CDER Prescription Drug Labeling Conference
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U.S. FOOD & DRUG ADMINISTRATION

Product Title and Initial U.S. Approval in the Highlights of Prescribing Information Draft Guidance*

Debra Beitzell, BSN
Clinical Advisor for Labeling
Labeling Policy Team, Office of New Drug Policy,
Office of New Drugs, Center for Drug Evaluation and Research, FDA

*Guidance for industry: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format* (January 2018) - subsequently referred to as the "Product Title Guidance" in this presentation

Disclaimer

- The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.

- The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.

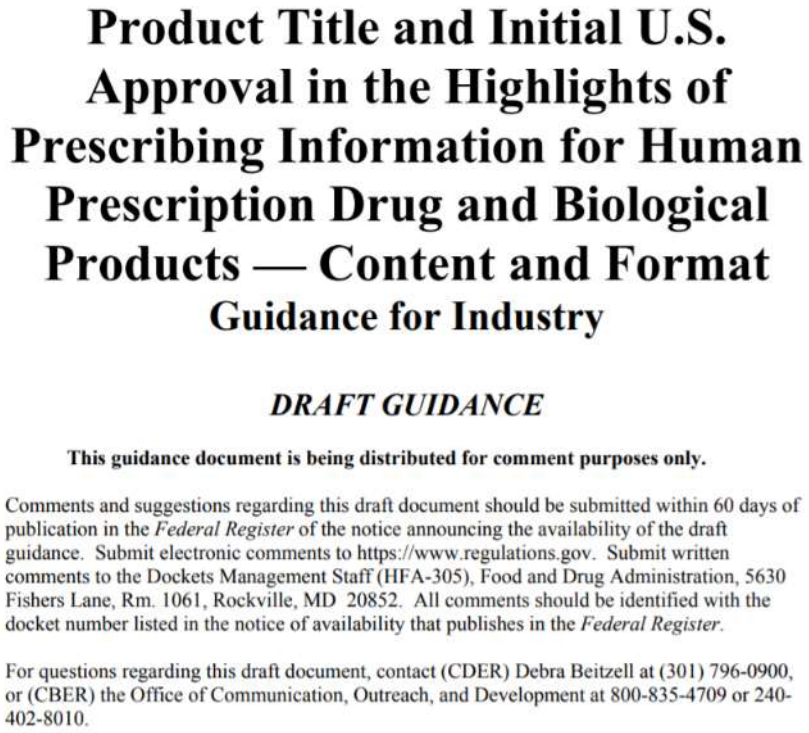
- Reference to any marketed products is for illustrative purposes only and does not constitute endorsement by the FDA.

Learning Objectives

Understand:

- Purpose and importance of accurate, clear, and consistent product titles
- Format and content recommendations for the product title
- Nomenclature resources available in the Product Title Guidance
- Purpose of and principles to follow for determining the year of initial U.S. approval

Product Title Guidance[1]



Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Debra Beitzell at (301) 796-0900, or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

- Provides content and format recommendations for the product title[2] and initial U.S. approval, for both common and less common labeling scenarios
- Contains appendices with dosage form and route of administration terminology
- Contains multiple examples illustrating recommendations

[1] When finalized this guidance will represent the Agency's current thinking.

[2] Recommendations pertaining to presentation of the required elements of the product title pertain only to the product title in Highlights of Prescribing Information

Product Title

Highlights: Product Title

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/YYYY
Section Title, Subsection Title (x.x) M/YYYY

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use
Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

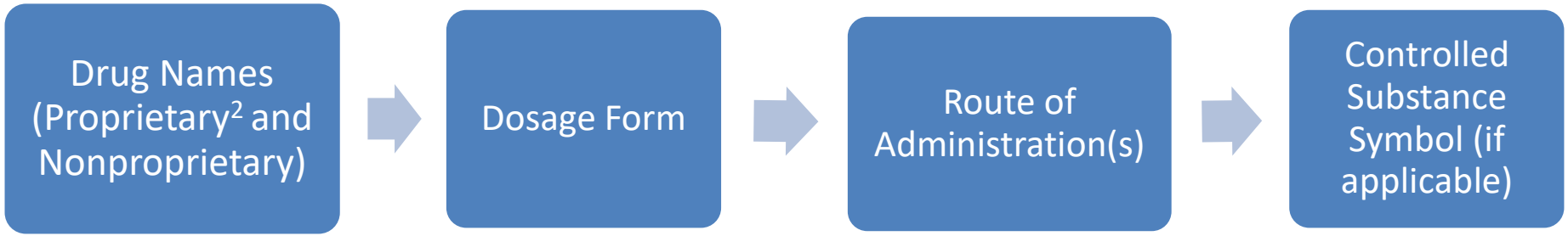
----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/YYYY

Required Components of the Product Title [1]



[1] 21 CFR 201.57(a)(2); [2] If the product has a proprietary name

Purpose of the Product Title

- Identifies the drug or biological product that is the subject of the prescribing information (PI)

Implications for Other Sections of the PI and Other Labeling

- Nomenclature developed for product title will be used in other sections of the PI and in other labeling
- Nomenclature should be consistent between product title, other sections of the PI and other labeling (e.g., dosage form in product title and dosage form under Dosage Forms and Strengths heading in Highlights of PI should be consistent)
- Some differences between product title and carton/container labeling are acceptable (e.g., formatting of proprietary name, number of lines that the information is presented on)

Product Title: Sources of Terminology (1 of 5)

Proprietary Name

- Proposed by applicant

Product Title: Sources of Terminology (2 of 5)

Established Name of Drug Products

- United States Pharmacopeia (USP) drug product monograph title (USP monograph), or if no USP monograph, use 21 CFR 299.4(e) and USP nomenclature guidelines[1] for guidance
- For products without a USP monograph, critical to develop established names that follow USP nomenclature guidelines because USP monographs are developed after NDA approval

Proper Name of Biological Products

- Name designated on the license[2]

[1] USP General Chapter <1121> *Nomenclature;* [2] 21 CFR 600.3(k); for further information, see Guidance for industry: *Nonproprietary Naming of Biological Products (January 2017)* and *Nonproprietary Naming of Biological Products: Update (March 2019)*

Product Title: Sources of Terminology (3 of 5)

Dosage Form

- For drug products, use the USP monograph, if there is one
- If there is no USP monograph, use USP[1] and the dosage form appendix in Product Title Guidance

[1]See General Chapters <1151> *Pharmaceutical Dosage Forms,* <5> *Inhalation and Nasal Drug Products – General Information and Quality Tests, and* <1121> *Nomenclature; existing USP monograph titles for specific drug products also can be used as examples of appropriate dosage form terminology*

APPENDIX A:
DOSAGE FORM TERMS FOR USE IN HUMAN DRUG PRODUCT LABELING

The following list of dosage forms has been created to assist the reader in selecting the proper dosage form terminology for use in the nomenclature of human drug products.

The basic dosage form terms appear along the left margin. Examples of how the basic dosage form terms are used when combined with other modifiers and/or routes of administration are provided as indented text.

- A **bolded and underlined** term means both the FDA and the United States Pharmacopeia (USP) recommend use of the term
- A **bolded** term means the FDA recommends use of the term
- An underlined term means USP recommends use of the term
- A term neither bolded nor underlined means the term is a nonpreferred term
- *Italicized* examples are the subject of discussion between the FDA and USP

Dosage form terms that appear only in bolded or underlined print are being discussed by the FDA and USP and represent terminology that may be changed at a later date. If the term is neither bolded nor underlined, then the term is a nonpreferred term and the reader is directed to preferred terminology. In some cases, USP monographs using nonpreferred terms still exist. However, these older, noncompliant terms found in monographs should not be cited as a precedent for future use of the dosage form terms.

Product Title Guidance: Dosage Form Appendix
(1 of 2)

Terminology

Aerosol

Aerosols are packaged under pressure. All aerosols are assumed to be metered except topical aerosols. Topical aerosols are assumed not to be metered unless labeling indicates they are metered.

inhalation aerosol — assumed to be for oral inhalation
lingual aerosol
nasal aerosol
topical aerosol

Bead — not preferred, see "Pellet"

Caplet — not preferred, see "Tablet"

Capsule

Capsules are assumed to be oral.
Note: In the past, the terminology "vaginal capsules" was used, but these drug products are now referred to as "vaginal inserts."

capsules
delayed-release capsules
extended-release capsules

Collodion — not preferred, see "Solution"
Note: Collodion is reserved for pyroxilin in alcohol and ether.

