ARNOLD & PORTER LLP

Drug Safety Regulatory Update

International Pharmaceutical Compliance Summit

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Drug Safety Regulatory Update

- Regulatory developments
- Drug safety proposals
- Outlook

Developments August-September 2004

- FDA reverses long standing position on suicidality and SSRIs with respect to adolescents
  - Based on unpublished controlled clinical trial data
- FDA Advisory Committee hears discussion on suicidality and SSRIs
  - Issue about testimony from Office of Drug Safety (ODS)
- Merck withdraws Vioxx (rofecoxib) from market due to cardiovascular risks

Developments
October-November 2004

- FDA issues Public Health Advisory about SSRI and suicidality in children, adults
- Controversy erupts about whether FDA “muzzled” another ODS scientist on COX-2 inhibitors
- FDA announces initiatives to strengthen drug safety

Developments November-December 2004

- Sen. Grassley holds hearings questioning FDA's competency, independence in drug safety matters
- FDA gives Tysabri (natalizumib) accelerated approval for MS, without long-term safety data
- FDA defends lack of further US action on SSRIs after UK tightens labeling on suicidality
- Study results do not show any survival advantage over placebo for IRESSA, which had been approved for the treatment of non-small cell lung cancer based on a surrogate endpoint

Developments
December 2004

- NCI and Pfizer stop ongoing trial of Celebrex (celecoxib) due to cardiovascular risks
- NCI stops all trials using naproxen due to cardiovascular risks
- FDA asks Pfizer to suspend DTC advertising for Celebrex
- FDA issues Public Health Advisory on COX-2 drugs, other information on naproxen

Developments
January-February 2005

- FDA issues release defending lack of US action on Adderall (amphetamine) after drug suspended by Health Canada
- FDA holds 3-day hearing of combined Drug Safety and Arthritis Drugs Advisory Committees on COX-2s
  - Conflict of interest charges emerge immediately afterwards
  - Celebrex given endorsement as safer than others
  - Sen. Grassley intervenes to get Dr. Graham on agenda to testify

Developments February 2005

- FDA and HHS Secretary announce new Drug Safety Oversight Board
  - Originally, members from FDA, other government agencies
- FDA and HHS also announce new Drug Watch Web page for emerging safety data and risk information
- Goal: New era of openness at FDA on safety issues
- Tysabri withdrawn from market by marketers after rare but fatal side effect

Developments
March 2005

- Senate hearings on drug safety, at which FDA is again criticized for lack of speed, internal conflicts, and failure to exercise power over industry
- FDA promises to issue risk management guidances between April 1 - June 30, 2005
- Bush budget request proposes 24% increase for post-approval safety program for drugs
- FDA says that chairs of advisory committees will be added to the Drug Safety Oversight Board

Developments
Vioxx Example

- Vioxx marketed from May 1999 to September 2004
- June 2000 “VIGOR” study showed more CV events in Vioxx group
- February 2001 advisory committee meeting
- April 2002 labeling change
- September 2004 “APPROVe” study showed excess CV events vs. placebo
- Product voluntarily withdrawn from the market

Developments
Vioxx Example

- Joint advisory committee meeting Feb. 2005 to discuss COX-2 class
- Committee members made various recommendations
  - Black box warnings, Dear HCP letter
  - Patient labeling
  - Use only where other treatments ineffective
  - Limit use to patients without CV problems
  - Restrict DTC advertising
  - Additional trials to understand the risks

FDA Risk Management Proposals

- Identify and minimize risks associated with product
- Maintain reasonable access and therapeutic benefits
- Thereby improving benefit/risk ratio
- To permit --
  - Safer use of high risk drugs
  - Approval of drugs not otherwise acceptable

Risk Management Guidances

- Three topics
  - Premarketing Risk Assessment
  - Good Pharmacovigilance Practices
  - Risk Minimization Programs
- Concept papers on each issued March 2003
- Draft Guidances issued May 2004
- Final Guidances not issued yet

