CERTIFICATE

Pursuant to the provisions of Rule 44 of the Federal Rules of Civil Procedure, I hereby certify that David L. Roeder, Associate Director for Regulatory Affairs, Office of Antimicrobial Products, Center for Drug Evaluation and Research, United States Food and Drug Administration, whose affidavit is attached, has custody of official records of the United States Food and Drug Administration.

In witness whereof, I have, pursuant to the provision of Title 42, United States Code, Section 3505, and FDA Staff Manual Guide 1410.23(1)(A)(6)(b), hereto set my hand and caused the seal of the Department of Health and Human Services to be affixed this 10 th day of December, 2009.

Carolyn Kachovec

Carolyn Kachovec, Director
Division of Dockets Management
Office of Public Information and Library Services
Office of Shared Services
Office of Management

By direction of the Secretary of
Health and Human Services

DECLARATION OF DAVID L. ROEDER

David L. Roeder declares as follows:

1. I am David L. Roeder, Associate Director for Regulatory Affairs, Office of Antimicrobial Products, Center for Drug Evaluation and Research, the United States Food and Drug Administration ("FDA").

2. In this capacity, I have custody of official records of FDA relating to new drug classification.

3. Attached is a copy of an index to the second supplemental administrative record in *Actavis Elizabeth LLC v. FDA,* Case No. 08-362 (D.D.C.).

4. Copies of the documents referred to in the index in paragraph 3, above, are part of the official records of FDA.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on December 10, 2009.

David L. Roeder

Index for Second Supplemental Administrative Record
Actavis Elizabeth LLC v. Sebelius et al., No. 09-362 (D.D.C.)

Description	Date	Bates Number
Draft MaPP 7500.3	5/20/2005	001984-001994

OFFICE OF NEW DRUGS

Drug and Application Classification

CONTENTS

PURPOSE

- This MAPP describes the classification codes assigned by the Center for Drug Evaluation and Research (CDER) to an application based on characteristics of the product proposed in the application. It describes the chemistry classification codes for new drug applications (NDAs); application classification codes that may be applied to NDAs, supplemental applications, or investigational new drug application (IND) submissions; and effectiveness supplement codes.

BACKGROUND

- The drug and application classification system provides a way of identifying drug applications upon initial receipt and describing applications throughout the review process. The system evolved from both a managerial and a regulatory need to identify and group product applications based on certain characteristics, including their relationships to products already approved or legally marketed in the United States. Classifying applications based on these characteristics contributes to the management of CDER's workload, promotes consistency across review divisions, enables retrospective analysis of trends, and facilitates planning and policy development.

REFERENCES

- Effectiveness Supplements, July 18, 1989, memo from Directors, ODEs I and II, to ODE I and II Division Directors and Supervisory CSOs

DEFINITIONS

- **Active Ingredient:** The entire active molecule, including both the active moiety and those appended portions of the molecule that make it a particular salt or other noncovalent derivative or ester.

- **Active Moiety:** The molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance (21 CFR 314.108(a)).

  Ordinarily, an ester of an approved drug is not considered a new active moiety, as most ester linkages are rapidly cleaved in vivo to provide the de-esterified molecule circulating in the blood. However, there can be exceptions to this. An ester that is stable, both in vitro and in vivo, is considered to be the active moiety, because the de-esterified molecule is devoid of activity (e.g., organic nitrates, in which the nitrate esters are the active moieties and the parent molecules (glycerol, isosorbide) are inert).

  In the case of drugs containing metal ions, the active moiety may be a coordination complex or chelate, rather than the metal ion itself, when the metal-ligand complex is sufficiently stable in vivo to be responsible for its physiologic-pharmacologic action. In such cases, the metal-ligand complex usually needs to be of clearly defined stoichiometry and to contain coordinate bonds with a bond strength comparable to covalent bonds (e.g., gadoteridol, in which the gadolinium-ligand complex is stable both in vitro and in vivo).