Concentrate — not preferred term for human drug products, see the appropriate dosage form (e.g., "Solution" or "Suspension")
Note: USP General Chapter <1121> *Nomenclature* refers to the USP Nomenclature Guidelines that currently restrict the use of "concentrate" to drug substances that are not intended for direct administration.

Product Title Guidance: Dosage Form Appendix (2 of 2)

Product Title: Sources of Terminology (4 of 5)

Route of Administration (ROA)

- If the ROA does not precede the dosage form (e.g., tablets, injection), use ROA appendix in Product Title Guidance
- ROA appendix contains most commonly used ROA terms

APPENDIX B:
ROUTE OF ADMINISTRATION TERMS FOR USE IN THE PRODUCT TITLE

The following table lists the most commonly used route of administration terms for use in the product title. This list is derived from the FDA Data Standards Manual Route of Administration list with minor differences made to create a list that is appropriate for use in the product title. If an applicant determines that a route of administration term different from any of the examples is appropriate, the applicant is encouraged to initiate discussions with the FDA.

Name	Definition
Buccal	Administration directed toward the cheek, generally from within the mouth
Dental	Administration to a tooth or teeth
Endocervical	Administration within the canal of the cervix uteri
Endotracheal	Administration directly into the trachea
Enteral	Administration directly into the intestines
Epidural	Administration on or over the dura mater
Extracorporeal (For certain radiopharmaceuticals, it may be appropriate to use the phrase "for radiolabeling" instead of the route of administration "extracorporeal."	Administration outside of the body
Hemodialysis	Administration through hemodialysate fluid

Product Title Guidance: ROA Appendix

Product Title: Sources of Terminology (5 of 5)

Controlled Substance Symbol

- Assigned by the Drug Enforcement Administration

Product Title: Format (1 of 2)

- Product title must be bolded[1]
- Proprietary name should be in UPPERCASE with rest of product title in lower case [2]
- Product title should be presented on a single line:

  MYDRUG (drugozide) capsules, for oral use ✓

- Avoid:

  MYDRUG (drugozide)
  Capsules, for Oral use ✗

[1] 21 CFR 201.57(d)(5); [2] Excluding the proprietary name, all text should be in lower case with limited exceptions (e.g., controlled substance symbol, acronyms for radioisotopes)

Product Title Format (2 of 2)

If there is no proprietary name, chemical component portion of nonproprietary name should be in UPPER-CASE and rest of product title should be in lower case (parentheses are omitted):

DRUGOZIDE capsules, for oral use 

Product Title: Multiple Dosage Forms

- Multiple Dosage Forms:

  MYDRUG (drugozide) tablets, for oral use
  MYDRUG (drugozide) capsules, for oral use

- Avoid:

  MYDRUG (drugozide) tablets and capsules, for oral use

Product Title: Fixed-Combination Drug Products

- Fixed-Combination Drug Products:

  MYDRUG (drugozide, drugazole, and drugomycin capsules), for oral use 

- Avoid:

  MYDRUG (drugozide/drugazole/drugomycin capsules), for oral use 

Product Title: Route of Administration

- If ROA does not precede dosage form, add “for [insert ROA] use”, preceded by comma:

  MYDRUG (drugozide injection), for intravenous or subcutaneous use ✓

- If ROA precedes dosage form:

  MYDRUG (drugozide) topical solution ✓

- Avoid:

  MYDRUG (drugozide) topical solution, for topical use ✗

Product Title: Examples of What NOT to Include

- **Additional dosage form descriptors** (e.g., “film-coated” for tablets, “powder” for a product requiring reconstitution, “solution” for an injectable product)
- **Methods of intravenous administration** (e.g., “infusion”, “bolus”)
- “**Only**” (e.g., “for topical use only”)
- **Abbreviations** (e.g., “IV”, “IM”)

Product Titles in Highlights of Prescribing Information Consistent with Requirements Under 21 CFR 201.57(a)(2) and Recommendations in Draft Guidance for Industry: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format*

