The Future of the Failure-to-Warn Claim

REMS, Medication Guides, and the (Potential) Erosion of the Learned Intermediary Doctrine

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Road Map

• FDA initiatives focusing on communication of drug risks directly to patients
• Innovative methods to convey risk information
• Potential effect on Learned Intermediary Doctrine
Brief History of Drug Warnings

• Early 1900s

• 1947: PDR

• 1970s: Patient Package Inserts (OCs)

• 1997: DTC TV Ads

• 1999: Medication Guides

• 1990s: Consumer Medication Information/Monographs

• 2007: REMS
REMS: Patient Counseling

- Counseling Tools
- Patient-Prescriber Agreements
- Patient Education
- Medication Guidelines
Counseling Tools

Proliar® (denosumab): Patient Counseling Chart for Healthcare

Proliar® (denosumab): What Patients Need to Know

What is Prolia®?

Prolia® is a prescription medicine used to:

- Treat osteoporosis in women after menopause who:
  - are at high risk for fracture
  - cannot use another osteoporosis medicine or other osteoporosis medicines did not work well
Medication Guide

TRADENAME® (Include phonetic spelling) Tablets, CII

TRADENAME is:
- A strong prescription pain medicine that contains an opioid (narcotic) that is used to treat moderate to severe around-the-clock pain.

Important information about TRADENAME:
- Get emergency help right away if you take too much TRADENAME (overdose). TRADENAME overdose can cause life threatening breathing problems that can lead to death.
- Never give anyone else your TRADENAME. They could die from taking it. Store TRADENAME away from children and in a safe place to prevent stealing or abuse. Selling or giving away TRADENAME is against the law.

Do not take TRADENAME if you have:
- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking TRADENAME, tell your healthcare provider if you have a history of:
- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:
- pregnant or planning to become pregnant. TRADENAME may harm your unborn baby.
- breastfeeding. TRADENAME passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements.

When taking TRADENAME:
- Do not change your dose. Take TRADENAME exactly as prescribed by your healthcare provider.
- Take X dose at the same time every day. Do not take more than X dose in XX hours. If you miss a dose, do not take TRADENAME. Take your next dose at your usual time the next day.
- Swallow TRADENAME whole. Do not cut, break, chew, crush, dissolve, or inject TRADENAME.
- Call your healthcare provider if the dose you are taking does not control your pain.
- Do not stop taking TRADENAME without talking to your healthcare provider.
- After you stop taking TRADENAME, flush any unused [insert dosage form i.e. tablet or patch] down the toilet.

While taking TRADENAME Do Not:
- Drive or operate heavy machinery, until you know how TRADENAME affects you. TRADENAME can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

The possible side effects of TRADENAME are:
- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:
- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, or you are feeling faint.

These are not all the possible side effects of TRADENAME. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. For more information go to dailymed.nlm.nih.gov

This Medication Guide has been approved by the U.S. FDA Issue: DATE
FDA-Approved Drugs with a Medication Guide
Usability of FDA-Approved Medication Guides

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CONCLUSION

Current medication guides are of little value to patients, as they are too complex and difficult to understand especially for individuals with limited literacy. Explicit guidance is offered for improving these print materials.
Only 1 out of 185 was found suitable for readability.
2014 FDA Report: Evaluating REMS

FDA Priority Project #1:

• "Providing benefit/risk information to patients"

• One purpose of this project is to identify ways for improving communication of the risk/benefit profile to patients.
Improving Patient Counseling
REMS

FDA proposes to:

- Conduct research into existing REMS patient counseling tools (e.g., patient counseling documents, patient-provider agreements, etc.), other patient counseling initiatives, and counseling literature to identify current tactics and strategies for patient counseling about medication benefits and risk.
Evaluation of patients’ knowledge:

a. An evaluation of patients’ understanding of the serious risks of Prolia (denosumab), including hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, serious infections, and dermatologic adverse reactions.
In order to ensure the benefits of Prolia® (denosumab) outweigh its risks, we determined that you were required to make the following REMS modifications:

1. Changes to the REMS goal statement

2. Changes to the Communication Plan

- Replacement of the Dear Healthcare Provider letter with a REMS Letter for Healthcare Providers and a REMS Letter for Professional Societies

- Addition of a Patient Counseling Toolkit which contains a Patient Counseling Tool for Healthcare Providers, a Patient Brochure, and copies of the product labeling and Medication Guide

- Addition of a Journal Information Piece

- Dissemination of Prolia REMS-related information at scientific Meetings

- Changes to the Prolia REMS website to reflect the aforementioned modifications
• Severe jaw bone problems (osteonecrosis of the jaw or ONJ) may happen when you take Prolia®

• ONJ is a potentially serious condition that can be seen as a sore in the mouth through which the jaw bone is sometimes visible. The jaw bone and gum tissue over the bone may heal slowly, or not heal at all
Some people have developed unusual fractures in their thigh bone.