  The active moiety in most radiopharmaceutical (or radioactive) drugs is the entire molecule, including the radioactive atom. However, in the case of simple salts (e.g., $Na^{131}I$), the active moiety of the drug is the ion (^{131}I).

- **Application Classification Codes:** Codes assigned to certain IND, NDA, and supplemental applications, when necessary, to identify and track applications with unique regulatory characteristics, including characteristics that could affect the nature or pace of review (see MAPP 6020.3, Priority Review Policy).

- **Chemistry Classification Code:** Codes that describe FDA's assessment of the relationship of the drug product in the application to active moieties and drug products already marketed or approved in the United States. Chemistry classification codes are usually mutually exclusive. However, a new combination (*4*) can contain a new molecular entity (*1*) or new salt (*2*). In such a case, the classification can be *Type 1,4*, *2,4*, or even *Type 1,2,4*.

- **New Molecular Entity (NME):** An active moiety that has not been previously approved or legally marketed as the active moiety in the United States in any drug product, either as a single ingredient, as part of a combination product, or as part of a mixture of stereoisomers.

- **New Chemical Entity (NCE):** As defined under 21 CFR 314.108(a), a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act).

- **Dosage Form:** The physical form of a drug product at the point that it is introduced into the body, or, when final preparation is required before introduction into the body, the physical form of the drug product in the package that bears instructions for final preparation (see the Orange Book, Appendix C; or the Electronic Orange Book, Uniform Terms).

- **Effectiveness (or Efficacy) Supplement Code:** A code that describes the type of supplemental application intended to make a significant change to the labeling of a drug.

- **Orange Book:** *Approved Drug Products With Therapeutic Equivalence Evaluations*, published by the FDA.

POLICY

General

- The chemistry classification code is tentatively assigned at the time of NDA submission and changes only if another drug product containing the same active moiety is approved first, or a reassessment of the validity of the assigned code is completed.

- A classification made under an IND (prior to submission of a marketing application) is optional and may be changed at the time the marketing application is submitted.

- When two or more NDAs for the same new active moiety are approved at the same time, the classification is changed for all but one. The NDA with the bulk of the efficacy data will be coded *Type 1* and the other NDA(s) reclassified, generally as *Type 3* or *Type 5*.

- Once the NDA is approved, codes are usually not subject to revision.

- Generally, only one chemistry classification code should be assigned, except that more than one code may be assigned to combination products (see *Type 4* and *Type 5*, subsection 5).

- **Chemistry Classification Codes**. The following codes are assigned to NDAs to describe their relationships to active moieties and drug products that are approved or legally marketed in the United States at the time the new application is submitted.

  Type 1 — New Molecular Entity

  1. An active moiety that has not been approved previously or marketed as the active moiety in

the United States in any drug product, either as a single ingredient, as part of a combination product, as part of a mixture derived from recombinant DNA technology or natural sources (e.g., isoforms of glycoproteins, botanical extracts), or as part of a mixture of stereoisomers. A pure enantiomer or a racemic mixture is a new molecular entity when neither has been approved previously or legally marketed. A pure enantiomer is not a new molecular entity when the racemate has been approved previously or legally marketed (see *Type 5*).

A **new *chemical* entity (*NCE*)**, as defined under 21 CFR 314.108(a), is a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Act. A **new *molecular* entity (NME)**, as defined above, is a drug that contains an active moiety that has never been approved by FDA or *marketed in the United States.* In most cases, a drug product that is classified as a new chemical entity will also be a new molecular entity, but there are exceptions. A drug product containing an active moiety that has been marketed without an application would be considered an NCE when submitted as an NDA but would ***not*** be considered an NME. For the purposes of classification under this MAPP, such an application would be classified as a *Type 7* NDA. On the other hand, a drug product containing an active moiety that had been neither approved by the FDA nor marketed in the United States, in combination with an active moiety that had already been approved by the FDA, would *not* be classified as an NCE, but it would be classified as an NME and new combination.

