Workshop Background
Prescribing information (sometimes referred to as “PI,” “package insert,” “prescription drug labeling,” and “professional labeling”) is intended to provide health care professionals with information needed to aid in prescribing prescription drugs and biologics and counsel patients on their safe and effective use. Designed to be informative, accurate, and evidence-based, the prescribing information (PI) is an important tool for health care professionals, and opportunities to ensure the utility of the PI are of interest to the U.S. Food and Drug Administration (FDA).

PI was first standardized by FDA in 1979. In the decade following the introduction of this initial format, the PI became increasingly lengthy and complex, thus making their use burdensome for health care professionals. FDA subsequently began to explore new or improved formats to increase utility. As part of this exploration, opinions were gathered from health care professionals and other stakeholders through forums such as focus groups, public meetings, and national surveys.

These efforts resulted in the proposal of a new rule to govern PI content and format in December 2000. Intended to make the information in the PI more informative and accessible and to promote better risk communication and fewer medication errors, this proposed rule was modified based on public comment. In January 2006, FDA issued a final rule called the “Physician Labeling Rule” (PLR) and outlined a phased implementation schedule for manufacturers to comply with the new standards (Table 1). All new drug applications, biologics license applications, or efficacy supplements approved by FDA after June 30, 2001, are required to be in compliance with the PLR format by June 30, 2013; any such applications approved prior to 2001 are encouraged, though not required, to introduce PLR formatting.

PLR introduced multiple content and format revisions to the previous PI, which are detailed in tables 2 and 3, respectively. These revisions include a Highlights section that contains a concise, half-page summary of the important information contained in the Full Prescribing Information (FPI); introduction of a table of contents; the reordering of some information based upon the frequency of use; the regrouping of some information based upon the manner in which it is used; and creation of a Patient Counseling Information (PCI) section for health care professionals to use when communicating with patients about important uses and risks of a drug. Illustrative examples of the PI prior to PLR (Appendix 1), the PI in the PLR format (Appendix 2), and PCI sections (Appendix 3 and 4) are included with this discussion guide.

In addition to PLR, FDA published final regulations requiring that the content of labeling be submitted electronically in a form that FDA can process, review, and archive. Structured Product Labeling (SPL), the electronic format adopted by FDA, allows for the posting of up-to-date PIs free of charge on publically available websites such as FDA’s online labeling repository and DailyMed (provided by the National Library of Medicine (NLM)). SPL provides a format for the exchange of information necessary for
initiatives associated with including the PI in electronic formats (e.g., electronic medical records and e-prescribing).

Workshop Objectives
Six years have passed since PLR was issued. While FDA is not considering changing the regulations, the Agency is interested in receiving feedback from key stakeholders that either develop or use PI. In addition, because regulatory requirements regarding the PCI section are not detailed, FDA has found that the content and format of this section varies considerably. This workshop, convened by the Engelberg Center for Health Care Reform at Brookings in cooperation with FDA, seeks to engage stakeholders in a discussion of the utility of the PI as a communication tool for health care professionals and to discuss which content in the PCI section is most useful for counseling patients. Comments and recommendations from the meeting will be considered as FDA develops strategies for improving PLR labeling.

Session I: Experience with PIs
This session will focus on experiences from everyday practice to illustrate ways in which the PI is accessed by health care professionals and discuss whether the PLR format, as currently implemented, is meeting health care professionals’ needs. Discussion questions may include the following:

- What do recently published reviews of compliance to the PLR format show?
- How is labeling information typically accessed and used by health care professionals (e.g., electronically vs. paper, only used for newly approved products, only used to answer specific questions, etc.)?
- What are the benefits of the PLR format over the old format?
- Is the PI in the PLR format meeting the needs of prescribers and other health care providers?
  - How often do providers refer to the PI to get specific information?
  - When providers refer to the PI, what specific information are they seeking (e.g., dosing information, consult for newly approved drugs, risk information, etc.)?
  - How is the Highlights section currently being used?
  - Is the Highlights section meeting its intended goal of providing a concise summary of the most important prescribing information? Is it too short/too long?

Session II: Opportunities to Encourage Clinicians’ Use of PIs
This session will discuss opportunities and strategies for encouraging use of the PI as a primary means of communicating drug information to health care professionals. Discussion questions may include the following:

- Would clinicians prefer to have more or all PIs in the PLR format?
- What sections (or specific information) of the PI could be more helpful or are difficult to use?
- What are some ideas for encouraging use of the PI as a primary resource for prescription drug information for clinicians?

