requires the three sponsors of the different brandname products to describe each product as different and difficult to switch -- substitutable-with-caution.

3. **Counter-detailing**

   Long a process of interest and debate on Capitol Hill – a way to get a more balanced message about new products/old products to the marketplace: REMS help address that objective.

4. **Comparative Effectiveness**

   Not happening now but FDA could require sponsors to inform the medical community about new comparative trial results. The new information would change the safety and risk/benefit profiles for existing products.

The Many Uses of REMS

Marketing License

Liability Shield

Negotiating Leverage

Savior of Drug Development?

Marketing License

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Speaker's Bureaus

Scripted Medical Science Liaisons

Aggressive Sales Force Goals

Prescriber Data Tracking

Targeted Journal Ads

"Seeding Studies"

Anti-Substitution Campaigns

Direct-to-Consumer Marketing

Marketing License?

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Targets of Industry Critics

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Mandated By FDA REMS

Marketing License

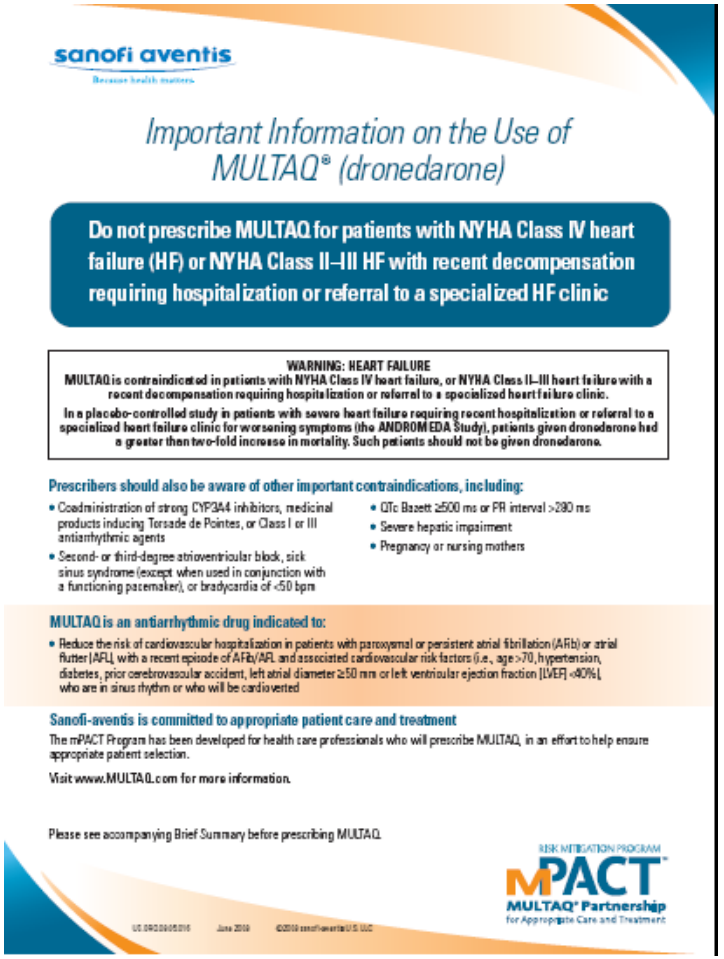
"Sanofi-Aventis will issue REMS

Print Advertisements in the following professional society journals, monthly for 24 months, following approval of the REMS:

Journal of the ACC

Circulation

Annals of Internal Medicine"



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 inducing 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 for more information.

Please see accompanying Brief Summary before prescribing MULTAQ.

