
POLICY AND PROCEDURES

Office of Pharmaceutical Quality**NDA Classification Codes**

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PURPOSE

This MAPP describes the new drug application (NDA) classification code assigned by the Center for Drug Evaluation and Research (CDER) to an NDA based on characteristics of the product in the application. This code was previously referred to as “Chemistry Classification Code.”

BACKGROUND

- The NDA classification code provides a way of categorizing new drug applications. The code evolved from both a management and a regulatory need to identify and group product applications based on certain characteristics, including their relationships to products already approved or 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.
 - The NDA classification codes are not determinative of classification for purposes of exclusivity. These codes are not indicative of the extent of innovation or therapeutic value that a particular drug represents.
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POLICY

- FDA tentatively assigns an NDA classification code by the filing date for a new application and reassesses the code at the time of approval. The reassessment will be based upon relationships of the drug product being approved to products already

approved or marketed in the United States at the time of approval. FDA may also reassess the code after approval.

- FDA can tentatively determine a classification code for an investigational new drug (IND) prior to submission of a marketing application. This can be useful particularly with regard to whether or not the active ingredient in the IND may be considered to contain a new molecular entity (NME). Any determination of the chemical type during the IND stage is performed as part of review and may be revised when the marketing application is submitted, or upon approval, or after approval.
- When two or more NDAs for the same active ingredient tentatively considered as an NME are submitted by the same applicant and approved at the same time, the classification is changed for all but one NDA. In this case, the decision as to which NDA should be coded *Type 1* may depend on factors other than timing. For example, the NDA with the bulk of the efficacy data could be coded *Type 1* and the other NDA(s) reclassified, generally as *Type 3* or *Type 5*.¹
- Generally, only one NDA classification code should be assigned, except that more than one code may be assigned to combination products (see *Type 4* and *Type 5*, subsection 4).

NDA Classification Codes

Type 1 — New Molecular Entity

A *Type 1* NDA is for a drug product that contains an NME.² An NME is an active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under section 505 of the Act³ or has been previously marketed as a drug in the United States. A pure enantiomer or a racemic mixture is an NME only when neither has been previously approved or marketed.

An NDA for a drug product containing an active moiety that has been marketed as a drug in the United States, but never approved in an application submitted under section 505 of the Act, would be considered *Type 7*, not *Type 1*.

An NDA for a drug-drug⁴ combination product containing an active moiety that is an NME in combination with another active moiety that had already been approved by the

¹ Even though the NDA(s) may be reclassified in this circumstance, the Agency does not consider the active moieties to be previously approved at the time of approval of these NDA(s). The reclassification is made only for administrative purposes.

² The terms *New Molecular Entity (NME)* and *New Chemical Entity (NCE)* are sometimes used interchangeably; however, they are distinct. An NCE is defined in 21 CFR 314.108(a) as “a drug that contains no active moiety that has been approved by the FDA in any other application submitted under 505(b) of the Act.” The term NME is not defined in the statute or regulations. An NME is an active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under section 505 of the Act or has been previously marketed as a drug in the United States.

³ This applies to applications approved or deemed approved from 1938 to the present.

⁴ For example, a drug-drug combination can include a fixed-combination drug product or a co-packaged drug product with two or more active moieties.

FDA would be classified as a new combination containing an NME (*Type 1,4*).

An active moiety in a radiopharmaceutical (or radioactive drug) which has not been approved by the FDA or marketed in the United States is classified as an NME.

In addition, if a change in isotopic form (e.g., a change from ^{131}I to ^{123}I , ^{12}C to ^{13}C) results in an active moiety that has never been approved by the FDA or marketed in the United States, the active ingredient is classified as an NME.

Type 2 — New Active Ingredient

A *Type 2* NDA is for a drug product that contains a new active ingredient, but not an NME. A new active ingredient includes those products 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 by the Agency or marketed in the United States, either alone, or as part of a combination product. Similarly, if any ester, salt, or noncovalent derivative has been marketed first, the unmodified parent molecule would also be considered a new active ingredient, but not an NME. 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.

If the active ingredient is a single enantiomer and a racemic mixture containing that enantiomer has been previously approved by the FDA or marketed in the United States, or if the active ingredient is a racemic mixture containing an enantiomer that has been previously approved by the FDA or marketed in the United States, the NDA will be classified as a *Type 2*.

Type 3 — New Dosage Form

A *Type 3* NDA is for 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 for examples of dosage forms.) 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 *Type 4* NDA is for a new drug-drug combination of two or more active ingredients. An application for a new drug-drug combination product may have more than one classification code if at least one component of the combination is an NME or a new active ingredient. The new product may be a physical or chemical (e.g., covalent ester or noncovalent derivative) combination of two or more active moieties.

A new ***physical combination*** may be two or more active ingredients combined into a single dosage form, or two or more drug products packaged together with combined labeling. When at least one of the active moieties is classified as an NME, the NDA is classified as a *Type 1,4* application. When none of the active moieties is an NME, but at

least one is a new active ingredient, the NDA is classified as a *Type 2,4* application.