Symptoms of thigh bone fracture include new or unusual pain in your hip, groin, or thigh.
**Skin problems may happen if you take Prolia®**

**Symptoms of skin problems include:**

- Dermatitis (redness, itching)
- Eczema (leathery dry skin, blisters that ooze or become crusty, skin peeling)
Sabril and Vision Loss

This picture is provided to show 2 main types of vision, and not to show or suggest actual or possible vision loss, which can vary from patient to patient and in severity.
Risk of Birth Defects with Qsymia®
(phentermine and topiramate extended-release) capsules CIV

cleft lip

Patient Guide to
THALOMID REMS™
Risk Evaluation and Mitigation Strategy (REMS)™ Program
Comprehension Challenges with Standardized Symbols on Device Labels

• 2016 Study
  – 38 standardized symbols were shown to 86 healthcare providers (members of the Association of Surgical Technologists)
  – Only 6 of the 38 standardized symbols (16%) were successfully comprehended by the healthcare providers
    • 5 of the 6 successful symbols had text accompanied within the symbol itself
  – 3 of the original 38 symbols (8%) were interpreted to mean the opposite of their intended meaning

FDA New Rule: Use of Symbols in Labeling  
(21 CFR 660, 801, 809)

- Final Rule, effective 9/13/2016
  - Allows optional use of graphics and symbols without explanatory text on medical device labels ("stand-alone symbols")
  - Allows use of "symbol statements" such as "Rx only" and "℞ only" for prescription devices
  - Intent: harmonize U.S. standards with European standards for use of symbols in medical device labels
  - Application: only medical devices, certain biologics, and combination products where the primary mode of action is the medical device
# FDA New Rule: Use of Symbols in Labeling

(21 CFR 660, 801, 809)

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Symbol Description</th>
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<tbody>
<tr>
<td>☢️</td>
<td>Biological risks</td>
</tr>
<tr>
<td>⚠️</td>
<td>Do not re-use</td>
</tr>
<tr>
<td>💡</td>
<td>Consult instructions for use</td>
</tr>
<tr>
<td>⚠️</td>
<td>Caution, consult accompanying documents</td>
</tr>
<tr>
<td>🍂</td>
<td>Fragile, handle with care</td>
</tr>
<tr>
<td>☁️</td>
<td>Keep away from sunlight</td>
</tr>
<tr>
<td>☑️</td>
<td>Protect from heat and radioactive sources</td>
</tr>
<tr>
<td>☔️</td>
<td>Keep away from rain</td>
</tr>
<tr>
<td>🔥</td>
<td>Lower limit of temperature</td>
</tr>
<tr>
<td>🔥</td>
<td>Upper limit of temperature</td>
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<tr>
<td>📈</td>
<td>Temperature limitation</td>
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<td>🎫</td>
<td>Batch code</td>
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<td>🔍</td>
<td>Catalog number</td>
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<td>Serial number</td>
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<td>🕗</td>
<td>Control</td>
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<tr>
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<td>Negative control</td>
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<td>Positive control</td>
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<tr>
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<td>Sterile</td>
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<tr>
<td>🕗</td>
<td>Sterilized using ethylene oxide</td>
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<tr>
<td>🕗</td>
<td>Sterilized using aseptic processing techniques</td>
</tr>
<tr>
<td>🕗</td>
<td>Sterilized using irradiation</td>
</tr>
<tr>
<td>🕗</td>
<td>Sterilized using steam or dry heat</td>
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<tr>
<td>🕗</td>
<td>Do not resterilize</td>
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<th>Symbol</th>
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<tbody>
<tr>
<td>🔴</td>
<td>Do not use if package is damaged</td>
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<tr>
<td>🔴</td>
<td>In Vitro Diagnostic medical device</td>
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<td>🔴</td>
<td>Patient number</td>
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<td>🔴</td>
<td>Humidity limitation</td>
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<tr>
<td>🔴</td>
<td>Atmosphere pressure limitation</td>
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<td>🔴</td>
<td>Sampling site</td>
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<tr>
<td>🔴</td>
<td>Fluid path</td>
</tr>
<tr>
<td>🔴</td>
<td>Non-pyrogenic</td>
</tr>
<tr>
<td>🔴</td>
<td>Contains or presence of natural rubber latex</td>
</tr>
<tr>
<td>🔴</td>
<td>Drops per milliliter</td>
</tr>
<tr>
<td>🔴</td>
<td>Liquid filter with pore size</td>
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<tr>
<td>🔴</td>
<td>One-way valve</td>
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FDA's Priority Projects

