

American College of Rheumatology
Rheumatology Program Directors' Conference
March 14, 2009

**Emerging Issues in FDA Regulation
and Physician-Industry Relations**

Bret Koplow, PhD, JD

The Regulatory & Legislative Climate

- In recent years, Congress lost faith in the FDA
 - Steady wave of drug and food safety controversies (2004-2009)
 - SSRIs
 - Seasonal flu vaccine
 - Vioxx
 - Spinach, peanut butter
 - Pet food and toothpaste imported from China
 - Avandia
 - Ketek
 - Heparin
 - Peanut butter – again
 - Leading to increased oversight, more prescriptive legislation (e.g., FDA Amendments Act), stalemates (e.g., stem cells, biosimilars), and a more risk-averse FDA

The Regulatory & Legislative Climate

- 2008 Election as Watershed
 - Significantly expanded Democratic majorities in House and Senate
 - Congressional leadership – forceful advocates for strong regulatory oversight of health care agencies and firms
 - Kennedy, Waxman, DeLauro, Stupak, Grassley
- White House takes a 180-degree turn
- Despite the economic situation, significant increases in health care spending are expected
 - Health care reform – expanded coverage
 - Health information technology – EHR, e-prescribing
 - Medical research, including stem cells
 - Hefty funding increases for FDA to support greater oversight

Agenda

- **Physician Relations with Industry**
 - Disclosure of manufacturer payments to health care entities
 - Dissemination of published information on unapproved uses of approved drugs, biologics, and devices
- **FDA Oversight and Regulation of Drug Safety**
 - Risk assessment and identification
 - Risk communication
 - Risk management
- **Biosimilars**

**Physician Relations with Industry:
“Physician Payments Sunshine Act” (S. 301)**

- Introduced by Sen. Chuck Grassley (R-IA)
- Requires disclosure of:
 - Payments (or transfers of value) made by a drug or device manufacturer to a physician or physician medical practice or group practice
 - Physician ownership interest in applicable manufacturers or GPOs
- Beginning in 2011, information would be posted to the web
- Covered transfers include:
 - Gifts
 - Honoraria
 - Speaking fees
 - Consulting fees
 - Travel
 - Services
 - Dividends
 - Profit distributions
 - Stock or stock option grants
 - Ownership or investment interests

**Physician Relations with Industry:
“Physician Payments Sunshine Act” (S. 301)**

- Exceptions include (among others):
 - Aggregate annual value of \$100 or less
 - Product samples for patient use and not intended to be sold
 - Educational materials that benefit patients or are intended for patient use
 - Short-term (90 days or less) loan of a device to permit its evaluation
 - Discounts, including rebates

Physician Relations with Industry: “Good Reprint Practices”

- In January, FDA issued final guidance outlining new policies regarding a manufacturer’s distribution to health care entities of copies of published medical or scientific journal articles and reference publications on unapproved uses of approved drugs, biologics, and devices
 - Health care entities include providers, hospitals, professional medical organizations, health plans, and drug formulary committees
- The guidance omitted a previously established condition that the manufacturer must intend to file with FDA a supplemental application for approval of the new use
- Rep. Waxman believes the new policy will both enable manufacturers to promote off-label uses and create a disincentive for companies to both fully develop evidence to support the new use and subject such evidence to the scrutiny of FDA reviewers

Drug Safety: Risk Assessment & Identification

- Current system mainly relies on passive surveillance to compile, analyze, and disseminate spontaneous AERs
 - Reporting requirements for manufacturers of drugs, biologics, devices, and special nutritional products (i.e., medical food, infant formula, dietary supplements)
 - Reporting is voluntary for providers and the public
 - Best used to identify signals of risks that should be studied
 - Limited usefulness due to:
 - Incomplete reports
 - Unreliable reports
 - Lack of standardized terminology
 - Underreporting
 - Unidentified duplicate reports
 - Unsuitable to conclusions of causality, incidence of AEs, or comparative risk
 - Reporting bias

Drug Safety: Risk Assessment & Identification

- Congress is requiring FDA to establish a post-market, active surveillance system
 - Using Federal and private sector health-related electronic records
 - Joint FDA-CMS “Sentinel” program to use Part D claims database to identify drug risks
 - FDA plans to validate signals of drug risks by accessing full-text EHRs
- Under 2007 law, DTC print ads must include FDA’s toll-free number and web address for reporting AEs
- Congress is expected soon to enhance FDA’s authority and duties to inspect facilities and imported products

Drug Safety: Risk Assessment & Identification

- FDA has new authority to mandate post-market studies or clinical trials where other post-market surveillance methods are deemed insufficient to:
 - Assess a known serious risk,
 - Assess a signal of serious risk, or
 - Identify an unexpected serious risk when available data indicate potential serious risk
- FDA increasingly using meta-analyses, especially to support strengthening warning labels, however –
 - Controversy regarding appropriate role
 - Results often not substantiated by later research
 - Variability in study design, lack of standardization

Drug Safety: Risk Communication

- FDA has new power to mandate specific changes to labeling regarding safety, as well to include results of certain pediatric drug studies
- New law requires FDA to publish on its website the “action package” for approval of a drug application
 - Includes records of FDA’s review of the application
 - Includes a summary of any critical issues or disagreements that emerged during review
 - Includes the proposed labeling
 - Excludes confidential and proprietary information

Drug Safety: Risk Communication

- **Clinical Trial Registry and Results Data Bank**
 - 2007 law significantly expanded the scope of the existing clinical trial registry operated by NIH
 - New program requires inclusion of any Phase II, III, or IV clinical trial of a drug or biologic, as well as any prospective study intended to support an application to market a medical device (e.g., 510(k), PMA, or HDE)
 - Requires expanded descriptive information
 - Preempts State and local registry and results database requirements
 - If trial funded by HHS agency, release of funds is conditioned on compliance with registry requirements
 - Civil monetary penalties

