
PROCEDURES

OFFICE OF NEW DRUGS**Determining the Established Pharmacologic Class for Use in the Highlights of Prescribing Information**

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PURPOSE

The purpose of this Manual of Policies and Procedures (MAPP) is to outline the process to be followed by Center for Drug Evaluation and Research (CDER) review staff when:

- Selecting or creating an established pharmacologic class (EPC) text phrase that will be associated with an approved indication and included under the INDICATIONS AND USAGE heading in the Highlights of Prescribing Information (Highlights) of approved labeling
- Assigning clinically meaningful and scientifically valid pharmacologic concepts (i.e., mechanism of action (MOA), physiologic effect (PE), and chemical structure (CS)¹) to each active moiety for use in indexing the labeling

This process involves the following organizational components of the Food and Drug Administration (FDA):

- Office of New Drugs (OND) pharmacology/toxicology (pharm/tox) reviewers
- OND Associate Director for Pharmacology and Toxicology or other designated pharm/tox staff

¹ Note that CS is also known as C/I (an abbreviation for chemical/ingredient), used in the U.S. Department of Veterans Affairs, Veterans Health Administration (VHA) National Drug File-Reference Terminology (NDF-RT).

- Other CDER review staff as appropriate (e.g., product quality (chemistry, manufacturing, and controls (CMC)) reviewers, microbiology reviewers, clinical pharmacology reviewers, and clinical reviewers)
 - Office of the Commissioner (OC)/Office of the Chief Scientist, health and regulatory data standards staff
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BACKGROUND

Established Pharmacologic Class in Indications and Usage in Highlights

The regulation 21 CFR 201.57(a)(6) requires that if a product is a member of an EPC, a concise statement under INDICATIONS AND USAGE in Highlights must identify the class in the following manner:

“(Drug) is a (name of class) indicated for (indication(s)).”

Pharmacologic class is a group of active moieties that share scientifically documented properties. Pharmacologic class is defined on the basis of any combination of three attributes of the active moiety: MOA, PE, and CS.

Established pharmacologic class is a pharmacologic class associated with an approved indication of an active moiety that the FDA has determined to be scientifically valid and clinically meaningful according to the following definitions:

- A *scientifically valid* pharmacologic class is one that is supported by submitted, documented, empiric evidence showing that the active moiety’s pharmacologic class is known (not just assumed on a theoretical basis) and is relevant and specific to a drug product’s indication.
- A *clinically meaningful* pharmacologic class is one where understanding of the pharmacologic effect enhances the ability of professionals to understand the physiologic basis of the drug product’s indication or to anticipate undesirable effects that may be associated with the active moiety or pharmacologic class.

The term used to describe the EPC in INDICATIONS AND USAGE in Highlights is called an EPC text phrase.

The 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*² provides more information to help applicants and

² We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

review staff identify the most appropriate EPC text phrase to be used with an approved indication of an active moiety found in INDICATIONS AND USAGE in Highlights.

Indexing of Labeling

Structured product labeling (SPL) indexing refers to the creation of one or more files that include machine-readable annotations to information that are linked to the original SPL file for the product submitted by the manufacturer or distributor. Linking the information in the indexing SPL files to the original SPL files enables users with computer systems (such as clinical decision support tools and electronic prescribing systems) to rapidly search and sort product information. The guidance for industry *Indexing Structured Product Labeling* provides more information on this process. The staff in the Office of the Chief Scientist creates a pharmacologic class SPL index file for each active moiety that is assigned an EPC text phrase. This SPL file is then processed, along with the other SPL files, and maintained in a repository that is available to reviewers through a software program, such as Pragmatic Regulated Product Labeling Listing and Registration (PRPLLR).³

EPC Concepts, Pharmacologic Concepts, and Identifier Codes

Each EPC text phrase is associated with a term known as an EPC concept. EPC concepts use a standardized format derived from the U.S. Department of Veterans Affairs, Veterans Health Administration (VHA) National Drug File-Reference Terminology (NDF-RT). Each EPC concept also has a unique standardized alphanumeric identifier code, used as the machine-readable tag for the concept. These codes enable SPL indexing. The exact EPC text phrase used in INDICATIONS AND USAGE in Highlights might not be identical to the wording used to describe the EPC concept, because the standardized language used for the EPC concept might not be considered sufficiently clear to the readers of the labeling.