Session III: Experiences with Patient Counseling Information and Opportunities to Encourage its Use
Specifically focusing on the PCI section of the PI, this session will discuss the information that health care professionals find most important in communicating about drugs with patients. Discussion questions may include the following:

- When counseling patients on a newly prescribed drug, what information do prescribers typically discuss and emphasize?
- What level of detail is most helpful to present in the PCI section? For example, which of the following should the PCI accomplish:
- Identify issues to discuss, with cross-references to the fuller discussions elsewhere in the PI?
- Fully present each topic without the need for referencing other parts of the PI?
- Balance the first two options.

- If the drug has FDA-approved patient labeling (e.g., patient package insert, Medication Guide, Instructions for Use), how much information from the patient-directed document should be included in the Patient Counseling Information section (e.g., administration instructions, unique storage/handling requirements)?

Table 1: Implementation Timeline for PI in the PLR Format

<table>
<thead>
<tr>
<th>Qualifying Date for NDA, BLA, or efficacy supplement*</th>
<th>Date that NDA/BLA applicants must submit proposed labeling in PLR format</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submitted 6/30/06 or after</td>
<td>At the time of submission</td>
</tr>
<tr>
<td>Pending on 6/30/06</td>
<td></td>
</tr>
<tr>
<td>Approved between 6/30/05 and 6/30/06</td>
<td>By 6/30/09</td>
</tr>
<tr>
<td>Approved between 6/30/04 and 6/29/05</td>
<td>By 6/30/10</td>
</tr>
<tr>
<td>Approved between 6/30/03 and 6/29/04</td>
<td>By 6/30/11</td>
</tr>
<tr>
<td>Approved between 6/30/02 and 6/29/03</td>
<td>By 6/30/12</td>
</tr>
<tr>
<td>Approved between 6/30/01 and 6/29/02</td>
<td>By 6/30/13</td>
</tr>
<tr>
<td>Approved prior to 6/30/01</td>
<td>Voluntary and encouraged compliance</td>
</tr>
</tbody>
</table>

*The PLR format applies to New Drug Applications (NDAs), Biologics License Applications (BLAs), and efficacy supplements.

Table 2: Overview of Content Revisions in PLR

<table>
<thead>
<tr>
<th>Section</th>
<th>Revision Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Highlights</strong></td>
<td>- Introduces half-page summary of most important prescribing information</td>
</tr>
<tr>
<td></td>
<td>- Located at the beginning of the PI</td>
</tr>
<tr>
<td></td>
<td>- References FPI for further information</td>
</tr>
<tr>
<td></td>
<td>- Includes pharmacological class</td>
</tr>
<tr>
<td><strong>Recent Major Changes in Highlights</strong></td>
<td>- Summarizes labeling changes made within the previous 12 months to Indications and Usage, Dosage and Administration, Boxed Warning, Contraindications, and Warnings and Precautions sections</td>
</tr>
<tr>
<td></td>
<td>- Located in Highlights with corresponding notation in margin of FPI</td>
</tr>
<tr>
<td><strong>Contents</strong></td>
<td>- Provides standardized order for FPI and orients prescriber</td>
</tr>
<tr>
<td></td>
<td>- Allows for hyperlinks in electronic formats</td>
</tr>
<tr>
<td><strong>Boxed Warning</strong></td>
<td>- Included in Highlights (up to 20 lines of text)</td>
</tr>
<tr>
<td></td>
<td>- Included as full text in FPI</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>- Includes only known hazards</td>
</tr>
<tr>
<td></td>
<td>- Includes only patient groups in which risk clearly outweighs potential benefit</td>
</tr>
<tr>
<td><strong>Adverse Reactions</strong></td>
<td>- Includes only reactions with some basis for causal relationship to drug</td>
</tr>
<tr>
<td></td>
<td>- Separates adverse reactions collected during clinical trials from those received from spontaneous reports</td>
</tr>
<tr>
<td></td>
<td>- Generally pools adverse reactions from all trials</td>
</tr>
<tr>
<td></td>
<td>- Contains contact information for reporting suspected adverse reactions (Highlights)</td>
</tr>
<tr>
<td><strong>Patient Counseling Information</strong></td>
<td>- Expands information from previous Precautions section</td>
</tr>
<tr>
<td></td>
<td>- Provides key information for prescribers when communicating with patients</td>
</tr>
<tr>
<td></td>
<td>- References FDA-approved patient labeling which is appended to end of PI</td>
</tr>
<tr>
<td>Section or Category</td>
<td>Revision Details</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Indications and Usage; Dosage and Administration | - Relocated to allow most frequently utilized information to come first in FPI  
- Includes limitations and conditions of use in *Indications and Usage* |
| Warnings and Precautions            | - Consolidates and reorganizes information from previous *Precautions* and *Warnings* sections into one section                                      |
| Drug Interactions; Use in Specific Populations | - Introduced to reorganize information from previous *Precautions* section into separate sections                                                   |
| Clinical Studies; Nonclinal Toxicology | - Required to be included in FPI (formerly optional)                                                                                           |
| Dosage Forms and Strengths          | - Selected information from *How Supplied* section now presented earlier in FPI  
- Moves *How Supplied* toward the end of FPI                                                                 |
| Typeface and presentation           | - Sets minimum font size at 8 point  
- Standardizes bold headers, tables, bullets, and white space                                                                                   |
Appendix 1: PI Example prior to introduction of PLR format, Maxalt (rizatriptan benzoate)*
Product example used to demonstrate format only.

