Drug Safety Labeling: A Legal Perspective

FDA Regulatory and Compliance Symposium
Aug 21-24, 2007

Dave Ceryak, Esq.
Assistant General Counsel, Regulatory Affairs
Eli Lilly and Company
How Are State Law Requirements Viewed In Relation to the Content of the Product Label?

OR

Labeling Requirements
Opposing Forces?

State Law/Product Liability

- All-inclusive Warnings
- Paper Records
- Duty to Warn Consumers
- Signal Disclosures = Admissions

Federal Laws and Regs

- Streamlined Warnings
- Electronic Labels
- Duty to Warn Physicians
- Unconfirmed Signal Communications
FDA’s Legal Authority Over the Product Label

Assessment and approval of drug labeling are inherent in FDA’s authority to determine safety and efficacy.

- FDA shall refuse NDA approval if investigations do not show “…whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof…” 21 USC 355(d)
- Drug label must
  - “…contain a summary of the essential scientific information needed for the safe and effective use of the drug.”
  - “…be informative and accurate and neither promotional in tone or false or misleading in any particular.”
  - be updated “when new information becomes available that causes the labeling to become inaccurate, false or misleading.” 21 CFR 201.56

FDA’s Enforcement Authority for Marketed Drugs

- Misbranding: not “false or misleading” under 21 USC 321(n), 352, 355(d)
- Withdrawal of NDA approval under 21 USC 355(e)
- Pending Legislation
Post-marketing Safety Label Changes

Prior Approval Supplement: 21 CFR 314.70(b)(2)(v)(A)

Changes Being Effected Supplement ("CBE")

- 21 CFR 314.70(c)(6)(iii)
- includes addition or strengthening of safety information
- "……holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change."
- Some view CBES as the basis for:

  Labeling Requirements

  FDA

  Company Confidential
  Copyright © 2000 Eli Lilly and Company
Post-marketing Safety Label Changes (cont’d)

CBEs remain subject to FDA approval or denial

CBE label changes remain subject to misbranding actions under 21 USC 352(a)

Exception to CBE regulations (“….changes to the information required in 210.57(a)…”) refers to PLR Highlights section

Pending Legislation
Product Liability “101”

Most cases are based on “failure to warn” claims under state law
  • Omission of risk information
  • Inclusion of misleading statement

“Learned Intermediary”: pharmaceutical manufacturers can satisfy duty to warn by informing physicians via the product label
  • Consumers cannot access products directly
  • Complexity of risk information and benefit-risk assessment

Preemption: Constitutional doctrine that federal law prevails over state law in the case of inconsistencies
  • Federal law is Food, Drug and Cosmetic Act as administered by FDA
  • State court makes a determination of adequacy of warnings under state law
  • Point of contention: Is an FDA-approved label a “ceiling,” or just a “floor?”
Opposing Forces?

Product Liability

- All-inclusive Warnings
- Paper Records
- Duty to Warn Consumers
- Signal Disclosures = Admissions

Federal Laws and Regs

- Streamlined Warnings
- Electronic Labels
- Duty to Warn Physicians
- Unconfirmed Signal Communications
Content of the Label

All-inclusive Warnings  Streamlined Warnings
Physician Labeling Rule (PLR)

PLR: Final rule issued by FDA effective June 30, 2006 that revises regulations on the content and format of the drug label

- USPI divided into 3 main sections: Highlights; Table of Contents; Full Prescribing Information
- ½ page limit for Highlights unless FDA grants waiver
- Warnings and precautions collapsed
- Clarification regarding inclusion of terms in the Adverse Reactions section
- Rule and Guidance Documents available at www.fda.gov/cder/regulatory/physlabel/
PLR: Product Liability Implications

1) Deciding What to Include in Highlights Section and when to seek waiver of ½ page limitation
Example: Warnings/Precautions

**FPI:** 21 CFR 201.57(c)(6)
This section must describe clinically significant adverse reactions,…other potential safety hazards,…limitations in use imposed by them,… and steps that should be taken if they occur.