• Focus on direct warnings to patients
• Utilization of graphics to convey risks
• Potential erosion of learned intermediary doctrine?
Learned Intermediary
Basics of the L.I. Doctrine

- Duty to warn runs to the *physician*, not the patient
  - Adequate warning to the LI = no breach of duty
  - Independent knowledge of risk = no causation
Learned Intermediary: The Beginning
Attempts to Weaken the Doctrine

- "Over-promotion"
- "Unconscious Influence"
- Physician Compensation
- Direct-to-Consumer Advertising
- FDA's Focus on Warnings to Patients
"Erosion" of Learned Intermediary

Perez vs. Wyeth Laboratories (N.J. 1999)

• "The 'Norman Rockwell' image of the family doctor no longer exists. Informed consent requires a patient-based decision rather than the paternalistic approach of the 1970s."

• "Because managed care has reduced the time allotted per patient, physicians have considerably less time to inform patients of the risks and benefits of a drug…"
"Erosion" of Learned Intermediary
Perez vs. Wyeth Laboratories (N.J. 1999)

Average wait for doctor: 62 minutes.
Average doctor visit: 7 minutes.
"Erosion" of Learned Intermediary

Johnson & Johnson vs. Karl (W.Va. 2007)

• Justifications for the LID are "largely outdated and unpersuasive."

• Specifically, "development of the internet as a common method of dispensing and obtaining prescription drug information."
"Erosion" of Learned Intermediary


• "Internet sites and medical databases give consumers access to a wealth of third-party and manufacturer-provided information about pharmaceutical products."

• "...a physician is no longer necessarily the consumer's sole source of information about the effects, benefits, and risks of the medications he or she takes."
Patient Sources of Information
Patient Sources of Information
Learned Intermediary

As a medical expert, the prescribing physician can take into account the propensities of the drug, as well as the susceptibilities of his patient. His is the task of weighing the benefits of any medication against its potential dangers. The choice he makes is an informed one, an individualized medical judgment bottomed on a knowledge of both patient and palliative.

5th Circuit, 1974
Wyeth, Inc. v. Weeks, 159 So. 3d 649, 673 (Ala. 2014)
Mendez Montes De Oca v. Aventis Pharma, 579 F. Supp. 2d 808, 812 (S.D. Tex. 2013)
Talley v. Danek Medical, Inc., 179 F.3d 154, 163 (4th Cir. 1999)
Mazur v. Merck & Co., Inc., 964 F.2d 1348, 1355, 1360 (3d Cir. 1992)
Humes v. Clinton, 792 P.2d 1032, 1039 (Kan. 1990)
Felix v. Hoffmann-LaRoche, Inc., 540 So. 2d 102, 104 (Fla. 1989)
Wyeth Laboratories, Inc. v. Fortenberry, 530 So. 2d 688, 691–92 (Miss. 1988)
Osburn v. Anchor Laboratories, Inc., 825 F.2d 908, 913 (5th Cir. 1987)
Swayze v. McNeil Laboratories, Inc., 807 F.2d 464, 469–70 (5th Cir. 1987)
Brooks v. Medtronic, Inc., 750 F.2d 1227, 1231 (4th Cir. 1984)
Timm v. Upjohn Co., 624 F.2d 536, 538 (5th Cir. 1980)
Learned Intermediary

- State of Play
  - The Learned Intermediary Doctrine's demise is not imminent
  - Plaintiffs will continue to try and chip away at it
  - FDA's ongoing focus on direct communication of risks to patients may provide ammunition for that effort
Preparing For Plaintiff's Efforts to Erode the Learned Intermediary Doctrine

• Physician/Prescriber Depositions
  – Develop multiple sources of information (medical school, literature, clinical experience, etc.)
  – Develop physician's use of plaintiff's medical history and susceptibilities in making prescribing decisions
  – Develop physician's independent knowledge of risks of prescription drugs
  – Demonstrate patient counseling tools are for use with patient and doctor
  – Develop fact that no matter how much information is available to patients, doctor makes ultimate decision
Preparing For Plaintiff's Efforts to Erode the Learned Intermediary Doctrine

• **Expert Depositions Where Failure to Warn Based on Patient Counseling Materials**
  – Be prepared with documents/questions showing intent of REMS patient counseling to be done in conjunction with HCP, not as a stand-alone piece

• **Plaintiff Depositions**
  – Develop story in deposition that plaintiff "relied" on doctor on whether and how to take medicine
  – Get all counseling materials (REMS)
  – Have background on DTC history to counteract plaintiff's general testimony that they "saw a TV ad" or saw internet advertising
Conclusion

• REMS Explosion
• What to expect from FDA on warnings
• Threats to L.I.D.
• Need for physician to comprehensively weigh risks and benefits
Thank You!

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