RISK MITIGATION PROGRAM

mPACT

MULTAQ® Partnership for Appropriate Care and Treatment

FDA Orders A Speakers Bureau

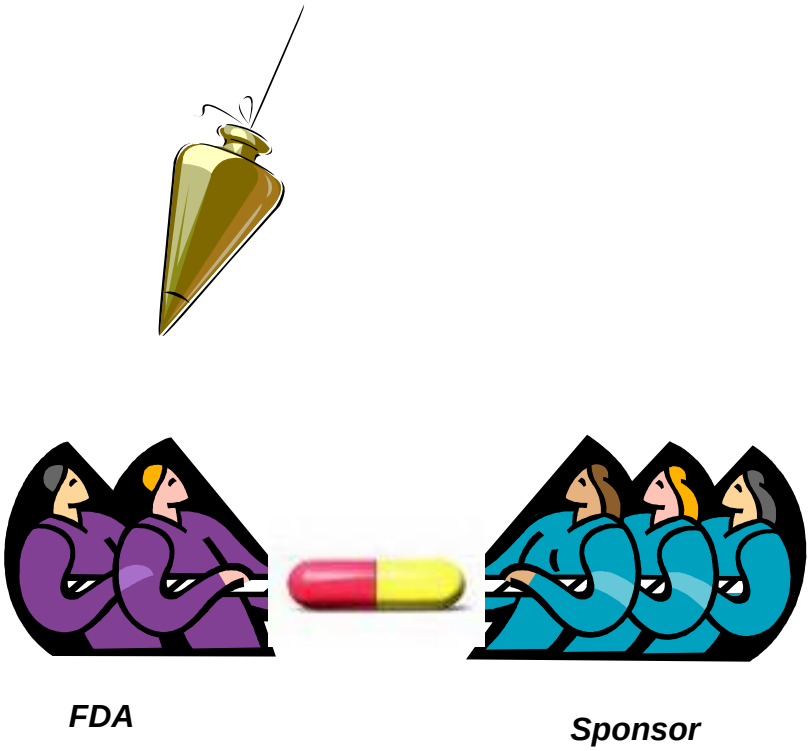
Stepping Into Marketing Management

Xenazine (tetrabenazine): 40-year-old tranquilizer, approved by FDA last August for Huntington's Disease –

- Prolonged and difficult three-year FDA review
- Suicidality concerns

- REMS for product includes "several educational vehicles"
  - "A trained Speaker's Bureau which will include local and regional thought leaders"
  - Speaker materials must be cleared through FDA-DDMAC

FDA Centric View



The Pendulum Swing

Who Controls The Drug?

New Law Gives FDA The Upper Hand

Future Swings Will Never Return to Pre-2007 Center Point

…But What About The Big Picture?