MAXALT®
(RIZATRIPTAN BENZOATE)
TABLETS
MAXALT-MLT®
(RIZATRIPTAN BENZOATE)
ORALLY DISINTEGRATING TABLETS

DESCRIPTION
Maxalt® contains rizatriptan benzoate, a selective 5-hydroxytryptamine 1D (5-HT_1D) receptor agonist.
Rizatriptan benzoate is described chemically as N,N-dimethyl-5-[1H-1,2,4-triazol-1-ylmethyl]-1H-indole-3-ethanamine monobenzoate and its structural formula is:

![Chemical Structure]

Its empirical formula is C_{20}H_{22}N_{2}O_{2}, representing a molecular weight of the free base of 309.4.
Rizatriptan benzoate is a white to off-white, crystalline solid that is soluble in water at about 42 mg per mL.
(expressed as free base) at 25°C.

Maxalt Tablets and Maxalt-MLT® Orally Disintegrating Tablets are available for oral administration in strengths of 5 and 10 mg (corresponding to 7.265 mg or 14.53 mg of the benzoate salt, respectively).
Each compressed tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, ferric oxide (red), and magnesium stearate.
Each lyophilized orally disintegrating tablet contains the following inactive ingredients: gelatin, mannitol, glycine, aspartame, and peppermint flavor.

CLINICAL PHARMACOLOGY
Mechanism of Action
Rizatriptan binds with high affinity to human cloned 5-HT_1B and 5-HT_1D receptors. Rizatriptan has
different affinities for other 5-HT_1 receptors: 5-HT_1A, 5-HT_1C, 5-HT_1D, and the 5-HT_1E receptor, but has
no significant activity at 5-HT_2, 5-HT_3, alpha- and beta-adrenergic, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors.

Current theories on the etiology of migraine headache suggest that symptoms are due to local cranial
vasodilation and to the release of vasoactive and pro-inflammatory peptides from sensory nerve
endings in an activated trigeminal system. The therapeutic activity of rizatriptan in migraine can most
likely be attributed to agonist effects at 5-HT_1D receptors on the extracerebral, intracranial blood
vessels that become dilated during a migraine attack and on nerve terminals in the trigeminal system.
Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release and
reduced transmission in trigeminal pain pathways.

Pharmacokinetics
Rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability
of the MAXALT Tablet is about 46%, and mean peak plasma concentrations (C_max) are reached in
Appendix 2: PI Example in PLR format, Maxalt (rizatriptan benzoate)

Product example used to demonstrate format only.
Appendix 3: PCI Example, Viibryd (vilazodone hydrochloride)
Product example used to demonstrate format only.
Appendix 4: PCI Example, Arzerra (ofatumumab)

Product example used to demonstrate format only.

17 PATIENT COUNSELING INFORMATION

Advise patients to contact a healthcare professional for any of the following:
- Signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion (see Warnings and Precautions (5.1) and Adverse Reactions (6.1))
- Bleeding, easy bruising, petechiae, pallor, worsening weakness, or fatigue (see Warnings and Precautions (5.2))
- Signs of infections including fever and cough (see Warnings and Precautions (5.2) and Adverse Reactions (6.1))
- New neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, or vision problems (see Warnings and Precautions (5.3))
- Symptoms of hepatitis including worsening fatigue, or yellow discoloration of skin or eyes (see Warnings and Precautions (5.8))
- New or worsening abdominal pain or nausea (see Warnings and Precautions (5.5))
- Pregnancy or nursing (see Use in Specific Populations (8.1, 8.3))

Advise patients of the need for:
- Periodic monitoring for blood counts (see Warnings and Precautions (5.2))
- Avoiding vaccination with live viral vaccines (see Warnings and Precautions (5.6))

Manufactured by:
GLAXO GROUP LIMITED
Greenford, Middlesex, UB6 0DN, United Kingdom.
U.S. Lab. 1909

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