

Draft Guidance for Industry: Referencing Approved Drug Products in ANDA Submissions

Guidance Purpose and Goals

- To help applicants submitting an abbreviated new drug application (ANDA) to seek approval of a generic drug to identify:
 - A reference listed drug (RLD), i.e., a previously approved drug product for which an applicant seeks approval of a generic drug;
 - a reference standard, i.e., the previously approved drug selected by FDA that an applicant must use in conducting any in vivo bioequivalence testing required to support approval of its ANDA; and
 - the basis of submission for the ANDA.



Statutory Background

Section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) permits any person to submit to the Food and Drug Administration (FDA) an ANDA to seek approval to market a generic drug.

The Cornerstone of ANDA Approval

To obtain approval for a generic drug, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug. Instead, the applicant relies on the FDA's finding that a previously approved drug product, i.e., the RLD, is safe and effective, and must demonstrate, among other things, that the proposed generic drug is the same as the RLD in certain ways.

Evidence to Support Approval of an ANDA

Among other things, an applicant must generally show that its proposed generic drug:

- Has the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD;
- Is bioequivalent to the RLD; and
- Meets the same high standards of quality and manufacturing as new drug products approved under new drug applications (NDAs).

Definitions

- Listed drug
- Reference listed drug
- Reference standard
- Basis of submission

Listed Drug

- A “listed drug” is a new drug that has been approved under section 505(c) of the FD&C Act for safety and effectiveness or under section 505(j) of the FD&C Act, and which has not been withdrawn for reasons of safety or effectiveness.
- A drug product is deemed to be a listed drug on the date of approval and is identified in FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations* (commonly referred to as the Orange Book).
- The electronic Orange Book is available at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>

Reference Listed Drug

- An RLD is the specific listed drug on which the ANDA applicant relies in seeking approval of its ANDA, i.e., the approved drug product the proposed generic drug is intended to duplicate.
- FDA identifies in the Orange Book listed drugs that are eligible to be RLDs.



FDA's Identification of Listed Drugs Eligible to be RLDs

- Because an ANDA applicant is relying on FDA's finding that the RLD is safe and effective, the RLD must be a drug product approved under section 505(c) of the FD&C Act for which FDA has made a finding of safety and effectiveness.
- Generally, FDA will not designate a drug product approved through the 505(b)(2) pathway as an RLD unless it is requested to do so and designation would ensure that the drug product approved is not shielded from generic competition.



Identification of Potential RLDs in the Orange Book

In the printed version of the Orange Book, an RLD will be identified by the “+” symbol.

ACETYLCYSTEINE

New NDA with RLD and RS

>A> TABLET, EFFERVESCENT;ORAL

>A> CETYLEV

>A> + ARBOR PHARMS LLC 500MG N207916 001 Jan 29, 2016 Jan NEWA

>A> +! 2.5GM N207916 002 Jan 29, 2016 Jan NEWA



Identification of Potential RLDs in the Orange Book

In the electronic Orange Book, an RLD is identified by “RLD” in the RLD column.

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD RS	Applicant Holder
RX	ARMODAFINIL	ARMODAFINIL	A200043	TABLET	ORAL	50MG	AB		MYLAN PHARMACEUTICALS INC
RX	ARMODAFINIL	ARMODAFINIL	A200043	TABLET	ORAL	150MG	AB		MYLAN PHARMACEUTICALS INC
RX	ARMODAFINIL	ARMODAFINIL	A200043	TABLET	ORAL	250MG	AB		MYLAN PHARMACEUTICALS INC
RX	ARMODAFINIL	NUVIGIL	N021875	TABLET	ORAL	50MG	AB	RLD	CEPHALON INC
RX	ARMODAFINIL	NUVIGIL	N021875	TABLET	ORAL	150MG	AB	RLD	CEPHALON INC
RX	ARMODAFINIL	NUVIGIL	N021875	TABLET	ORAL	200MG		RLD	CEPHALON INC
RX	ARMODAFINIL	NUVIGIL	N021875	TABLET	ORAL	250MG	AB	RLD RS	CEPHALON INC
DISCN	ARMODAFINIL	ARMODAFINIL	A200156	TABLET	ORAL	100MG			WATSON LABORATORIES INC
DISCN	ARMODAFINIL	ARMODAFINIL	A200156	TABLET	ORAL	200MG			WATSON LABORATORIES INC
DISCN	ARMODAFINIL	NUVIGIL	N021875	TABLET	ORAL	100MG		RLD	CEPHALON INC