Each active moiety also may be assigned MOA, PE, and CS standardized indexing concepts, which are also linked to unique standardized alphanumeric identifier codes. MOA, PE, and CS standardized indexing concepts may or may not be related to the therapeutic effect of the active moiety for a particular indication, but they should still be scientifically valid and clinically meaningful. Even if the MOA, PE, and CS standardized indexing concepts are not known with certainty to be related to the therapeutic effect, they may still be useful for identifying drug interactions and permitting other safety assessments for a moiety based upon appropriate and relevant considerations, such as enzyme inhibition and enzyme induction. MOA, PE, and CS concepts are maintained in a standardized format as part of the NDF-RT hierarchy.

³ See PRPLLR at <http://elist/prpllr/>.

RESPONSIBILITIES

- **Pharm/tox reviewers** are responsible for:
 - Reviewing primary and secondary pharmacology information submitted by applicants.
 - Reviewing and ensuring that the EPC text phrases proposed for use in INDICATIONS AND USAGE in Highlights are scientifically valid and clinically meaningful. Clinical reviewers should be consulted for all terms, particularly to ensure that the terms are clinically meaningful and input from other CDER review staff should be obtained as needed.
 - Ensuring that all EPC text phrases are described consistently using previously selected text phrases for the EPC and found in the repository maintained by the OND Associate Director for Pharmacology and Toxicology (or designee) and the OC/Office of the Chief Scientist.⁴
 - Justifying the use of an EPC text phrase that is different from the EPC text phrase previously selected for another member of the pharmacologic class, when necessary.
 - Proposing a new EPC text phrase for a new pharmacologic class if the applicant has not proposed one or if the one proposed by the applicant is not appropriate, and working with other disciplines and with the OND Associate Director for Pharmacology and Toxicology (or designee) to ensure the scientific validity and clinical meaningfulness of the new EPC text phrase.
 - Identifying the scientifically valid and clinically relevant pharmacologic MOA, PE, and CS indexing concepts for each active moiety using standardized MOA, PE, and CS concept hierarchies based on the VHA NDF-RT.
 - Reviewing and ensuring that any additional use of MOA, PE, and CS to describe moiety attributes (such as enzyme inhibition and enzyme induction), when necessary, is scientifically valid and clinically meaningful. (The pharm/tox reviewer should also consult with other CDER review staff such as clinical pharmacology, product quality (CMC), and microbiology reviewers when the data to be reviewed are primarily from these disciplines (see below)).

⁴ This repository is currently accessed using the PRPLLR software (<http://elist/prpllr/>).

- **Other CDER review staff** (e.g., product quality (CMC) reviewers, microbiology reviewers, clinical pharmacology reviewers, and clinical reviewers), when consulted, are responsible for:
 - Reviewing data relevant to the selection of a scientifically valid EPC text phrase when the data are related primarily to the particular discipline. (For example, microbiology reviewers may be responsible for reviewing data in support of EPC text phrases for antimicrobial products. CMC reviewers may be involved in reviewing data associated with CS concepts.)
 - Reviewing and ensuring that any use of MOA, PE, and CS to describe moiety attributes is scientifically valid and clinically meaningful when the data to be reviewed are primarily from these disciplines.
 - Participating in discussions with the review team regarding pharmacologic class issues.
- **OND Associate Director for Pharmacology and Toxicology** or designee is responsible for:
 - Moderating discussions and helping to resolve differing professional opinions — if differences of opinion exist — as to the appropriate EPC text phrase for a particular active moiety or class of active moieties
 - Coordinating the creation of new EPC text phrases and corresponding indexing concepts as needed
 - Obtaining EPC concepts and EPC concept codes for newly created EPC text phrases from VHA NDF-RT staff
 - Notifying the OC/Office of Chief Scientist of all changes, including updated and newly assigned EPC text phrases; EPC concepts; and MOA, PE, and CS indexing concepts (and associated concept codes) for all active moieties as they are approved and as new indications are added

PROCEDURES

For new drug applications/biologics license applications (NDAs/BLAs), the review of the EPC text phrase begins after the filing period and continues throughout the application review cycle. The pharm/tox reviewer should include comments on selection of the EPC text phrase in his or her review. The selected EPC text phrase can be included in the Drug Information section (Section 2.1) of the Pharmacology/Toxicology NDA/BLA Review and Evaluation template under the Pharmacologic Class heading.