TABLETS	**"tablets"** LEVITRA (vardenafil hydrochloride) tablets, for oral use INVOKANA (canagliflozin) tablets, for oral use LIPTRUZET(ezetimibe and atorvastatin) tablets, for oral use CLOZARIL (clozapine) tablets, for oral use LATUDA (lurasidone hydrochloride) tablets, for oral use ONFI (clobazam) tablets, for oral use, CIV LUNESTA (eszopiclone) tablets, for oral use, CIV ZOMIG (zolmitriptan) tablets, for oral use ELIQUIS (apixaban) tablets, for oral use REVATIO (sildenafil) tablets, for oral use CYCLOPHOSPHAMIDE tablets, for oral use BIKTARVY (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets), co-packaged for oral use KISQALI FEMARA CO-PACK (ribociclib tablets; letrozole tablets), co-packaged for oral use **"delayed-release tablets"** ACIPHEX (rabeprazole sodium) delayed-release tablets, for oral use ASACOL HD (mesalamine) delayed-release tablets, for oral use **"extended-release tablets"** UCERIS (budesonide) extended-release tablets, for oral use INTUNIV (guanfacine) extended-release tablets, for oral use OXTELLAR XR (oxcarbazepine) extended-release tablets, for oral use APLENZIN (bupropion hydrobromide) extended-release tablets, for oral use ENVARSUS XR (tacrolimus extended-release tablets), for oral use **"orally disintegrating tablets"** FAZACLO (clozapine) orally disintegrating tablets STAXYN (vardenafil hydrochloride) orally disintegrating tablets ZOMIG-ZMT (zolmitriptan) orally disintegrating tablets MAXALT-MLT (rizatriptan benzoate) orally disintegrating tablets

Approved Example Product Titles[1]

[1] Approved Product Title Examples

Initial U.S. Approval

Highlights: Initial U.S. Approval

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See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

Initial U.S. Approval

- Four-digit year in which FDA initially approved a new molecular entity, new biological product, or new combination of active ingredients[1]
- Year of initial U.S. approval must be displayed on line immediately beneath the product title[1] in bold type[2]

[1] 21 CFR 201.57(a)(3); [2] 21 CFR 201.57(d)(5)

Purpose of Initial U.S. Approval [1]

- For new products, assists with increasing prescriber vigilance and reporting of suspected adverse reactions

- For older products, informs prescriber that a drug has been marketed for an extended period of time

[1] See Agency's response to Comment #15 in the Preamble to the 2006 Physician Labeling Rule (71 FR 3922, January 24, 2006)

Initial U.S. Approval: Basic Principles for Drug Products

- Single active moieties – year in which active moiety was first approved, regardless of salt, dosage form, ROA, or indication

- Fixed-Combination Drug Products/Co-Packaged Drug Products – novelty of combination is determining factor

Initial U.S. Approval: Example #1

APLENZIN (bupropion hydrobromide) extended-release tablets, for oral use

- NDA approved in 2008
- Initial U.S. approval is 1985

Why?

- 1985 is the year of first FDA approval of the active moiety bupropion (as bupropion hydrochloride tablets)

