Referencing Approved Drug Products in ANDA Submissions

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General Framework for ANDAs

- Approval of generic drug starts with listed drug – generally an innovator drug approved under section 505(c) of the FD&C Act
- ANDA relies on FDA's finding of safety and effectiveness for RLD
- Requires demonstration of "sameness" of a number of characteristics + additional information to permit reliance on RLD

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

Guidance for Industry: Referencing Approved Drug Products in ANDA Submissions

- Clarify terms:
  - Listed drug
  - Reference listed drug
  - Reference standard
  - Basis of submission
- How to request:
  - Designation of an RLD
  - Selection of a reference standard

Listed Drug

- Approved under:
  - Section 505(c) of the FD&C Act for safety and effectiveness OR
  - Section 505(j) of the FD&C Act

AND

- Has not been withdrawn for reasons of safety or efficacy

Reference Listed Drug

- The listed drug an ANDA relies upon in seeking approval
- FDA identifies RLDs in the Orange Book

Identification of RLDs in Orange Book

Printed version:

- Identified by “+” symbol

APIXABAN					
TABLET;ORAL					
ELIQUIS					
+	BRISTOL MYERS SQUIBB	2.5MG		N202155 001	Dec 28, 2012
+		5MG		N202155 002	Dec 28, 2012

Identification of RLDs in Orange Book

Electronic version:

- Identified by RLD in RLD column

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	APIXABAN	ELIQUIS	N202155	TABLET	ORAL	2.5MG		RLD		BRISTOL MYERS SQUIBB CO PHARMACEUTICAL RESEARCH INSTITUTE
RX	APIXABAN	ELIQUIS	N202155	TABLET	ORAL	5MG		RLD	RS	BRISTOL MYERS SQUIBB CO PHARMACEUTICAL RESEARCH INSTITUTE

Choosing an RLD

- ANDA applicant must choose RLD
- Questions?
  - Submit controlled correspondence

Petitioned ANDAs

- May submit ANDA with change from listed drug:
  - Route of administration
  - Dosage form
  - Strength
  - One different active ingredient (in a fixed combination drug product)
- See 21 CFR 314.93

RLD for Petitioned ANDA

- Must be the same as the listed drug identified in approved suitability petition

Reference Standard

- Product applicant must use in conducting in vivo bioequivalence study
- Selected by FDA
- Identified in Orange Book

Identification of Reference Standard

Printed version:

- Identified by “!” symbol

APIXABAN
TABLET;ORAL
ELIQUIS

+	BRISTOL MYERS SQUIBB	2.5MG	N202155 001	Dec 28, 2012
+!		5MG	N202155 002	Dec 28, 2012

Identification of Reference Standard

Electronic version:

- Identified by RS in RS column

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	APIXABAN	ELIQUIS	N202155	TABLET	ORAL	2.5MG		RLD		BRISTOL MYERS SQUIBB CO PHARMACEUTICAL RESEARCH INSTITUTE
RX	APIXABAN	ELIQUIS	N202155	TABLET	ORAL	5MG		RLD	RS	BRISTOL MYERS SQUIBB CO PHARMACEUTICAL RESEARCH INSTITUTE

Basis for ANDA Submission

- ANDA must contain basis for ANDA submission
- Usually this is the RLD
  - Exception: Petitioned ANDAs

Basis of Submission – Petitioned ANDA

1) The RLD – must be the same as the listed drug in the approved suitability petition
2) Reference to suitability petition's FDA-assigned docket number
3) Copy of correspondence approving the suitability petition

Examples

Example #1: RLD in Active Section

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	MOMETASONE FUROATE	MOMETASONE FUROATE	A207989	SPRAY, METERED	NASAL	EQ 0.05MG BASE/SPRAY	AB			AMNEAL PHARMACEUTICALS
RX	MOMETASONE FUROATE	MOMETASONE FUROATE	A091161	SPRAY, METERED	NASAL	EQ 0.05MG BASE/SPRAY	AB			APOTEX INC
RX	MOMETASONE FUROATE	NASONEX	N020762	SPRAY, METERED	NASAL	EQ 0.05MG BASE/SPRAY	AB	RLD	RS	MERCK SHARP AND DOHME CORP

RLD and RS

Identify RLD:

- Form FDA 356h Field 20
- ANDA section 1.12.11

Identify RS:

- ANDA sections 1.12.11, 2.7.1, 5.2, and 5.3.1

Example #2: RLD in Disc Section

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	AZELASTINE HYDROCHLORIDE	AZELASTINE HYDROCHLORIDE	A203660	SOLUTION/DROPS	OPHTHALMIC	0.05%	AT			AKORN INC
RX	AZELASTINE HYDROCHLORIDE	AZELASTINE HYDROCHLORIDE	A078621	SOLUTION/DROPS	OPHTHALMIC	0.05%	AT			APOTEX INC RICHMOND HILL
RX	AZELASTINE HYDROCHLORIDE	AZELASTINE HYDROCHLORIDE	A202305	SOLUTION/DROPS	OPHTHALMIC	0.05%	AT		RS	SANDOZ INC
RX	AZELASTINE HYDROCHLORIDE	AZELASTINE HYDROCHLORIDE	A078738	SOLUTION/DROPS	OPHTHALMIC	0.05%	AT			SUN PHARMA GLOBAL INC
DISCN	AZELASTINE HYDROCHLORIDE	OPTIVAR	N021127	SOLUTION/DROPS	OPHTHALMIC	0.05% **Federal Register dete ation that product was not discontinued thdrawn for safety or efficacy reasons**		RLD		MYLAN SPECIALTY LP

RLD

RS


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