REMS And The Healthcare System

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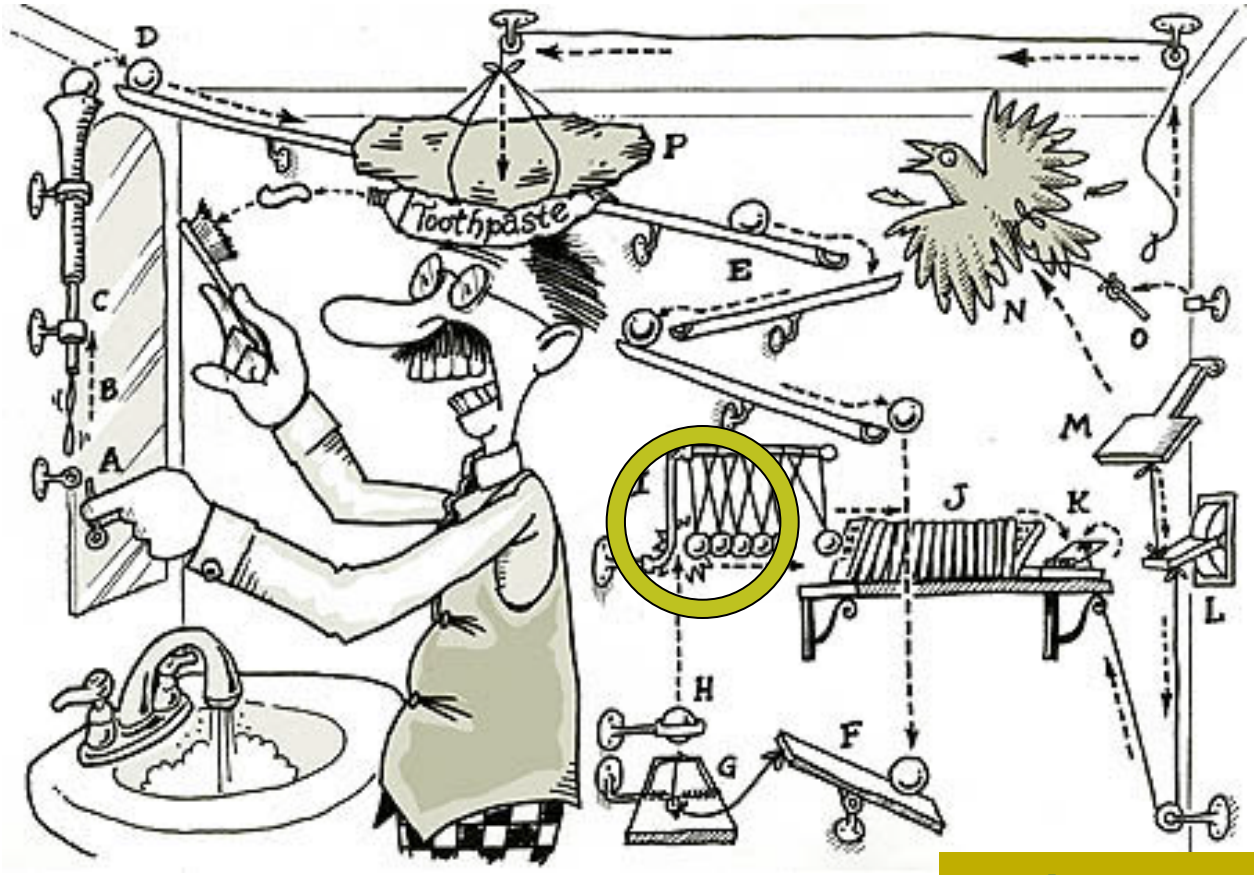

There's A LOT More To The Story

Providers Push Back

"REMS with elements to assure safe use essentially create a whole new class of drugs from the delivery system and cost perspectives."

KAISER PERMANENTE®

"ASCO has noted with growing concern the process by which REMS are imposed without input from the physician community."

ASCO®

Health Care Reform: One Class At A Time

The RPM Report

- **Opioid REMS Will Be Largest Undertaking To Date**
  - Wake Up Call For Health Care System
- **76 Speakers During 2009 Meeting**
  - **Patients, Providers, Pharma Too**

"FDA considers the industry wide group as one of many stakeholders there to provide them with a view or some input, and then they will collate all this, interpret it, integrate it and then come up with a set of recommendations which we will then be mandated to implement.

"We have not been able to really sit down with the agency and discuss the best way forward for this novel and unprecedented activity. It has a laudable goal but we have got to get it right."

--One Pharma Exec

Exhibit 1

Opioid REMS: By The Numbers

28 Million: Long-acting opioid prescriptions per year
4 Million: Patients treated each year
5.2 Million: Estimated number of Americans who use pain medicines "non-medically" each month
1 Million: Number of physicians registered by the Drug Enforcement Agency
680,000: Estimated number of active prescribers registered by DEA
167,000: Estimated number of Emergency Department visits for non-medical use of of opioids.
13,800: Opioid drug poisoning deaths in 2006
9,179: Reports of inadvertent use by children to Poison Control (2003-2006)
1,274: Comments submitted to FDA on docket on class-wide REMS (as of Feb. 1)
24: Companies with products covered by the proposed REMS
5: Public Meetings held by FDA so far on opioid REMS. (A sixth will take place this Spring).

SOURCE: FDA, Industry Working Group on Opioid REMS

The Future of REMS

PDUFA V Comes Up In 2012

Questions?

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