An NDA for 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 is classified as 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 marketed or approved, however, such a product would no longer be considered a *new* combination and the NDA would thus be classified as a *Type 2*.

Type 5 — New Formulation or Other Differences (e.g., new indication, new applicant, new manufacturer)

A *Type 5* NDA is for 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. The product involves changes in inactive ingredients that require either bioequivalence studies or clinical studies for approval and is submitted as an original NDA rather than as a supplement by the applicant of the approved product.
2. The product is a duplicate of a drug product by another applicant (same active ingredient, same dosage form, same or different indication, or same combination), and
 - (a) requires bioequivalence testing (including bioequivalence studies with clinical endpoints), but is not eligible for submission as a section 505(j) application; or
 - (b) requires safety or effectiveness testing because of novel inactive ingredients; or
 - (c) requires full safety or effectiveness testing because it is:
 - (i) subject to exclusivity held by another applicant, or
 - (ii) a product of biotechnology and its safety and/or effectiveness are not assessable through bioequivalence testing, or
 - (iii) a crude natural product, or
 - (iv) ineligible for submission under section 505(j) because it differs in bioavailability (e.g., products with different release patterns); or
 - (d) the applicant has a right of reference to the application.
3. The product contains an active ingredient or active moiety 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 physical or chemical combination, or as part of a

mixture derived from recombinant DNA technology or natural sources.

4. The product is a combination product that differs from a previously 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. In the latter case, the NDA would be classified as a *Type 2,5*.
5. The product 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.
6. The product differs in bioavailability (e.g., superbioavailable or different controlled-release pattern) and, therefore, is ineligible for submission as an abbreviated new drug application (ANDA) under section 505(j).
7. The product 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

This NDA classification code is no longer used and is replaced with *Type 9* and *Type 10*. This classification is retained in the MAPP for historical reasons.

A *Type 6* NDA was used for an NDA received prior to July 27, 2009,⁵ for 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), ester(s), or other noncovalent derivative(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 — Previously Marketed But Without an Approved NDA

A *Type 7* NDA is for a drug product that contains an *active moiety* that has not been previously approved in an application, but has been marketed in the United States. This classification applies only to the first NDA approved for a drug product containing this (these) active moiety(ies).

Type 7 NDAs include, but are not limited to:

- (1) The first post-1962 application for an active moiety marketed prior to 1938.

⁵ July 27, 2009 is the date of implementation of the Document Archiving, Reporting and Regulatory Tracking System (DARRTS), which made *Type 6* obsolete.

- (2) The first application for an active moiety first marketed between 1938 and 1962 that is identical, related or similar (IRS)⁶ to a drug covered by a Drug Efficacy Study Implementation (DESI) notice.
- (3) The first application for an IRS drug product first marketed after 1962.
- (4) The first application for an active moiety that was first marketed without an NDA after 1962.

Type 8 — Rx to OTC

A *Type 8* NDA is for a drug product intended for over-the-counter (OTC) marketing that contains an active ingredient that has been approved previously or marketed in the United States only for dispensing by prescription (OTC switch). A *Type 8* NDA may provide for a different dosing regimen, different strength, different dosage form, or different indication from the product approved previously for prescription sale.

If the proposed OTC switch will apply to all indications, uses, and strengths of an approved prescription dosage form (leaving no prescription-only products of that particular dosage form on the market), the application holder should submit the change as a supplement to the approved application. If the applicant intends to switch only some indications, uses, or strengths of the dosage form to OTC status (while continuing to market other indications, uses, or strengths of the dosage form for prescription-only sale), the applicant should submit a new NDA for the OTC products, which would be classified as *Type 8*.

Type 9 — New Indication or Claim, Drug Not to be Marketed Under *Type 9* NDA After Approval

A *Type 9* NDA is for a new indication or claim for a drug product that is currently being reviewed under a different NDA (the “parent NDA”), and the applicant does not intend to market this drug product under the *Type 9* NDA after approval. Generally, a *Type 9* NDA is submitted as a separate NDA so as to be in compliance with the guidance for industry on *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*.

Note: When the *Type 9* NDA is submitted, it will be given the same NDA classification as the pending NDA. When one application is approved, the other will be reclassified as *Type 9* regardless of whether it was the first or second NDA actually submitted. After the approval of a *Type 9* NDA, FDA will “administratively close” the *Type 9* NDA and thereafter only accept submissions to the “parent” NDA.

Type 10 — New Indication or Claim, Drug to be Marketed Under *Type 10* NDA After Approval

⁶ FDA’s regulation at 21 CFR 310.6(b)(1) states that: “An identical, related, or similar drug includes other brands, potencies, dosage forms, salts, and esters of the same drug moiety as well as any of drug moiety related in chemical structure or known pharmacological properties.”

