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 of Structured Product Labeling (SPL).

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

- Office of New Drugs (OND) pharmacology/toxicology (pharm/tox) reviewers, team leaders, supervisors and division directors.

- OND Associate Director for Pharmacology and Toxicology or other designated pharm/tox staff.

[1] Note that CS is also known as chemical/ingredient (CI), used in the U.S. Department of Veterans Affairs, Veterans Health Administration (VHA) Medication Reference Terminology (MED-RT).

- Other CDER review staff as appropriate (e.g., product quality (PQ) reviewers, microbiology reviewers, clinical pharmacology reviewers, and clinical reviewers).

- Office of the Commissioner (OC)/Office of Digital Transformation (ODT)/Office of Data, Analytics, and Research (ODAR).

BACKGROUND

Established Pharmacologic Class in Indications and Usage in Highlights

- The regulation 21 CFR 201.57(a)(6) requires that if a drug[2] is a member of an EPC, a concise statement under the Indications and Usage heading 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 one or 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, and 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 enhances the ability of health care practitioners to understand the physiologic effects related to the indication or to anticipate undesirable effects that may be associated with the active moiety or pharmacologic class.

- The term used to describe the EPC under the Indications and Usage heading in Highlights is called an EPC text phrase. A publicly available list of EPC text phrases is available on the *FDA's Labeling Resources for Human Prescription*

[2] For the purposes of this MAPP, references to drugs and drug and biological products include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) that are regulated as drugs.

Drugs website at https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs.

- 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* (October 2009) provides more information to help applicants and review staff identify the most appropriate EPC text phrase to be used with an approved indication of an active moiety under the Indications and Usage heading in Highlights.[3]

Indexing of Pharmacologic Class in Structured Product Labeling

- Indexing of SPL refers to the creation of one or more files that include machine-readable annotations, which do not appear in printed labeling, that enable users with clinical decision support tools and electronic prescribing systems to rapidly search and sort drug information. The guidance for industry *Indexing Structured Product Labeling* (June 2008) provides more information on this process.

- ODAR staff 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 FDA reviewers through a software program, such as Pragmatic Regulated Product Labeling Listing and Registration. This information is publicly available through the National Library of Medicine DailyMed website at https://dailymed.nlm.nih.gov/dailymed/.

EPC Concepts, Pharmacologic Concepts, and Identifier Codes

- Each EPC text phrase is associated with a term known as an EPC concept. EPC concepts are phrases that use a standardized format derived from the Medication Reference Terminology (MED-RT).[4] 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 EPC text phrase used under the Indications and Usage heading in Highlights might not be identical to the EPC concept. The EPC concepts use standardized nomenclature to facilitate maintenance of the MED-RT. Whereas, the EPC text phrase is written to be clearly understood by health care practitioners.

- Each active moiety may be assigned MOA, PE, and CS concepts, which are also linked to unique standardized alphanumeric identifier codes, used as the machine-readable tags for these concepts. MOA, PE, and CS concepts are either

[3] For the most recent version of a guidance, refer to the *Search for FDA Guidance Documents* website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.
[4] The MED-RT is maintained by the VHA in the U.S. Department of Veterans Affairs.

derived from MED-RT or new concepts can be proposed. MOA, PE, and CS concepts are scientifically valid and clinically meaningful, but they may or may not be related to the therapeutic effect of the active moiety for a particular indication. 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 possible drug interactions and performing other safety assessments for a moiety based upon moiety attributes (such as enzyme inhibition and enzyme induction).

RESPONSIBILITIES

OND Pharm/tox reviewers are responsible for:

- Reviewing primary and secondary pharmacology EPC-related information submitted by applicants.

- Reviewing the scientific validity and clinical meaningfulness of the EPC text phrases proposed for use under the Indications and Usage heading in Highlights, along with other staff as indicated below.

- 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.

- Consulting clinical reviewers for proposed EPC text phrases to ensure that the phrases are clinically meaningful.

- Consulting other CDER review staff (e.g., clinical pharmacology reviewers, PQ reviewers, microbiology reviewers) when the EPC-related data are primarily from these disciplines.

- Ensuring all EPC text phrases are described consistently using previously selected text phrases for the EPC found in the repository maintained by the ODAR staff.

- 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.

- Identifying the scientifically valid and clinically meaningful MOA, PE, and CS indexing concepts for each active moiety using standardized MOA, PE, and CS concept hierarchies based on the MED-RT.

- Reviewing and ensuring any additional use of MOA, PE, and CS indexing concepts to describe moiety attributes (such as enzyme inhibition and enzyme induction), when necessary, is scientifically valid and clinically meaningful.

Other CDER review staff (e.g., PQ reviewers, microbiology reviewers, clinical pharmacology reviewers, 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. PQ reviewers may be involved in reviewing data associated with CS concepts.

- Reviewing and ensuring that any use of MOA, PE, and CS indexing concepts 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 EPC-related issues.