Choosing an RLD

- An ANDA applicant must choose an RLD.
- If the applicant has a question about which listed drug it should identify as the RLD, the applicant may submit a control to FDA prior to submission of its ANDA.
- If FDA has not designated an RLD for the drug product the ANDA applicant intends to duplicate, the applicant may submit controlled correspondence to FDA asking it to designate an RLD for that drug product.
- If FDA has designated an RLD for the drug product but the potential applicant seeks to refer to a different drug product as its RLD, the applicant may submit a citizen petition to request that FDA designate that different listed drug as an additional RLD.

RLD for a Petitioned ANDA

- Under the law, an ANDA applicant may submit an ANDA for a generic drug that is not the *same* as its RLD because it has one different active ingredient (in a fixed combination drug product), or has a different route of administration, dosage form, or strength than that of the RLD, if the applicant first obtains permission from FDA under a citizen petition. Such petitions are referred to as *suitability petitions*.
- The RLD for a “Petitioned ANDA” must be the same as the listed drug identified in the approved suitability petition.

The Role of an RLD in an ANDA

- The RLD is the listed drug to which the ANDA applicant must show its proposed generic drug is the same with respect to active ingredient(s), dosage form, route of administration, strength, conditions of use, and (with certain permissible exceptions) labeling.
- The ANDA applicant must also demonstrate that the proposed generic drug is bioequivalent to the RLD.
- If the applicant seeks to change its RLD, the applicant must submit a new ANDA.

Reference Standard

- If bioequivalence is not self-evident, there are a variety of methods by which bioequivalence may be demonstrated, including in vivo studies (in human subjects), in vitro studies (conducted in a laboratory), or both.
- A “reference standard” is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval of an ANDA.

FDA's Selection of a Reference Standard

- To facilitate generic drug development, FDA generally selects a single reference standard to ensure the greatest level of consistency between a generic drug and its RLD and among generic drugs.
- Where the RLD is marketed, ordinarily it is also the drug product selected by FDA as the reference standard.
- But, where the RLD has been discontinued from marketing for other than safety or effectiveness reasons, FDA may select a different approved drug to serve as the reference standard.

FDA's Selection of a Reference Standard

- FDA usually selects as the reference standard the highest strength available for drug products with multiple strengths.
- In instances in which FDA cannot select the RLD as the reference standard and there are multiple approved generic products to that RLD, FDA usually selects the generic market leader, based on units sold, as the reference standard.

Selection of a New Reference Standard

- In making a decision whether to select a new reference standard, FDA may consider, among other things:
 - Whether the listed drug that is the reference standard is no longer marketed;
 - Whether the RLD has been withdrawn from sale for reasons of safety or effectiveness*;
 - Whether selecting a new reference standard would help prevent a shortage of a particular drug product or category of drug products.
- Now FDA also will consider selecting a new reference standard when FDA determines the quantity of the current reference standard in distribution is so limited that a potential ANDA applicant is not able to obtain a sufficient quantity for in vivo testing.

* When FDA has made a determination that an RLD has been withdrawn for reasons of safety or effectiveness, FDA will not select a new reference standard.