2. An active ingredient that is a chemical combination of two or more active moieties that have, or have not, been previously approved or marketed as a physical combination, if the chemical bond is stable both in vivo and in vitro and is a non-ester covalent bond, an ester bond, or a coordinate bond with a bond strength comparable to a covalent bond.

3. An active ingredient in a radiopharmaceutical (or radioactive drug) in which the active moiety has not been approved by the FDA or marketed in the United States. In addition, a change in the isotope from a stable isotope to a radioactive isotope or from one radioactive isotope to another, (e.g., a change from ^{131}I to ^{123}I), resulting in an active moiety with different physiochemical characteristics (i.e., nuclear and physical properties) that has never been approved by the FDA or marketed in the United States is considered an NME.

Type 2 — New Active Ingredient (New Salt, New Noncovalent Derivative, New Ester)

An active ingredient whose active moiety has been previously approved or marketed in the United States, but whose particular ester, salt, or noncovalent derivative of the unmodified parent molecule has not been approved or marketed in the United States, either alone or as part of a combination product. If the ester, salt, or noncovalent derivative is approved or marketed first, the unmodified parent molecule would be classified as a *Type 2*. The indication for the drug product does not need to be the same as that of the already marketed product containing the same active moiety (see *Type 5* below for classification of stereoisomeric active

ingredients).

Type 3 — New Dosage Form

A new dosage form of an active ingredient that has been approved or marketed in the United States by the same or another applicant but in a different dosage form. (See the Orange Book, Appendix C; or the Electronic Orange Book, Uniform Terms.) The indication for the drug product does not need to be the same as that of the already marketed drug product. Once a new dosage form has been approved for an active ingredient, subsequent applications for the same dosage form and active ingredient should be classified as *Type 5*.

Type 4 — New Combination

A drug product containing two or more active moieties that have not been previously approved or legally marketed together in the United States. A new combination product may have more than one chemical classification because each component of the combination may also have a chemical classification code (e.g., a new combination containing a new molecular entity would be classified *Type 1,4*). The new product may be a chemical (e.g., covalent ester or noncovalent derivative) or a physical combination of two or more active moieties.

An active ingredient that is a ***chemical combination*** of two or more previously approved or marketed active moieties that are linked by an ester bond that is not stable in vivo is considered to be a *Type 2,4* application if the active moieties have not been previously marketed or approved as a physical combination. If the physical combination has been previously legally marketed or approved, however, such a product would no longer be considered a *new* combination and would thus be classified as a *Type 2*. A physical combination does not refer to the non-ester covalent bond, ester bond or a coordinate covalent bond that is stable both in vivo and in vitro, as defined in *Type 1*.

A new ***physical combination*** may be two or more active ingredients combined into a single dosage form, or two or more active moieties packaged together with combined labeling. When at least one of the active moieties in the new physical combination has not been previously approved or legally marketed in the United States, the product is considered a *Type 1,4* drug.

Type 5 — New Formulation or New Manufacturer, Same or New Indication

A product, other than a new dosage form, that differs from a product already approved or marketed in the United States because of one of the following:

1. It involves changes in inactive ingredients that require either bioequivalence studies or clinical studies for approval and is submitted as an original new drug application rather than as a supplement by the applicant of the approved product.

2. It is a duplicate of a drug product by another applicant (same active moiety, same salt, same active ingredient, same dosage form, same or different indication, or same combination), and

   (a) it requires bioequivalence testing (including bioequivalence studies with clinical endpoints) but is not eligible for submission as a 505(j) application; or

   (b) it requires safety or effectiveness testing because of novel inactive ingredients; or

   (c) it requires full safety or effectiveness testing because

      (i) it is subject to marketing exclusivity held by another applicant, or

      (ii) it is a product of biotechnology and its safety and/or effectiveness are not assessable through bioequivalence testing, or

      (iii) it is a crude natural product, or

      (iv) it is ineligible for submission under 505(j) because it differs in bioavailability (e.g., superbioavailable products, products with different release patterns); or

   (d) the applicant has a right of reference to the application.

