# Guidance for Industry and Review Staff

## Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information

Good Review Practice

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**
**Center for Biologics Evaluation and Research (CBER)**

**October 2009**
**Labeling**

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*Contains Nonbinding Recommendations*

# Guidance for Industry and Review Staff[1] Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information

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## I. INTRODUCTION

This guidance is intended to provide applicants and review staff with a definition of established pharmacologic class and to help them identify the most appropriate word (term) or phrase that describes the established pharmacologic class for a drug or biological product for inclusion in the *Indications and Usage* section of Highlights of Prescribing Information (*Highlights*) of approved labeling.[2]

Although not specifically required, the pharmacologic class can also appear in other sections of labeling. This guidance only applies to the use of the pharmacologic class in the *Indications and Usage* section of *Highlights*.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required. Although guidance documents do not legally bind FDA, review

[1] This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, *drug* and *drug product* are used to refer to human prescription drug and biological products that also meet the definition of *drug* under the Federal Food, Drug, and Cosmetic Act.

staff may depart from guidance documents only with appropriate justification and supervisory concurrence.

## II. BACKGROUND

In January 2006, we published a final rule that amended the requirements for the content and format of approved labeling (prescribing information) for human prescription drug and biological products.[3] The new prescribing information format is intended to make it easier for health care professionals to access, read, and use to make prescribing decisions.

The rule requires the following statement to appear under the *Indications and Usage* section of *Highlights* if a drug is a member of an established pharmacologic class:[4]

> "(Drug) is a (name of class) indicated for (indication(s))."

If a drug does ***not*** have an ***established*** pharmacologic class as determined through the process described below, the name of class component of this statement should be omitted from the *Indications and Usage* section of *Highlights*.

Knowing the established pharmacologic class can provide health care professionals with important information about what to expect from a drug and how it relates to other therapeutic options. Such information can also help reduce the risk of duplicative therapy and drug interactions, as well as provide important treatment information in cases of drug overdose.

We are in the process of using structured product labeling (SPL) to index certain types of prescribing information content for all drug products.[5] Because of its importance, pharmacologic class is being indexed in the first phase of this process. In general, we will make indexing decisions based on the prescribing information and the selected terminologies.[6] Therefore, it is important that the appropriate established pharmacologic class appear in *Highlights*. For more information about SPL, see the FDA Data Standards Council Web site on Structured Product Labeling Resources.[7]

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[3] See 21 CFR parts 201, 314, and 601 *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products* (January 24, 2006; 71 FR 3922).

[4] See 21 CFR 201.57(a)(6).

[5] See the guidance for industry *Indexing Structured Product Labeling* (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).

[6] If an appropriate term is not available in an existing terminology, we will work with the relevant terminology maintenance organizations to identify a new term.

[7] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

## III. DEFINITIONS

### A. Pharmacologic Class

For purposes of this guidance, a *pharmacologic class* is a group of drugs that share scientifically documented properties. Specifically, for purposes of this guidance, *pharmacologic class* is defined on the basis of any one of the following three attributes of the drug:

1. **Mechanism of action (MOA)** — Pharmacologic action at the receptor, membrane, or tissue level

2. **Physiologic effect (PE)** — Pharmacologic effect at the organ, system, or whole body level

3. **Chemical structure (CS)**

### B. Established Pharmacologic Class

An ***established*** pharmacologic class is represented by a term or phrase that is scientifically valid ***and*** clinically meaningful according to the following definitions:

- A *scientifically valid* pharmacologic class is supported by documented and submitted empiric evidence showing that the drug's pharmacologic class is known, not theoretical, and relevant and specific to the indication.

- A *clinically meaningful* pharmacologic class term or phrase enhances the ability of professionals to understand physiologic effects related to the indication or to anticipate undesirable effects that may be associated with the drug or pharmacologic class.

## IV. IDENTIFYING AN ESTABLISHED PHARMACOLOGIC CLASS

It is often possible to identify multiple scientifically valid pharmacologic classes. However, only pharmacologic classes that are also ***clinically meaningful*** will be considered to be established pharmacologic classes. Consider the following examples:

- Drug A
  MOA = Beta-adrenergic blocker
  PE = Negative inotropy and chronotropy
  CS = Benzeneacetamide

  In this case, the most clinically meaningful term is the MOA because the term immediately informs clinicians of the many physiologic effects that can be expected with this drug product, both desirable and undesirable.

  "Drug A is a ***beta-adrenergic blocker*** indicated for treatment of hypertension."

- Drug B
  MOA = Inhibitor of reabsorption of sodium and chloride ions in the kidney
  PE = Loop diuretic
  CS = Anthranilic acid derivative

  In this case, the most clinically meaningful term is the PE because the MOA is localized in the kidney and the PE reflects the full activity of the drug product.

  "Drug B is a ***loop diuretic*** indicated for treatment of edema associated with congestive heart failure."

- Drug C
  MOA = GABA A and B Modulator
  PE = Increased GABA activity
  CS = Benzodiazepine

  In this case, the most clinically meaningful term is the CS because this chemical class is well known and the term immediately informs clinicians of the important physiologic effects with this drug product.