In some cases, a scientifically valid and clinically meaningful pharmacologic class may not exist for a particular moiety used for a specific indication. In these cases, it is acceptable to omit an EPC text phrase from INDICATIONS AND USAGE in Highlights; it is generally expected that this will occur infrequently, as it is desirable to use an EPC text phrase when possible.

The following process should be followed for all new NDA/BLA labeling reviews, efficacy supplements that include data to support a new indication, and prior approval labeling supplements with proposed labeling that conforms to the requirements of 21 CFR 201.56 and 201.57 (physician labeling rule conversions).

Reviewing the Proposed Established Pharmacologic Class

New drug products containing already approved active moieties

- The pharm/tox reviewer should:
 - Check the EPC text phrase in the applicant’s proposed labeling against the FDA EPC text phrases found in the SPL repository for each active moiety in the drug product; evaluate whether it is consistent with an existing FDA EPC text phrase
 - Use the proposed EPC text phrase in labeling if it is the same as in the repository and appropriate for the indication under review
 - Identify — or verify if already present in the SPL repository — the scientifically valid and clinically meaningful pharmacologic MOA, PE, and CS indexing concepts for the active moiety using standardized MOA, PE, and CS concept hierarchies.
 - Consult with other CDER review staff to identify — or verify if already present in the SPL repository — additional scientifically valid and clinically meaningful MOA, PE, and CS concepts that describe such things as enzyme inhibition and enzyme induction, when necessary (see additional information about these concepts under Creating a New Established Pharmacologic Class Text Phrase)

New indication for previously approved product or active moiety

- If the EPC text phrase for a specific indication in a new NDA/BLA or a supplement differs from that of previously approved products containing the same active moiety, the pharm/tox reviewer should:
 - Consider if the EPC text phrase in the repository for that active moiety is acceptable for the new indication; or

- Consider if another EPC text phrase in the repository might be more appropriate. If another EPC text phrase from the repository is chosen, the pharm/tox reviewer should:
 - Note the existing EPC text phrase in his or her review
 - Justify the selection of the new EPC text phrase
 - Notify the OND Associate Director for Pharmacology and Toxicology (or designee), so that the updated EPC is added to the active moiety in the repository
- If there is no appropriate EPC text phrase in the repository for the new indication, the pharm/tox reviewer should follow the procedure described below for creating a new EPC text phrase.

New active moiety

- If the new NDA/BLA is for a product containing a new active moiety, the pharm/tox reviewer should review and consider the EPC text phrases assigned to similar active moieties. Selection of an existing EPC text phrase for active moieties in the same class is desirable.
- If an existing EPC text phrase is chosen, the pharm/tox reviewer should:
 - Note the EPC text phrase in his or her review
 - Justify its selection
 - Review the MOA, PE, and CS concepts assigned to the active moiety in the SPL repository to ensure that these concepts are scientifically valid and clinically meaningful for the particular product
 - Report any changes or discrepancies to the OND Associate Director for Pharmacology and Toxicology (or designee)
- The pharm/tox reviewer should select — or verify if already present in the SPL repository — additional scientifically valid and clinically meaningful MOA, PE, and CS concepts that describe such things as enzyme inhibition and enzyme induction, when necessary. The pharm/tox reviewer should consult with the clinical pharmacology and clinical reviewers on the review team as necessary on these concepts.

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- If there is no appropriate EPC text phrase in the SPL repository, the pharm/tox reviewer should follow the procedure described below for creating a new EPC text phrase.

Creating a New Established Pharmacologic Class Text Phrase

- When there is no appropriate existing EPC text phrase for an active moiety, the pharm/tox reviewer should review supportive pharmacology data and the applicant's proposed EPC text phrase to verify that a new EPC text phrase should be created.
- When creating a new EPC text phrase, the reviewer should consider the principles outlined in the 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*.
- For each active moiety, the pharm/tox reviewer should also select, as part of creating the new EPC text phrase, scientifically valid and clinically meaningful MOA, PE, and CS concepts to be used for SPL indexing.
- The pharm/tox reviewer should consult with the clinical pharmacology reviewers on the review team to select additional scientifically valid and clinically meaningful MOA, PE, and CS concepts that describe such things as enzyme inhibition and enzyme induction, when necessary. The VHA NDF-RT should be used as the source of these concepts.⁵
- The pharm/tox reviewer should discuss the selection of the new EPC text phrase and the MOA, PE, and CS SPL indexing concepts with other members of the review team and division leadership. This is critical to ensure that the EPC text phrase and the pharmacologic indexing concepts are clinically meaningful and scientifically valid.

Discussion of the EPC text phrase may occur during regularly scheduled milestone meetings or outside these meetings via email or other venues. Because pharmacology information about an active moiety may be submitted during the investigational new drug application phase of drug development, reviewers should begin to consider appropriate EPC text phrases at this time so as to be prepared for discussions and decisions during the NDA/BLA phase. The OND Associate Director for Pharmacology and Toxicology (or designee) should be included in these discussions to help ensure consistency across and within OND review divisions. The pharm/tox reviewer should:

⁵ The full list of NDF-RT codes for MOA, PE, and CS can be found through the NCI Term Browser at <http://nciterms.nci.nih.gov/ncitbrowser/pages/vocabulary.jsf?dictionary=National%20Drug%20File%20-%20Reference%20Terminology&version=June2012>.

- Capture the outcome of these discussions in his or her review
- Note the EPC text phrase and SPL pharmacologic indexing concepts and justify his or her selection based on the conclusions of the team
- In those rare cases where the review team concludes that there is no text phrase that is scientifically valid and clinically meaningful, it is acceptable for the labeling to not include an established pharmacologic class.
- The pharm/tox reviewer should notify the OND Associate Director for Pharmacology and Toxicology (or designee) of the EPC text phrase and SPL pharmacologic indexing concepts assigned to the new active moiety so that the information can be added to the repository.

Requesting an EPC Concept for a New Established Pharmacologic Class

- Whenever a new EPC text phrase is created by the FDA, the OND Associate Director for Pharmacology and Toxicology (or designee) should request an EPC indexing concept and NDF-RT unique identifier code (NUI) for that EPC text phrase from the VHA NDF-RT.⁶

Maintenance of the FDA Established Pharmacologic Class in the SPL Repository

- Concepts and codes identified by reviewers and review divisions as scientifically valid and clinically meaningful for a specific active moiety should be maintained and regularly updated by the OND Associate Director for Pharmacology and Toxicology (or designee), together with the OC/Office of the Chief Scientist using its standard operating procedure.

REFERENCES

1. Final rule “Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products” (71 FR 3922; January 24, 2006, effective June 30, 2006)
2. 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*
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

⁶ EPC concepts and their NUIs are associated with each EPC text phrase and are listed for each active moiety in the FDA pharmacologic class SPL indexing file. Standardized EPC indexing concepts and NUIs are maintained by the VHA as part of its NDF-RT.

3. Guidance for industry *Indexing Structured Product Labeling*
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>
 4. FDA Pharmacologic Class Web page
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>
 5. U.S. Department of Veterans Affairs, Veterans Health Administration, National Drug File-Reference Terminology codes for mechanism of action, physiologic effect, and chemical structure is available through the NCI Term Browser at
<http://nciterms.nci.nih.gov/ncitbrowser/pages/vocabulary.jsf?dictionary=National%20Drug%20File%20-%20Reference%20Terminology&version=June2012>
 6. Pragmatic Regulated Product Labeling Listing and Registration software Web site
<http://elist/prplr/>
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EFFECTIVE DATE

This MAPP is effective upon date of publication.