3. It contains an active ingredient that has been previously approved or marketed in the United States only as part of a combination. This applies to active ingredients previously approved or marketed as part of a manufactured combination, a mixture derived from recombinant DNA technology or natural sources, or a mixture of stereoisomers (e.g., a pure enantiomer when the racemic mixture has been previously approved or marketed).

4. It contains as an active ingredient a stereoisomeric enantiomer as part of a racemic mixture, and the pure enantiomeric form of the active ingredient has been previously approved or legally marketed.

5. It is a combination product that differs from a previously legally marketed combination by the removal of one or more active ingredients or by *substitution of a new ester or salt* or other noncovalent derivative of an active ingredient for one or more of the active ingredients. The latter would be classified as a *Type 2,5.*

6. It contains a different strength of one or more active ingredients in a previously approved or marketed combination. A *Type 5* NDA would generally be submitted by an applicant other than the holder of the approved application for the approved product. A similar change in an approved product by the applicant of the approved product would usually be submitted as a supplemental application.

7. It differs in bioavailability (e.g., superbioavailable, different controlled-release pattern) and, therefore, is ineligible for submission as an abbreviated new drug application (ANDA) under 505(j).

8. It involves a new plastic container that requires safety studies beyond limited confirmatory testing (see 21 CFR 310.509, Parenteral drug products in plastic containers, and MAPP 6020.2, Applications for Parenteral Products in Plastic Immediate Containers).

Type 6 — New Indication or Claim, Same Applicant

A drug product that duplicates a drug product already approved or marketed in the United States by the same applicant, except that it is intended for a new indication or claim (same active moiety or combination of active moieties, same salt(s), same dosage form, and same formulation (including all ingredients used in the manufacturing process whether or not they are present in the final dosage form)).

Type 7 — Drug Already Marketed but Without an Approved NDA

A drug product containing one or more active ingredients that are or have been marketed in the United States as active ingredients at the time of application or in the past without an approved NDA. Includes, but is not limited to:

1. The first post-1962 application for an active ingredient marketed prior to 1938

2. The first application for a DESI-related product first marketed between 1938 and 1962 without an NDA

3. The first application for a DESI-related product first marketed after 1962 without an NDA. The indications may be the same as, or different from, the marketed drug product.

4. The first application for a product that was first marketed without an NDA after 1962

Type 8a — Partial Rx to OTC Switch

An application by the holder of an approved NDA for the OTC marketing of only some of the indications, uses, or strengths of a previously approved prescription dosage form (while continuing to market other indications, uses, or strengths of the dosage form for prescription-only sale). An application by the holder of an approved NDA to switch to OTC status all prescription indications, uses, and strengths of the dosage form (leaving no prescription only products of that particular dosage form on the market) must be submitted as a Type 8b NDA. A Type 8a NDA may provide for a different dosing regimen, different strength, different dosage form, or different indication from the product approved previously for prescription sale.

Type 8b— Full Rx to OTC Switch

An application by the holder of an approved NDA to switch to OTC status all prescription indications, uses, and strengths of the dosage form (leaving no prescription only products of that particular dosage form on the market).

- **Application Classification Codes.** All appropriate letters should be included in the overall classification of the application, whether it is an original application (IND or NDA), or a supplemental application. Some of these classifications can be made only at the time of approval or only after submission of a marketing application, while others can be used at any stage of the drug development process and carried over to the NDA review.

  Where a code is used only for INDs or only for NDAs, the type of application is specified in the definition. Where the code is used on both INDs and NDAs, the definition uses the term "application."

  Type AA — Application for an AIDS Drug

  The drug product is indicated for the treatment of AIDS or HIV-related disease.