Premarketing Risk Assessment

- Goal: To improve the identification, quantification, and understanding of safety before the decision to market
- Considerations for the premarket safety database
  - Size of database
  - Nature of studies (e.g., long-term vs. short)
  - Detecting unanticipated interactions (e.g., drug-drug)
  - Special considerations (e.g., chronic use, titration)
  - For all drugs: QTc interval, hepatotoxity, polymorphic metabolism, etc.
  - Followup on early signals

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

- Recognizes inherent limitations on premarketing risk assessment
- Goal: To improve identification and evaluation of safety issues emerging after marketing commences
- Approaches include registries, data mining techniques, surveys, and studies of safety signals

Risk Minimization Action Programs (RiskMAP)

- Not applicable to most drugs
  - Rx requirement and physician labeling usually adequate
- Individualized decision based on --
  - Nature and rate of known risks versus benefits
  - Population at risk or likely to benefit most
  - Existence and risks/benefits of alternatives
  - Reversibility of adverse event
  - Preventability of adverse event
  - Probability of benefit

RiskMAP Elements

- Specific **goal** or goals, stated as maximum risk reduction
- Specific **objectives** that result in processes or behaviors leading to achievement of the goal
- Specific **tools** (actions, processes or systems) intended to attain the defined objectives
- Methods for **evaluation** of the effectiveness of the tools in attaining objectives

RiskMAP Tools

- Designed to achieve one or more objectives
- Should maintain widest access to product with least burden on health care system that is comparable with adequate risk minimization
- Three basic categories
  - Targeted Education and Outreach
  - Reminder Systems
  - Performance-Linked Access Systems

FDA Examples of Education and Outreach Programs

- Dear Health Care Practitioner letters
- Patient labeling such as MedGuides and Patient Package Inserts
- Training programs for practitioners or patients
- Continuing Education for practitioners
- Prominent professional or public notifications
- Focused or limited promotional techniques such as product sampling or DTC advertising

FDA Examples of Reminder Systems

- Patient written agreement or acknowledgement forms
- Certification programs for practitioners
- Special reeducation programs for practitioners or patients to reinforce appropriate use
- Limits on amount dispensed or duration of Rx
- Specialized product packaging to enhance safety
- Specialized systems or records that attest to safety steps having been satisfied (*e.g.*, Rx stickers)

FDA Examples of Performance-Linked Access Systems

- Compulsory reminder systems (*e.g.*, no drug unless pharmacy has evidence of compliance)
- Limit of Rx to specially certified health care practitioners
- Dispensing limited to specially certified pharmacies or practitioners
- Dispensing to patients only after evidence of safe-use condition (*e.g.*, lab test results)

Outlook -- Do FDA's Drug Safety Proposals Go Far Enough?

- Finalize risk management guidances
- IOM review of post-approval safety system
- Dissenting scientist dispute resolution process
- Drug safety oversight board
- Release of emerging safety information
- Find permanent head of ODS

Outlook -- Legislative Proposals

- Create independent drug safety agency or remove drug safety office from Office of New Drugs
- Mandatory labeling change authority
- Mandatory post-approval study authority
- Authority to require prior review of drug advertisements
- DTC restrictions in early post-approval period
- Authority to suspend DTC ads pending completion of safety studies

Outlook -- Beyond Risk Management

- What might FDA do to change the drug approval process?
- Long-term hope: new technologies
- Short-term options
  - Review different drugs differently
  - Expand use of accelerated approval regulations
  - Create a peri-approval period for all drugs

Outlook -- Treat Different Drugs Differently

- "Life-saving" drugs vs. "life-style" drugs
  - Explicitly vary data requirements, review times among candidates
  - Changes in PDUFA agreements, ICH guidances needed?