**Highlights:** 21 CFR 201.57(a)(10)
A concise summary of the most clinically significant information required under paragraph (c)(6) of this section…including information that would affect decisions about whether to prescribe a drug, recommendations for patient monitoring that are critical to safe use of the drug, and measures that can be taken to prevent or mitigate harm.
PLR: Product Liability Implications (cont’d)

2) Conversion of approved USPI to PLR format

A. Exclusion of Safety Terms

**Proposed Rule:** more narrow definition of ADR
- **Existing:**
  - “…undesirable effect, reasonably associated with use of a drug…”
- **Proposed:**
  - “…unintended response…for which there is a reasonable possibility that the product caused the response…”

**Final Rule:** Leave definition as is, “clarify intent”
- “…[existing] definition of adverse reaction….is appropriate for labeling, but [it] requires clarification…to minimize including information in labeling that does not help prescribers use the drug safely and effectively (i.e., adverse events that are not related to use of the drug)…”

B. Consistency with Core Data Sheet, Previous Regulatory Discussion and Documentation
PLR: Product Liability Implications (cont’d)

3) “Adverse Events” versus “Adverse Reactions”
   – Tables?
   – Process considerations

4) Subsequent Label Updates: CBE or PAS?
   – If label change impacts Highlights, it requires submission of a prior approval supplement. 314.70(b)(2)(v)(C) and (c)(6)(iii)
Electronic Labels

Paper Records

Electronic Labels
Structured Product Labeling (SPL)

Since 2005, FDA has required the content of labeling to be submitted in the SPL standard in order to support health information technology and eHR.

– 21 CFR 314.50(1)

With PLR, content of USPI “Highlights” section required to be coded

– Specified Coding Dictionaries

Labels in SPL format available on DailyMed (www.dailymed.nlm.nih.gov)
eLabel: Product Liability Implications

Potential Differences Between Highlights in Written and SPL Formats

eHR Implications of Decisions to Exclude Information from Highlights

Additional Coding Step for Adverse Events May Require Additional *Clinical* Judgments

MEDRA → Label (PDF) → SNOMED
Duty to Warn....Whom?

Duty to Warn Consumers  Duty to Warn Physicians
Flow of Product Information Via the “Learned Intermediary”

- **Sponsor**
  - Reasonably Foreseeable Risks and Adequate Directions for Safe Use

- **Healthcare Professional**
  - Informed Consent for Treatment

- **Patient**
Duty to Warn.......Whom?

“Learned Intermediary” Principle Adopted by Courts and Built Into FDA’s Regulatory Structure:

Drug labeling must include “…adequate information for its use…under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended…” 21 CFR 201.100(d)(1)

*Johnson and Johnson Corp. v. Karl:* “…manufacturers of prescription drugs are subject to the same duty to warn consumers about the risks of their products as other manufacturers…” (emphasis added) (W. Va. June 27, 2007)

Role of Drug Information Targeted to Consumers?
- PPIs and MedGuides
- DTC Advertising
- Clinical Trial Results Databases
- FDA Web Site

Implications for Product Liability and Labeling Practices
Disclosure of Unconfirmed Safety Signals

Signal Disclosures = Admissions

Unconfirmed Signal Communications
Disclosure of Unconfirmed Signals: Product Liability Implications

Communication of “Emerging” Drug Safety Information
- FDA Guidance: Drug Safety Information – FDA’s Communication to the Public (March, 2007)
- “Emerging” = potentially important drug safety issue that FDA is reviewing but “has not yet been fully analyzed or confirmed.”

Public Disclosure of CBES
- FDA Draft Guidance: Public Availability of Labeling Changes in “Changes Being Effected” Supplements (September, 2006)

Pending Legislation
Concluding Thoughts.....and Questions