Drug Safety: Risk Communication

- **Clinical Trial Registry and Results Data Bank (cont'd)**
 - Requires certain links to trial results that form primary basis of an efficacy claim, or that are conducted post-clearance or approval
 - If considered at an FDA advisory committee meeting, posted summary of the meeting
 - FDA assessment of results, if trial conducted for pediatric exclusivity or post-market as a condition of approval
 - Any FDA public health advisory
 - FDA action package
 - Certain NIH information (e.g., Medline citations)
 - Any agreement in place that restricts the right of the principal investigator to publish or disclose trial results
 - By late Sept. 2010: technical and non-technical summaries to be posted, if FDA determines they may be included without being misleading or promotional

Sonnenschein.
SONNENSCHNEIN NATH & ROSENTHAL LLP

13

Drug Safety: Risk Communication

- Direct-to-Consumer Advertising
 - FDA has new power to require prior submission of DTC television ads and to mandate inclusion of specific disclosures in such ads, including the date of the drug's approval, if in the absence of such disclosures, the ad would be false or misleading
 - FDA occasionally has "requested" moratorium on DTC ads (e.g., Bextra, Celebrex)
 - FDA conditioned approval of Symlyn on Amylin's agreement to severely restrict advertising to consumers and providers
 - Many lawmakers support empowering FDA to impose, on a case-by-case basis, a 2-year moratorium on DTC advertising

Sonnenschein.
SONNENSCHNEIN NATH & ROSENTHAL LLP

14

Drug Safety: Risk Management

- New law empowers FDA to require Risk Evaluation and Mitigation Strategies (REMS)
 - **Pre-approval** – In conjunction with a new or generic drug application, or
 - **Post-approval** – Based on new safety information, if REMS is deemed necessary to ensure the drug's benefits outweigh its risks
- Each REMS includes a timetable for reassessing the adequacy of the strategy
- The risks FDA is authorized to regulate were explicitly expanded in 2007 to include risk of abuse, misuse, and accidental or intentional overdose

Sonnenschein.
SONNENSCHNEIN NATH & ROSENTHAL LLP

15

Drug Safety: Risk Management

- A REMS may be required to include methods for alerting providers and patients about risks, as well as restrictions on product distribution or use
- Available REMS education and outreach tools include:
 - "Dear Doctor" letters
 - Provider training (e.g., product-focused CME) or certification as a condition of prescribing
 - MedGuides, patient package inserts
 - Public health alerts
 - DTC ads highlighting appropriate use or product risks
 - Patient-targeted education programs, such as disease management

Sonnenschein.
SONNENSCHNEIN NATH & ROSENTHAL LLP

16

Drug Safety: Risk Management

- Available REMS tools also include reminder/prompting systems:
 - Informed consent
 - Testing to verify provider knowledge upon or periodically after completing required training
 - Specialized packaging
 - Registry for providers, patients, or pharmacists
 - Specialized recordkeeping attesting that specific safety measures have been taken
- REMS may also restrict prescribing, distribution, or dispensing to specified settings or specialties
- REMS may require evidence of the patient's safe use of the product (e.g., lab tests, suicidality evaluation)

Sonnenschein.
SONNENSCHNEIN NATH & ROSENTHAL LLP

17

Biosimilars

- Congress is poised to establish a pathway for expedited approval of a follow-on version of a biological drug
 - H.R. 1427: Introduced this week by Reps. Waxman, Pallone, Deal, and Emerson
 - Senate companion expected to be introduced by Sens. Schumer, Collins, Brown, and Vitter
 - Rival House bill expected to be introduced next week by Reps. Eshoo, Barton, and Inslee
- Such drugs are commonly referred to as "follow-on biologics" or "biosimilars," rather than "generics"
 - Since no two biologics are exactly the same, and it can be difficult or impossible to assure that any two biological drugs have the same benefits and risks

Sonnenschein.
SONNENSCHNEIN NATH & ROSENTHAL LLP

18

Biosimilars: Current Controversies

- **Interchangeability/Substitutability:** Should pharmacists be allowed to substitute a biosimilar for the reference biologic without the prescriber's approval or knowledge?
- **Clinical Trial Mandates:** Should clinical trials on the biosimilar be required?
- **Exclusive Marketing Rights for the Reference Biologic:** How long should the reference biologic be assured exclusive marketing rights?
- **Eligibility for Extension of the Reference Biologic's Exclusivity:** Should the right to exclusively market the reference biologic be extended, and if so, by how much, for proving new uses of the product or demonstrating its safety and efficacy in children?
- **Market Exclusivity for the First Approved Biosimilar Application:** Should the first licensed biosimilar be granted a period of market exclusivity during which FDA may approve no subsequent application referencing the same reference biologic?
- **Scope of Biological Product Classes Encompassed:** Should all biological drug classes be eligible for licensure as a biosimilar, or should more complex reference biologics, such as blood and plasma derived products, vaccines, and complex recombinant proteins like Factor VIII, be excluded, at least until they can be adequately characterized?

Sonnenschein.
SONNENSCHN NATH & ROSENTHAL LLP

19

For more information:

Bret Koplow, PhD, JD
(202) 408-9111
Bkoplow@Sonnenschein.com

Sonnenschein Nath & Rosenthal LLP
1301 K Street, NW
Suite 600, East Tower
Washington, DC 20005-3364

Sonnenschein.
SONNENSCHN NATH & ROSENTHAL LLP

Sonnenschein
SONNENSCHN NATH & ROSENTHAL LLP