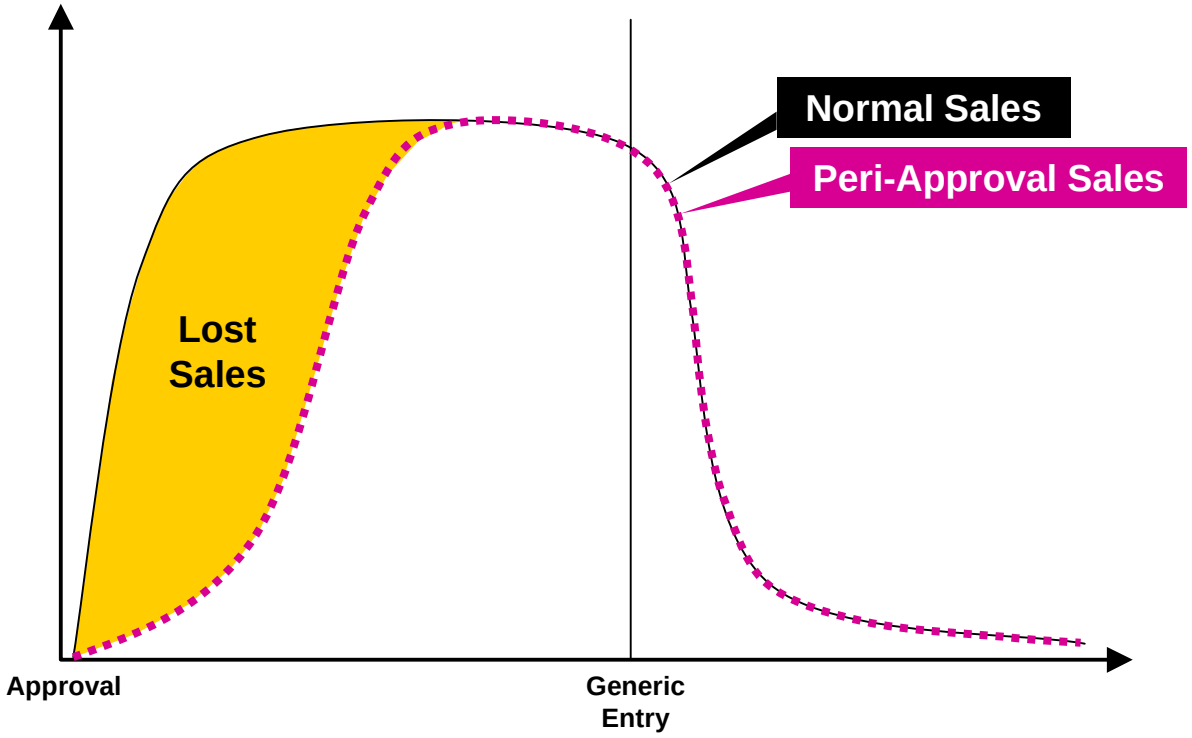
Outlook -- Expand Use of Accelerated Approval Rule

- Subpart H covers life-threatening or serious illnesses
- Subpart H permits FDA to --
  - Impose RiskMAP requirements (prevent off-label use? mandate ADE reporting by physicians, hospitals? restrict prescribing to specialists?)
  - Require Phase 4 studies (controlled safety studies?)
  - Preclear promotional materials (delay DTC ads?)
  - Withdraw approval expeditiously

Outlook -- Create a Peri-Approval Period

- Essentially, apply Subpart H to all new drugs
- Premise: A new drug must either (1) be tested exhaustively preapproval or (2) be subject to intense post-approval monitoring, testing, and controlled use, before unrestricted general Rx marketing
- Would not delay approvals, but put all drugs on probation
- Would require new regulations (but possibly not new legislation)

Outlook -- Effects of Peri-Approval



Outlook -- Conclusions

- FDA's Drug Watch Web Page could post unreviewed, preliminary data on safety issues
- Public pressure may lead FDA to be more cautious
  - FDA may raise approval standards or lower the bar for accelerated approval or RiskMAPs
  - More drugs could enter peri-approval limbo status
- Congress may enact further changes
- Companies need to prepare for changes