Reference Standards and the Orange Book

- Prior to 2017, the column in the Orange Book labeled “RLD” at times indicated the drug product FDA selected as the reference standard, leading to the confusion about which drug is the RLD and which drug is the reference standard.
- Starting in 2017, FDA intends to modify the Orange Book to clarify which drugs are RLDs and which are reference standards.



Identification of the Reference Standard in the Orange Book

In the printed version of the Orange Book, the reference standard selected by FDA for a drug product will be identified by the “!” symbol.

ACETYLCYSTEINE

New NDA with RLD and RS

>A> TABLET, EFFERVESCENT;ORAL

>A> CETYLEV

>A> + ARBOR PHARMS LLC 500MG N207916 001 Jan 29, 2016 Jan NEWA

>A> +! 2.5GM N207916 002 Jan 29, 2016 Jan NEWA

Identification of the Reference Standard in the Orange Book

In the electronic Orange Book, a reference standard is identified by “RS” in the RS column.

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	ARMODAFINIL	ARMODAFINIL	A200043	TABLET	ORAL	50MG	AB			MYLAN PHARMACEUTICALS INC
RX	ARMODAFINIL	ARMODAFINIL	A200043	TABLET	ORAL	150MG	AB			MYLAN PHARMACEUTICALS INC
RX	ARMODAFINIL	ARMODAFINIL	A200043	TABLET	ORAL	250MG	AB			MYLAN PHARMACEUTICALS INC
RX	ARMODAFINIL	NUVIGIL	N021875	TABLET	ORAL	50MG	AB	RLD		CEPHALON INC
RX	ARMODAFINIL	NUVIGIL	N021875	TABLET	ORAL	150MG	AB	RLD		CEPHALON INC
RX	ARMODAFINIL	NUVIGIL	N021875	TABLET	ORAL	200MG		RLD		CEPHALON INC
RX	ARMODAFINIL	NUVIGIL	N021875	TABLET	ORAL	250MG	AB	RLD	RS	CEPHALON INC
DISCN	ARMODAFINIL	ARMODAFINIL	A200156	TABLET	ORAL	100MG				WATSON LABORATORIES INC
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DISCN	ARMODAFINIL	NUVIGIL	N021875	TABLET	ORAL	100MG		RLD		CEPHALON INC

Requesting Selection of a Reference Standard

If there is no reference standard in the Active Section of the Orange Book (i.e., in the section entitled “Prescription Drug Product List” or “Over-the-Counter Drug Product List”) for a drug product the applicant intends to duplicate, a potential applicant may submit controlled correspondence to FDA asking it to select a reference standard for that drug product.

Requesting Selection of a Reference Standard

If there is a reference standard in the Active Section of the Orange Book for a drug product the applicant intends to duplicate but there are limited or no quantities in distribution, or a potential ANDA applicant believes a reference standard other than the one selected by FDA is appropriate, then the potential applicant may submit a citizen petition to FDA to request that it select that different listed drug as a reference standard.

Basis for ANDA Submission

- Regulations require an ANDA to contain a “basis for ANDA submission” (referred to as the basis of submission or BOS).
- In most instances, the RLD should be referred to in an ANDA as the basis of submission.
- The RLD should be provided as the BOS on Form FDA 356h and in the appropriate sections of the ANDA (e.g., section 1.12.11).

Basis of Submission – Petitioned ANDAs

The basis of submission for a petitioned ANDA is:

- (1) the RLD, which must be the same as the listed drug identified in the approved suitability petition;
- (2) a reference to the suitability petition's FDA-assigned docket number; and
- (3) a copy of FDA's correspondence approving the suitability petition.

More detail is provided in the guidance.

Basis of Submission and the Reference Standard

While the reference standard is not part of the basis of submission, it should be identified in the relevant sections of the ANDA that include information pertaining to bioequivalence, e.g.,

- section 1.12.11 which provides information about the drug product including bioequivalence, and
- 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods.



Please contact CDERSBIA@fda.hhs.gov with any questions. Thank you.