OND Pharmacology/Toxicology Division Director or other tertiary pharm/tox reviewer is responsible for:

- Reviewing and confirming acceptability of the EPC text phrase to include under the Indications and Usage heading in Highlights as proposed by the pharm/tox review team. Alternatively, reviewing whether there is no EPC text phrase that is scientifically valid and clinically meaningful to include under this heading. These activities may occur as part of the overall review and approval of the pharm/tox review for a new drug application (NDA), biologic licensing application (BLA), or supplement.

OND Associate Director for Pharmacology and Toxicology (or designee) is responsible for:

- Moderating discussions and helping to resolve issues when differing professional opinions exist about an EPC text phrase. Helping to identify the appropriate EPC text phrase to include under the Indications and Usage heading in Highlights for a particular active moiety or class of active moieties.

- Ensuring a consistent approach to selecting EPC text phrases across all CDER-approved drugs, as appropriate.

- Coordinating the creation of new EPC text phrases and corresponding MOA, PE, and CS indexing concepts as needed.

- Obtaining EPC concepts and EPC concept codes for newly created EPC text phrases from MED-RT staff. (ODAR staff may also obtain these concepts and codes.)

- Notifying ODAR staff 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 NDAs, BLAs, and supplements to these applications that include new proposed indications, the review of the EPC text phrase begins after the filing period and continues throughout the application or supplement review. The pharm/tox reviewer includes the selected EPC text and comments on how the EPC text phrase was selected in their NDA, BLA, or supplement review. The pharm/tox reviewer ensures the EPC text phrase is discussed with the review team.

When the labeling is being finalized, the pharm/tox reviewer ensures the selected EPC text phrase is included under the Indications and Usage heading in Highlights, unless there is no EPC text phrase that is scientifically valid and clinically meaningful to include under this heading in the Highlights.

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 the Indications and Usage heading in Highlights. Use an EPC text phrase in the Highlights when possible. If an EPC text phrase is omitted, the pharm/tox reviewer documents this in their NDA, BLA, or supplement review.

The following processes are followed for all NDA and BLA labeling reviews, reviews of efficacy supplements that include data to support a new indication, and reviews of prior approval labeling supplements that propose conversion of labeling to the "physician labeling rule" content and format described in the 2006 FDA final rule, ''Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products."[5]

1. Reviewing the Proposed Established Pharmacologic Class

a. New drugs that contain active moieties approved in other drugs

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

i. The OND pharm/tox reviewer:

1. Compares the proposed EPC text phrase(s) under the Indications and Usage heading in the Highlights of the applicant's proposed labeling with the FDA EPC text phrases found in the SPL repository for each active moiety in the drug; and evaluate whether they are consistent.

2. Includes the proposed EPC text phrase under the Indications and Usage heading in the Highlights if it is the same as in the SPL repository and appropriate for the indication for the drug under review.

3. Identifies or verifies if the active moiety is already present in the SPL repository with standardized MOA, PE, and CS concept hierarchies.

4. Consults 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 indexing concepts that describe moiety attributes (such as enzyme inhibition and enzyme induction), when necessary.

b. New indication for an active moiety in a previously approved drug

i. If the applicant's proposed EPC text phrase for an active moiety for a specific proposed indication in an NDA, BLA, or supplement is the same as for previously approved drugs containing the same active moiety, the pharm/tox reviewer confirms the EPC text phrase is appropriate for the indication under review.

ii. If the applicant's proposed EPC text phrase for an active moiety for a specific proposed indication in an NDA, BLA, or supplement differs from that of previously approved drugs containing the same active moiety, the pharm/tox reviewer:

1. Helps determine if the EPC text phrase in the SPL repository for that active moiety is acceptable for the new proposed indication; or

2. Helps determine if another EPC text phrase in the SPL repository might be more appropriate. If another EPC text phrase from the SPL repository is chosen, the pharm/tox reviewer:

a. Justifies the selection of the new EPC text phrase rather than the existing EPC text phrase in the SPL repository for that active moiety.

b. Notifies the OND Associate Director for Pharmacology and Toxicology (or designee), so that the updated EPC for the active moiety is added in the SPL repository.

3. If there is no appropriate EPC text phrase for the active moiety in the SPL repository for the proposed indication in an NDA, BLA, or supplement, the pharm/tox reviewer follows the procedures described below for creating a new EPC text phrase.

iii. The pharm/tox reviewer also identifies, or verifies if already present in the SPL repository, the scientifically valid and clinically meaningful MOA, PE, and CS indexing concepts for the active moiety using standardized MOA, PE, and CS concept hierarchies. Although, these concepts may already be identified for the active moiety, some MOA and PE concepts differ for different indications. Verify these are appropriate for the new indication.

c. New active moiety

i. If the NDA or BLA is for a drug containing a new active moiety, the pharm/tox reviewer reviews and helps to determine if any of the EPC text phrases assigned to similar active moieties in the SPL repository are appropriate for the new active moiety for the proposed indication. If clinically meaningful and scientifically valid, selection of an existing EPC text phrase for active moieties in the same class is desirable for a consistent use of EPC text phrases.

1. If an existing EPC text phrase is chosen, the pharm/tox reviewer:

a. Justifies its selection in their review.

b. Reviews 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 new active moiety.

c. Reports any changes or discrepancies to the OND Associate Director for Pharmacology and Toxicology (or designee).

d. Includes the proposed EPC text phrase under the Indications and Usage heading in the Highlights.

2. The pharm/tox reviewer selects additional scientifically valid and clinically meaningful MOA, PE, and CS concepts that describe moiety attributes (such as enzyme inhibition and enzyme induction), if

appropriate. The pharm/tox reviewer consults with the PQ, clinical pharmacology and clinical reviewers on the review team as necessary.

If there is no appropriate EPC text phrase in the SPL repository, the pharm/tox reviewer follows the procedures for creating a new pharmacologic class text phrase, described immediately below.

2. Creating a New Established Pharmacologic Class Text Phrase

a. When there is no appropriate existing EPC text phrase for an active moiety for the proposed indication in the SPL repository, the pharm/tox reviewer reviews supportive pharmacology data and the applicant's proposed EPC text phrase to help determine if it is appropriate to create a new EPC text phrase for the active moiety.

b. When creating a new EPC text phrase for the active moiety, the pharm/tox reviewer follows the recommendations 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* (October 2009).

c. For each active moiety, the pharm/tox reviewer also selects, 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.

d. The pharm/tox reviewer consults with other members of the review team to select additional scientifically valid and clinically meaningful MOA, PE, and CS concepts that describe moiety attributes (such as enzyme inhibition and enzyme induction), when necessary. The MED-RT is used as the source of these concepts.[6]

e. The pharm/tox reviewer discusses 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 pharm/tox and clinical division leadership. This action ensures the EPC text phrase and the pharmacologic indexing concepts are clinically meaningful and scientifically valid.

f. Discussion of the EPC text phrase among review team members 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 (IND)

[6] The full list of MED-RT codes for MOA, PE, and CS can be found through the National Cancer Institute Enterprise Vocabulary Services (EVS) on the *FDA Terminology* website at https://www.cancer.gov/research/resources/resource/196.

application phase of drug development, the review team begins to determine appropriate EPC text phrases at this time to be prepared for discussions and decisions during the NDA, BLA, and supplement phase. The OND Associate Director for Pharmacology and Toxicology (or designee) is included in these discussions to help ensure consistency across and within OND review divisions. The pharm/tox reviewer:

i. Captures the outcome of these discussions in their review.

ii. Notes the EPC text phrase and the MOA, PE and CS indexing concepts and justifies the selection based on the conclusions of the team.

g. The pharm/tox reviewer notifies the OND Associate Director for Pharmacology and Toxicology (or designee) of the EPC text phrase and the MOA, PE and CS indexing concepts assigned to the new active moiety so that the information can be added to the SPL repository.

h. In a rare case where the review team concludes that there is no EPC text phrase that is scientifically valid and clinically meaningful for the active moiety for the proposed indication, it is acceptable for the labeling to not include an EPC text phrase.

3. Requesting an EPC Concept for a New Established Pharmacologic Class

a. When a new EPC text phrase is created by the FDA, the OND Associate Director for Pharmacology and Toxicology (or designee) requests an EPC indexing concept and MED-RT alphanumeric unique identifier code (NUI) for that EPC text phrase from the MED-RT.[7] The request for an EPC indexing concept or other pharmacologic indexing concepts and their associated codes may also originate from ODAR staff.

4. Maintenance of the FDA Established Pharmacologic Class in the SPL Repository

a. Concepts and codes identified by reviewers and review divisions as scientifically valid and clinically meaningful for a specific active moiety are maintained and regularly updated in the SPL repository by ODAR staff using their standard operating procedure. The OND Associate Director for Pharmacology and Toxicology (or designee) alerts ODAR staff to new concepts or other changes that need to be incorporated into the SPL repository.

[7] 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 MED-RT.

REFERENCES

- Final rule: *"Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products"* (71 FR 3921; January 24, 2006, effective June 30, 2006).

- 21 CFR 201.56: *Requirements on content and format of labeling for human prescription drug and biological products*.

- 21 CFR 201.57: *Specific requirements on content and format of labeling for human prescription drug and biological products described in 201.56(b)(1)*.

- 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* (October 2009).

- Guidance for Industry – *Indexing Structured Product Labeling* (June 2008).

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
07/18/2013	N/A	N/A
07/25/2018	Rev. 1	Not identified.
7/18/2025	Rev. 2	Updated to align with current OND organizational structure, applicable UFA commitments, and contemporary CDER workflow procedures and best practices.