  Type C — Application Integrity Policy Applies — Review Continues

  Due to the public health importance of the drug product, review of the NDA continues although the Application Integrity Policy (AIP) has been applied to the application, and there is an ongoing validity assessment of the data (see Compliance Policy Guide (CPG) 7150.09). The C code replaces the F code previously associated with the application.

  Type D — Application Integrity Policy Applies — Data Invalid

  The AIP has been applied to the application. The validity assessment concluded the data in this application were not valid. The D code replaces the C or F code previously associated with the application.

  Type E — Subpart E Drug

  The drug product is being developed (IND) or evaluated (NDA) under the special procedures for drugs intended to treat life-threatening or severely debilitating illnesses codified at 21 CFR 312 subpart E, and 21 CFR 314.125(c).

  Type F — Application Integrity Policy Applies — Review Deferred

The AIP has been applied to this application. Substantive review of it is deferred pending the outcome of a validity assessment of the submitted data as provided for by CPG 7150.09. This code remains in the system when the applicant withdraws the application before the audit is completed or after the validity assessment is completed.

Type G — Application Integrity Policy Applies — Data Validated

The AIP has been applied to the application. A validity assessment was performed on the application as provided for by CPG 7150.09, and the questions regarding the reliability of the data were satisfactorily resolved. The G code replaces the F or C code previously associated with the application.

Type H — Accelerated Approval

The drug product is intended for a serious or life-threatening illness and provides a meaningful benefit over existing treatments **and** was submitted for review under the provisions of 21 CFR 314 subpart H (Accelerated Approval). The H code remains until all requirements under subpart H are either fulfilled or no longer applicable, at which time the H code is replaced with the K code.

Type K — Termination of Subpart H Requirements

The drug product was approved under the provisions of 21 CFR 314 subpart H. None of the requirements established under 21 CFR 314.510, 314.520, or 314.530 are necessary for the safe and effective use of the drug product. After traditional approval, the K code replaces the H code previously assigned to the application.

Type N — Nonprescription Drug

The drug product is labeled for over-the-counter (OTC) marketing. Applications will be labeled with an N designator whether all indications, or only some, are nonprescription.

Type V — Designated Orphan Drug

The drug product has been designated as a drug for a rare disease or condition under section 526 of the Act.

- **Effectiveness (or Efficacy) Supplement Codes**

The following classification codes should be used for supplemental applications.

SE1 A new indication or a significant modification of an existing indication, including removal of a limitation to use, such as second-line status.

SE2 A new dosage regimen, including an increase or decrease in daily dosage, or a change in frequency of administration.

SE3 A new route of administration without a change of any kind in formulation for the drug product. Under CDER's guidance, *Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*, a separate NDA would be submitted for a new route of administration that requires a new formulation.

SE4 A comparative efficacy claim naming another drug.

SE5 A change in labeling that significantly alters the patient population to be treated, such as addition of pediatric use and/or dosing information, geriatric use and/or dosing information, or addition of use in another gender (e.g., in pregnancy, or in women of child-bearing potential).

SE7 A supplemental application that completes the requirements for the clinical studies required as a condition of approval under 21 CFR 314.510 subpart H.

SE8 A labeling supplement proposing any changes in the labeling of a new drug other than the changes described under SE1 through SE7, that requires clinical data, as defined for the purpose of assessing user fees, to form the primary basis of approval. The clinical data may be cross-referenced to another application/supplement.

RESPONSIBILITIES

The OND Review Division Project Management Staff will:

1. Determine, in consultation with the appropriate reviewers and/or team leaders, the chemical and any application classification codes for new INDs and NDAs and effectiveness codes for approved NDAs. Responsibility for determining the chemical classification lies with ONDC.

2. Ensure that all appropriate classification codes are entered into COMIS upon receipt of a new IND, NDA, or supplemental application and update as needed.

3. Ensure that when two or more applications for the same new active moiety are approved at the same time, the Division Document Room changes the classification of all but one (see *Policy: General*).

EFFECTIVE DATE

This MAPP is effective upon date of publication.