Initial U.S. Approval: Example #2

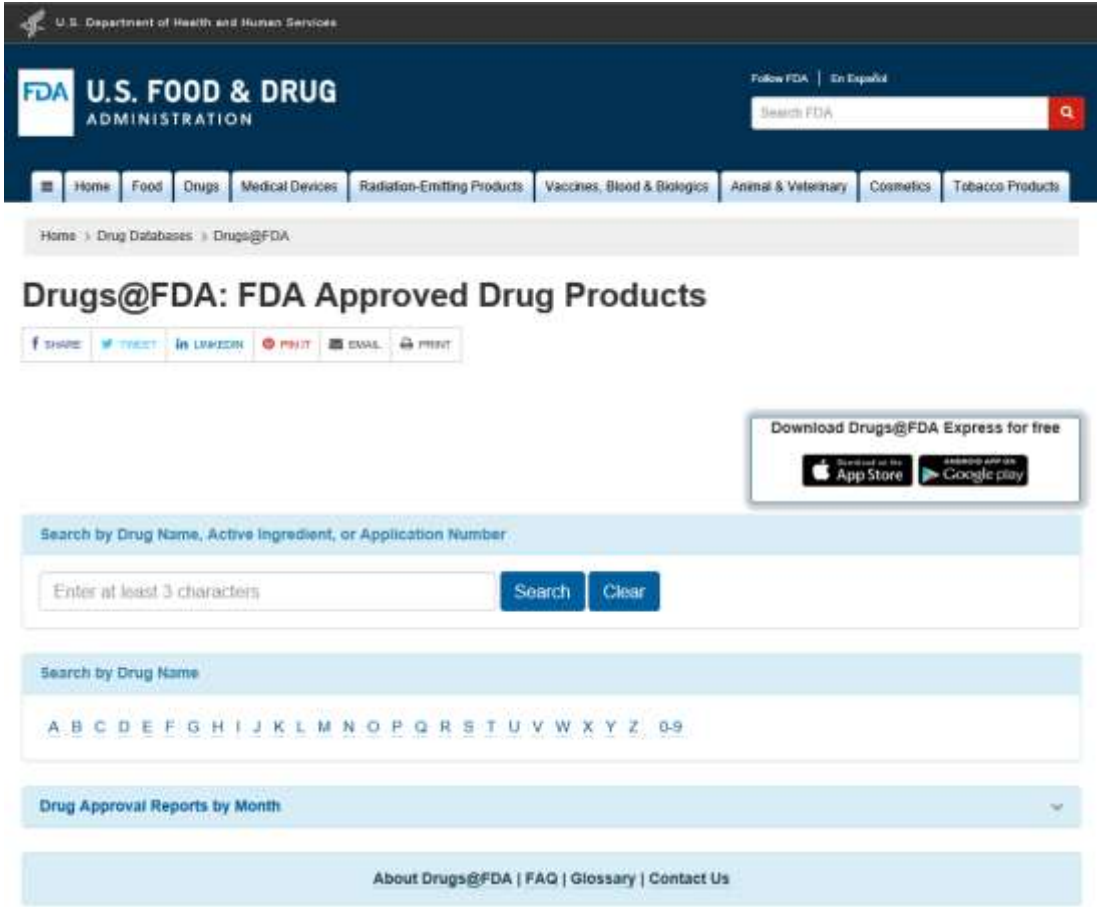
VYTORIN (ezetimibe and simvastatin) tablets, for oral use

- NDA approved in 2004
- Initial U.S. Approval is 2004

Why?

- 2002 is year of first FDA approval of ezetimibe tablets
- 1991 is year of first FDA approval of simvastatin tablets
- 2004 is year of first FDA approval of the novel combination of ezetimibe and simvastatin as VYTORIN

How to Determine the Initial U.S. Approval



To determine the year of initial U.S. approval, perform a search in Drugs@FDA by active moiety and find the earliest year of approval

Challenge Question #1

Which product title is consistent with the recommendations in the Product Title Guidance:

a. **MYDRUG (drugozide) film coated tablets, for oral use**

b. **MYDRUG (drugozide) Tablets**

c. **MYDRUG (drugozide) tablets, for oral use**

d. **MYDRUG (drugozide) tablets, for oral administration**

Challenge Question #2

Which of the following impact the determination of the year of initial U.S. approval:

a. Dosage form

b. Salt form

c. Indication

d. a. and b.

e. None of the above

Summary

- Product titles should convey clear, accurate, and consistent information in both content and format to provide for easy identification of the PI
- The Product Title Guidance contains important resources, including recommendations for developing nonproprietary names and dosage form and ROA terminology, to help ensure accurate and consistent use of product nomenclature across labeling
- The Product Title Guidance provides recommendations on a variety of labeling scenarios to assist with accurate determination of the year of initial U.S. approval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Back-Up Slides

Initial U.S. Approval: Additional Recommendations (1 of 2)

- Controlled substances – controlled substances approved after 11/25/15, initial U.S. approval is later of (1) date the application is approved or (2) date DEA issues an interim final rule controlling the drug

- Racemates – if product is only one enantiomer of already approved racemate drug product, initial U.S. approval is that of the racemate

Initial U.S. Approval: Additional Recommendations (2 of 2)

- DESI drugs – the year of the original approval of the NME, not the year of post-approval DESI update
- Previously marketed unapproved drugs – year of first NDA approval
- Previously approved drugs re-introduced into market – year of the original approval, regardless of reason for removal from market

Initial U.S. Approval Example #3

TYBOST (cobicistat tablets), for oral use

- NDA approved in 2014
- Initial U.S. approval is 2012

Why?

- 2012 is year of first approval of cobicistat as a component of the fixed combination drug product of elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate tablets