  "Drug C is a ***benzodiazepine*** indicated for management of anxiety disorders."

- Drug D
  MOA = Unknown
  PE = Altered neurotransmitter activity
  CS = Aminoketone

  In this case, the MOA is unknown and the PE and CS are not clinically meaningful. Therefore, an established pharmacologic class is not included in the *Indications and Usage* statement in *Highlights*.

  "Drug D is indicated as an aid to smoking cessation treatment."

- Drug E
  MOA = Cyclooxygenase inhibitor
  PE = Decreased prostaglandin production
  CS = Nonsteroidal anti-inflammatory drug

  In this case, all three terms are clinically meaningful, but the most commonly used grouping term is the CS.

  "Drug E is a ***nonsteroidal anti-inflammatory drug*** indicated for relief of acute pain and inflammation."

It may be appropriate to include a combination of established pharmacologic classes if more than one attribute of the drug is clinically meaningful. For example, a drug may have clinically meaningful and scientifically valid MOA and PE terms that can be combined in the established pharmacologic class statement.

> "Drug F is an ***mTor inhibitor immunosuppressant*** indicated for prophylaxis of organ rejection."

Another example of appropriate use of multiple established pharmacologic classes is when the CS provides additional meaningful information to prescribers beyond that provided by MOA or PE alone.

> "Drug G is a ***thiazide diuretic*** indicated for treatment of edema associated with congestive heart failure."

Many drug products contain more than one drug. These drugs can be members of the same or different pharmacologic classes. These pharmacologic classes can apply to the same or different indications. The following examples illustrate different situations that may be encountered:

- For products with more than one drug where all drugs are in the same pharmacologic class:

  > "Product X is a combination of Drug H and Drug I, both ***HIV nucleoside analog reverse transcriptase inhibitors***, indicated for use in combination with other antiretroviral agents for treatment of HIV infection."

- For products with more than one drug where the drugs are from different pharmacologic classes:

  > "Product Y is a combination of Drug J, a ***thiazide diuretic***, and Drug K, a ***potassium-sparing diuretic***, indicated for hypertension."

  Note: For drugs that are not combination products but are approved for use with other drug products named specifically by proprietary name or nonproprietary name in the *Indications and Usage* section, the pharmacologic class for the concomitant drug should not be included in this statement. However, the pharmacologic class for the concomitant drug can appear in a separate statement in the section.

For most drug products, one established pharmacologic class will be identified. However, in rare cases, multiple indications may result in multiple established pharmacologic classes:

> "Drug L is an ***antidote*** indicated to prevent or lessen hepatic injury when administered intravenously within 8 to 10 hours after ingestion of a potentially hepatotoxic quantity of acetaminophen."

> "Drug L is a ***mucolytic*** indicated as an adjuvant therapy for patients with abnormal, viscid, or inspissated mucous secretions in such conditions as chronic bronchopulmonary disease, acute bronchopulmonary disease, pulmonary complications of cystic fibrosis, tracheostomy care, pulmonary complications associated with surgery, use during anesthesia, post-traumatic chest conditions, atelectasis due to mucous obstruction, and diagnostic bronchial studies."

## V. IDENTIFYING THE MOST APPROPRIATE TERM TO DESCRIBE AN ESTABLISHED PHARMACOLOGIC CLASS

For new drugs that are undergoing review for marketing approval, we will review the applicant's proposed established pharmacologic class and supporting evidence submitted based on the criteria defined in section III.B.

When identifying a term to describe an established pharmacologic class for a drug, it is important to consider other drugs that share MOA, PE, or structural similarity. The use of misleading or potentially confusing pharmacologic class terms can be avoided by achieving consistency in terminology, where appropriate, across drugs used for similar purposes. The FDA has published a list of established pharmacologic class terms used for the established pharmacologic class in the *Indications and Usage* section of *Highlights* as well as a list of the related pharmacologic class MOA, PE, and CS indexing terms for use in SPL.[8]

## VI. INCORPORATING ESTABLISHED PHARMACOLOGIC CLASS INFORMATION INTO THE HIGHLIGHTS SECTION

According to 21 CFR 314.70(b)(2)(v)(C) and 21 CFR 601.12(f)(1), for approved drugs for which the applicant plans to update the labeling or convert the labeling to a format consistent with the final rule, the addition of an established pharmacologic class term to the *Indications and Usage* section of *Highlights* of approved drug labeling is a change that must be proposed and submitted in a prior-approval labeling supplement.

A new established pharmacologic class term that has not been previously approved for another drug product can be included in the *Highlights* of a drug product's labeling at the time of final labeling approval if the pharmacologic class is scientifically valid and clinically meaningful.

Parentheses should be used for common abbreviations in the following format:

> Examples: Proton Pump Inhibitor (PPI), Nucleoside Reverse Transcriptase Inhibitor (NRTI)

Parentheses should not be used to indicate auxiliary or less-important pharmacologic class terms.

[8] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.