A *Type 10* NDA is for a drug product that is a duplicate of a drug product that is the subject of either a pending or approved NDA, and the applicant intends to market the drug product under this separate *Type 10* NDA after approval. A *Type 10* NDA is normally for a drug product that has a new indication or claim, and it may have labeling and/or a proprietary name that is distinct from that of the original NDA.

Note: When the *Type 10* NDA is submitted, it will be given the same NDA classification as the original NDA unless that NDA is already approved. When one application is approved, the other will be reclassified as *Type 10* regardless of whether it was the first or second NDA actually submitted.

Medical Gas — A Designated Medical Gas Certification Request Submitted Under Section 576 of the FD&C Act

A designated medical gas certification request is a request submitted under Section 576 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to certify a medical gas as a designated medical gas.⁷ The requests for Designated Medical Gas Certification for Use in Humans will result in assignment of an NDA number and will have the effect of an approved NDA unless denied within 60 days of filing.

RESPONSIBILITIES

Office of New Drugs (OND) Review Division Project Management Staff will:

- Request a determination of NDA classification codes for new and proposed NDAs from the appropriate Quality Assessment Team.
- Prior to approval of the NDA, request confirmation from the Quality Assessment Team that the NDA classification is still correct.

Quality Assessment Team will:

- Determine the NDA classification codes for new or proposed NDAs, and file a written determination to the administrative record of the IND and/or NDA.
- Prior to approval of the NDA, reassess the NDA classification and document the final classification in the administrative record for the NDA.

Office of Pharmaceutical Quality (OPQ) Regulatory Business Process Manager will:

- Update the administrative record with the current NDA classification code by the filing date.

⁷ See FDA guidance for industry on *Certification Process for Designated Medical Gases*.

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- At the time of approval, verify the classification code with the Quality Assessment Team, and update, as necessary.
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POINTS TO CONSIDER

ESTERS

FDA's regulations at 21 CFR 314.108(a) define the term "active moiety" to mean "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." Esters are, thus, the only molecules containing only covalent bonds for which the active moiety is not the entire molecule. Esters are comprised of an alcohol and an acid fragment, and because either or both of the fragments may be "responsible for the physiological or pharmacological action of the drug substance," either or both may be considered an "active moiety." Whether the ester is stable in vivo, i.e., not metabolized to its constituent alcohol and acid fragments, is not a consideration in the "active moiety" determination. For example, the Agency determined that for purposes of NCE exclusivity, fluticasone furoate contained a previously approved "active moiety," fluticasone, despite the fact that there is no evidence of in vivo cleavage of the ester.⁸

METAL-CONTAINING SUBSTANCES

In the case of drugs containing metals, other than salts, the active moiety may be a coordination complex or chelate of the metal (e.g., gadobutrol), rather than the metal ion itself. This is the case when the complex or chelate has at least one metal-ligand bond that can be considered to be a covalent bond.

To determine whether a metal-ligand bond is covalent, the Agency applies a "weight-of-evidence" test for covalency based on a consideration of data based on factors, such as:

- Evidence of bond energies, and inter-atomic distances consistent with covalent bonds;
- Evidence of existence as independent entity (e.g., elutes in a single chromatographic peak);
- A substantially large equilibrium constant for dissociation of the complex in water (e.g., on the order of 10^{20} for gadolinium contrast agents⁹);
- Observed geometry predicted by theory; and
- A well-defined stoichiometry.

⁸ NDA 22-051: Clinical Pharmacology Biopharmaceutics Review, p. 10, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022051s000_ClinPharmR.pdf; Pharmacology Review, p. 26 http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022051s000_PharmR.pdf.

⁹ Caravan P, Ellison JJ, McMurry TJ, & Lauffer RB, 1999, Gadolinium (III) chelates as MRI contrast agents: structure, dynamics, and applications, Chemical Reviews, 99(9):2293-2352.

REFERENCES

1. IUPAC [International Union of Pure and Applied Chemistry] Compendium of Chemical Terminology -- the Gold Book, <http://goldbook.iupac.org/>.
 2. Orange Book: *Approved Drug Products With Therapeutic Equivalence Evaluations*, published by the FDA, <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.
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DEFINITIONS

- **Act:** the Federal Food, Drug, and Cosmetic Act.
 - **Active Ingredient:** A component of the drug product that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The component can be a single chemical substance that includes the appended portions of the molecule that make it a particular salt or other noncovalent derivative or ester. The component can also be a naturally-derived mixture.
 - **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)).
 - **Dosage Form:** The physical manifestation containing the active and inactive ingredients that delivers a dose of the drug product. This includes such factors as: (1) the physical appearance of the drug product, (2) the physical form of the drug product prior to dispensing to the patient, (3) the way the product is administered, and (4) the design features that affect frequency of dosing.
 - **NDA Classification Code:** Codes that describe FDA's assessment of the relationship of the drug product in the application to its active moieties and to drug products already marketed or approved in the United States. NDA 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 other coding.
 - **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 Act.
 - **New Molecular Entity (NME):** An active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under section 505 of the Act or has been previously marketed as a drug in the United States.
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EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions