



**RESEARCH ARTICLE**

**COMPARATIVE STUDY OF REFERENCE PRODUCTS IN GENERIC DRUG  
DEVELOPMENT IN U.S. AND EUROPE**

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**INTRODUCTION**

- According to the U.S. Food and Drug Administration (FDA), generic drugs are identical or within an acceptable bioequivalent range to the brand-name counterpart with respect to pharmacokinetic and pharmacodynamic properties.
- Therefore, generics are considered (by the FDA) identical in dose, strength, route of administration, safety, efficacy, and intended use.
- When generic products become available, the market competition often leads to substantially lower prices for both the original brand name product and the generic forms.

**Definition of Generic Drug Product**

- "Medicinal product which has same qualitative and quantitative composition in active substances as well as same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies".

**Basic Generic Drug Requirements**

- Same active ingredient(s), Same route of administration, Same dosage form, Same strength, Same conditions of

**ABSTRACT**

Generic medicines are those where patent protection has expired of innovator drug and which may be produced by manufacturers other than the innovator company. So for develop a new Generic drugs it should be bioequivalent to Reference drug. A standard reference product may avoid possible significant variations among generic drug products and their brand name counterparts Reference product are regulated in different countries. In USA they are listed in Approved drug products list with therapeutic equivalence evaluation commonly known as "orange book" with the patent information. It includes all products that have been approved by FDA for safety and effectiveness, alphabetically by ingredients in the products. In Europe, reference drug is known as Reference Medicinal Product or European Reference Product. In the present article focuses on the regulation of Reference product in U.S. and Europe.

use, Inactive ingredients already approved in a similar NDA

**ANDA Submission**

- The applicant Should Provide :
- The name of the RLD, the NDA or ANDA number of the RLD, the holder of the application for the RLD.
- To demonstrate the comparison to the RLD, applicants provide:

A statement that the conditions of use for the generic product have been previously approved for the RLD, information to show that the active ingredient(s) is the same as the RLD, information to show that the route of administration, dosage form and strength are the same as those of the RLD, as applicable, information to indicate the strength of the generic drug product used in the in vivo bioequivalence studies (fasting and fed) to demonstrate bioequivalence of the generic drug product to the RLD.

**Regulation of RLD in U.S**

**Definition**

"A Reference Listed Drug (RLD) is an approved drug product to which new generic versions are compared to show that they

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are bioequivalent. A drug company seeking approval to market a generic equivalent must refer to the Reference Listed Drug in its Abbreviated New Drug Application (ANDA).

- RLD is generally the innovator drug product (“Brand”) which is marketed on the basis of a full dossier (e.g., New Drug Application) that includes chemical, biological, safety, clinical efficacy, labeling, etc
- A standard RLD may avoid possible significant variations among generic drug products and their brand name counterparts.
- RLD is listed in Approved Drug Products with Therapeutic Equivalence Evaluations, “Orange Book”,
- A reference listed drug means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.
- By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart.
- And it results if generic drugs were compared to different reference listed drugs. However, in some instances when listed drugs are approved for a single drug product, a product not designated as the reference listed drug and not shown to be bioequivalent to the reference listed drug may be shielded from generic competition.
- A firm wishing to market a generic version of a listed drug that is not designated as the reference listed drug may petition the Agency through the Citizen Petition procedure.
- When the Citizen Petition is approved, the second listed drug will be designated as an additional reference listed drug and the petitioner may submit an Abbreviated New Drug Application citing the designated reference listed drug.
- In addition, there are two situations in which two listed drugs that have been shown to be bioequivalent to each other may both be designated as reference listed drugs.
- The first situation occurs when the in vivo determination of bioequivalence is self-evident and a waiver of the in vivo bioequivalence may be granted.
- The second situation occurs when the bioequivalence of two listed products may be determined through in vitro methodology.

#### Orange book

- The reference listed drug is identified by the symbol “+” in the Prescription and Over-the-Counter (OTC) Drug Product Lists. These identified reference listed drugs represent the best judgment of the Division of Bioequivalence at this time.
- Its official title is *Approved Drug Products with Therapeutic Equivalence Evaluations*. Commonly known as the Orange Book due to the orange cover of the original print version, it is the Food and Drug Administration's list of all drugs approved in the United States as safe and effective. In addition to listing all approved drugs, the Orange Book is also the

authoritative source of information on the therapeutic equivalence of drug products.

#### 505(b)(2) drugs

- There are three pathways for FDA drug approval. New drugs go through the 505(b) (1) process of submitting a New Drug Application (NDA) proving safety and effectiveness. Generics use the 505(j) pathway, which requires only proof of bioequivalence to an existing product via an abbreviated NDA (ANDA).

#### “Big RLD” Versus “Little rld”

- Reference listed drug, is that referring, generally, to a drug approved under an NDA (i.e., the “big RLD”), or to the particular reference standard identified in FDA’s Orange Book with a “+” (i.e., the “little rld”).
- RLD is listed in Approved Drug Products with Therapeutic Equivalence Evaluations, “Orange Book”, ([www.fda.gov/cder/orange/default.htm](http://www.fda.gov/cder/orange/default.htm))

#### Parameters

##### Size

- If the RLD is less than or equal to 17 mm in its largest dimension,<sup>21</sup> the generic product should be no more than 20 percent larger than the RLD in any single dimension (the resulting dimension not to exceed 17 mm) and no more than 40 percent larger than the RLD in volume.<sup>22</sup>
- If the RLD is greater than 17 mm in its largest dimension, the generic product should be no larger than the RLD in any single dimension or in volume.
- We recommend that the largest dimension of a tablet or capsule should not exceed 22 mm and that capsules should not exceed a standard 00 size.

##### Shape

- It recommend manufacturing tablets and capsules that have a similar shape or have a shape that has been found to be easier to swallow compared with the shape of the RLD.
- Evaluating and comparing the largest cross sectional areas of the RLD and generic product is one strategy to quantify changes in shape.<sup>24</sup> Tablets and capsules that have a larger cross sectional area (e.g., tablets that are rounder) would generally be more difficult to swallow than tablets or capsules of the same volume but with smaller cross sectional areas.

#### Strengths and Dosage Forms

- Generic drugs should have same medicinal products (reference products) with the same active pharmaceutical ingredient(s) in the same strength(s) and the same dosage form(s) with the same route of administration.
- The information about the authorised medicinal products can be retrieved from the so called Orange Book (“*Approved Drug Products with Therapeutic Equivalence Evaluations*”), which is presented on the FDA website.

- In the USA, if the original reference product is withdrawn (discontinued), another product is defined by the FDA as RLD, which has usually been authorised as ANDA itself and not as NDA.

#### **For example**

#### **Indapamide**

- former RLD: Lozol 2.5 mg, Sanofi Aventis US, NDA, discontinued
- current RLD: Indapamide 2.5 mg, Mylan, ANDA

#### **Composition**

- As information about the quantitative composition is usually not accessible, only the qualitative composition of the reference products can be compared.
- US legislation is not requesting that the excipients of the generic product should be identical to those of the reference product.

#### **API Form**

- In the FD&C Act information is requested to show that the active ingredient of the new drug is the same as that of the reference listed drug.
- Examples of chiral substances where the enantiomers show differences in pharmacokinetic and/or pharmacodynamic<sup>25</sup>, i.e. where the generic product has to contain the identical form as the reference product:
  1. Dopa and Methotrexat (the L-enantiomers are transported actively and hence resorption is better compared to the D-enantiomers)
  2. Verapamil (bioavailability of S-(-)-form lower than R-(+)-form but S-(-)-form more effective)

#### **Dissolution Profile**

- Dissolution profile of RLD and generic drug should be comparable and same.
- The BE guidance's contain important details about the types of dissolution studies appropriate for the RLD and test products, along with information on waiver of an in vivo bioequivalence data requirement for any additional strengths for which approval is sought For any recommended dissolution study, it is critical that the appropriate comparison data be provided (e.g., the current recommendation is that comparison data for 12 individual test units versus 12 individual RLD units be provided, with each strength of the test product evaluated against the corresponding strength of the RLD).
- If there is evidence within the ANDA that the appropriate unit studies were not conducted, or a supplemental study has been omitted, FDA will refuse to receive the ANDA.

#### **Protection period of the reference product**

- Protection period of reference product should be known.
- Patents in the USA are usually granted for 20 years.

- Even though patents do not affect submissions of ANDAs, patent information has to be filed along with the ANDA application. Patent information for the reference listed drug is provided in the Orange Book on the FDA website.
- ([http://ntp.niehs.nih.gov/iccvam/suppdocs/feddocus/fda/fda\\_cmcsomcell.pdf](http://ntp.niehs.nih.gov/iccvam/suppdocs/feddocus/fda/fda_cmcsomcell.pdf))
- Applicants are required to list each patent issued by the U.S. Patent and Trademark Office that claims the drug substance, drug product, or that claims a use of the RLD that is cited by the ANDA

#### **Labelling**

- It contains side-by-side labeling comparison of container(s) and carton(s) with the RLD for each strength and package size.
- All differences should be highlighted and annotated. Applicants should indicate the RLD version used for the side-by-side comparison.
- It contains the prescribing and patient information in text-based PDF, Microsoft WORD and SPL formats. Applicants should identify the RLD version used for the side by side comparison.
- It contains the RLD labeling and a comparison of that labeling to the draft labeling for the generic product.
- Applicants should also submit the RLD package insert, Medication Guide, one container label, and one outer carton, if applicable, for each strength and package size listed in the application.
- It contains the RLD professional and patient inserts, Medication Guide, one (1) RLD container label, and one (1) RLD outer carton label for each strength and package size, if applicable.
- Contains the risk evaluation and mitigation strategy (REMS) and all supporting documents, if the RLD has a REMS.
- A REMS for an ANDA must have the same Medication Guide and patient package insert.

#### **Chemistry, Manufacturing, and Control**

##### *Inactive Ingredients*

- Applicants should calculate the maximum daily intake (MDI) for the inactive ingredient and provide the name of the RLD, if applicable.
- The applicant should calculate the amount of inactive ingredient that is delivered per dose or per day (MDI) based on dosing recommendations indicated in the RLD label.
- Changes to Non-Exception Inactive Ingredients in Parenteral, Ophthalmic, and Otic Products
- Parenteral drug products generally must contain the same inactive ingredients and in the same concentration as the RLD.
- However, specific changes (from the RLD drug product) are permitted for certain inactive ingredients (i.e., preservatives, buffers, and antioxidants), which are considered exception inactive ingredients.

- For all other inactive ingredients, an ANDA whose subject is a parenteral drug product must be qualitatively and quantitatively the same (Q1/Q2 same) as the RLD
- However, even if an inactive ingredient is determined to be quantitatively the same as the RLD in a controlled correspondence response, the proposed concentration should be justified with reference to the IID in the event that it falls within the upper limit of the Q1/Q2 threshold.
- In other words, if an inactive ingredient is demonstrated to be quantitatively the same as the RLD (Same implies 95% but 105% of the RLD concentration or amount), yet exceeds the IID limit for the applicable route of administration, FDA will refuse-to-Receive the ANDA
- An ANDA concerning an ophthalmic drug product should be Q1/Q2 the same as the RLD with respect to all of its components, or include data from appropriate bioequivalence studies.

### **Scoring and Conditions of Use**

- Functional Scoring Configurations That Are Inconsistent With the RLD
- FDA will refuse-to-accept an ANDA if there are inconsistencies in the scoring configuration between the RLD and test product that have not been reviewed and approved by FDA before submission of the ANDA.
- Inconsistencies in scoring configuration between the RLD and the test product may not facilitate this demonstration.
- For example, if a RLD 10 mg tablet is scored to enable administration of a 5 mg dose (and a 5 mg dose is supported by the label) and the test product is unscored and does not offer a 5 mg strength, an ANDA applicant will be unable to demonstrate that the test product can be administered in a manner consistent with the dosing recommendations of the RLD.

### **Bioequivalence and clinical deficiencies**

- Module 5 contains all of the clinical study report data needed to support the application and demonstrate that the generic is bioequivalent to the RLD
- Certain drug products may be eligible for a waiver from conducting in vivo BE studies typically required to support the ANDA.
- For example, parenteral drug products, in addition to both ophthalmic and optic solutions, may be eligible for a waiver of BE studies, provided that their formulations are considered Q/Q same as the RLD.
- If the drug product is determined not to be Q/Q same as the RLD, FDA will refuse to receive the ANDA based on the determination that the drug product is ineligible for a waiver due to unpermitted formulation differences.
- For ophthalmic solutions, it is critical to also complete and include the BE Comparative Physicochemical Data of Ophthalmic Solution Drug Products of the ANDA submission to further support the waiver request.
- This captures key information/data relevant to both the test product and the RLD.

- If this is omitted, FDA will refuse to receive the ANDA despite a determination that the test formulation is Q/Q same as the RLD

### **Reference Listed Drug in Europe**

#### **Reference medicinal product in Europe**

#### **Definition**

- A definition of reference medicinal product is that the reference product shall mean a medicinal product authorized, in accordance with the provisions of Article 8. It lays down the principle that no medicinal product may be placed on the market of a Member State unless a marketing authorization has been issued.
- Article 6(1) contains the notion of global marketing authorization as the initial marketing authorization and any additional strengths, pharmaceutical forms, administration routes or presentations, as well as any variations and extensions. Each product within the global marketing authorization may be chosen as the reference product.
- Reference must be made to the dossier of a reference product for which a marketing authorization has been granted in the Community on the basis of a complete dossier. The application form in Module 1 of the dossier for the generic product should clearly identify the reference product.
- Reference must be made to a product which is or has been authorized, i.e. a marketing authorization has been granted for the reference product but it may have ceased to exist. Therefore an application for a generic medicinal product cannot be filed simultaneously with an application for a reference product.

#### **“European reference medicinal product”**

- A generic application can also be submitted in a Member State where the reference medicinal product has never been authorized. In this case, the applicant has to identify in the application form the name of the Member State in which the reference medicinal product is or has been authorized. It is also a prerequisite that the period of data exclusivity has expired in the Member State of the reference medicinal product.
- At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State shall transmit, within a period of one month, a confirmation that the reference medicinal product is or has been authorized together with the full composition of the reference product and if necessary other relevant documentation.
- The documentation requested must be relevant for the assessment of the generic medicinal product submitted.
- Test products for a generic product are normally compared with the corresponding dosage form of an innovator medicinal product (reference product).
- The choice of reference product should be justified by the applicant.

- If there is a significant difference between the reference products originating from the same manufacturer concerned Member States may request information from the first Member State on the reference product, namely on the composition, manufacturing process and finished product specification.
- Where additional bioequivalence studies are required, they should be carried out using the product registered in the concerned Member State as the reference product

#### **Information to be Submitted by the Member State of the European Reference Medicinal Product:**

- It will also be an integral part of the Preliminary Assessment Report (PrAR) to be prepared by the RMS.

The minimum of information to be provided is

1. Confirmation of current or past authorisation of the ERP:
2. Date of authorisation
3. Date of expiry, withdrawal of the authorisation by the MAH, or
4. Withdrawal by the MS
5. If the authorisation has expired or been withdrawn, confirmation that MA of the ERP has not been withdrawn or lapsed due to safety reasons or a change in the risk/benefit ratio
6. Full composition (qualitative and quantitative) of the ERP
7. This minimum of information as defined in the legislation is deemed to be necessary for the start of the procedure by the RMS.

#### **Strength and pharmaceutical composition**

- 'Same qualitative and quantitative composition'
- This requirement that the generic and reference products have the same qualitative and quantitative
- Composition extends only to the active substance(s) and not to the other ingredients of the product. However, differences in excipient composition or differences in impurities must not lead to significant differences as regards safety and efficacy. The competent authorities will evaluate these differences in the light of all scientific knowledge at their disposal.

#### **Pharmaceutical form**

- This criterion relating to the same pharmaceutical form contained in the definition of generic medicinal product is evaluated taking into consideration the standard terms for pharmaceutical dosage forms established by the European Pharmacopoeia.
- A generic product and a reference product may be considered to have the same pharmaceutical form if they have the same form of administration as defined by the Pharmacopoeia.

#### **Bioequivalence**

- Bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal

product meets the relevant criteria as defined in the appropriate detailed guidelines.

- Such exemptions from the need to demonstrate bioequivalence should be justified in module 1 of the dossier and in the clinical overviews.

#### **Reference Products for Bioequivalence Studies**

- A medicinal product to be used as a reference in a bioequivalence study conducted in support of a generic/hybrid application must be a version of the original medicinal product that is authorised within the Community.
- Consequently bioequivalence studies performed with a product not authorised within the EEA will not be considered acceptable.
- A generic product referring to a generic product is not possible and therefore it is not possible for an applicant to use another generic product as the reference product in a bioequivalence study to support a generic application, even if the relevant strength of the reference product is not available because it is no longer marketed.
- In situations where the applicant has definitively established that the relevant strength of the same pharmaceutical form of a reference product is not available in the EU, it may be possible for the applicant to use:

1. A different strength of the same pharmaceutical form of the reference product or if not available
  2. A different pharmaceutical form (e.g. a different immediate-release oral pharmaceutical form) of the reference product other than that applied for as the reference product for the bioequivalence study to support a generic application.
- In general the cumulative strength of the reference product should be the same as the strength that the applicant has applied for, thus maintaining the direct link with the reference product.
  - However it may be justified to use different strengths when pharmacokinetics is linear and a potency correction is performed.

#### **Data exclusivity and market protection period for reference medicinal products**

The medicinal product, once authorised, can however only be placed on the market 10 or 11 years after the authorisation of the reference medicinal product, depending on the protection period applicable for the reference medicinal product. The protection period in the concerned Member State must also be taken into consideration before placing the medicinal product on its market.

#### **Labelling**

- Once the generic medicine is authorised, the same information will appear in the 'product information' of the generic medicine (the summary of product

characteristics, the labelling and the package leaflet) as in the product information of the reference medicine.

- The only differences relate to any differences in excipients and any patented indications.
- If precautions are necessary because of an excipient, they will be described both on the label and in the package leaflet of the generic medicine.
- If the reference medicine is benefiting from patent protection for some indications, these cannot appear in the product information of the generic medicine

requirement is, that the reference product “is or has been authorised”; that means reference can be made to a product not authorised and marketed anymore. and generics can only refer to the reference product, not to another generic

Here, it is accompanied that essentials of reference listed drug in generic drug development is mentioned. And Parameters like size, shape, composition, strengths, dissolution profile, scoring, packaging, labeling, BA/BE, and CMC sections as per U.S and Europe are included. From comparison of regulation of Reference drug in U.S. is more developed.

**Table.1** Comparison of regulation of RLD in US and Europe

Terms	USA	EUROPE
RLD regulatory agency	U.S.FDA	EMA HMA MAA
Application Listed in	NDA Orange book	European Pharmacopeia
Definition	For ANDA submissions in US the reference listed drug (US innovator) should be used as reference product for bioequivalence studies A reference listed drug means the listed drug identified by the FDA as the drug product upon which an applicant relies in seeking approval of its ANDA	For generic applications in EU bioequivalence needs to be demonstrated versus a European reference product. A drug product whose marketing authorization in the EU has been granted on the basis of a complete dossier
Reference drug known as	Reference Listed Drug.	Reference Medicinal Product or European Reference Product
RLD Referred As	For the USA, ANDAs have to refer to the RLD, which is authorised and listed in the Orange Book. In the USA, if the original reference product is withdrawn (discontinued), another product is defined by the FDA as RLD, which has usually been authorised as ANDA itself and not as NDA	For the EU, the requirement is, that the reference product “is or has been authorised”; that means reference can be made to a product not authorised and marketed anymore.
Selection of RLD	Reference Listed Drug (RLD) in the Orange Book usually the highest strength if formulations are proportionally similar.	In EU, generics can only refer to the reference product, not to another generic The bioequivalence study should in general be conducted at the highest strength
Linear Pharmacokinetics		Highly soluble drug and any safety concern: Lower strength acceptable Problems of sensitivity of the analytical method: Highest strength Acceptable.
Bioequivalence Requirement: Fast/FED	As OGD recommendation In the US the different strengths need to be proportionally similar. The definitions of proportional and proportionally similar differ slightly between the US and EU. In the US they must be produced by the same manufacturer.	No such requirement In the EU the qualitative composition of the different strengths need to be identical and the quantitative composition proportional.
Biowaiver for additional dose strengths:		In the EU the manufacturing process for the different strengths must be the same
Acceptance Criteria for bioequivalence for special class drug: Narrow therapeutic index drugs 90 % confidence interval Log transformed data	C <sub>max</sub> , AUC <sub>0-t</sub> 80-125	C <sub>max</sub> , AUC <sub>0-t</sub> 90.00-111.11
Dissolution Requirements	Only official media	Multimedia(min. 3 media’s from PH range 1-7) 12 units data
NDC (National drug Code) NO. Prescription status Labels	<b>Labelling Requirements:</b> Required (10 digit) R <sub>x</sub> Vials/carton/pil Vials/carton/pil	Not Required POM (prescription only medicine) Vials/carton/pil/SmPC Not Required
Side by side comparison		In Europe patent information not given in such book. The medicinal product, once authorised, can however only be placed on the market 10 or 11 years after the authorisation of the reference medicinal product, depending on the protection period applicable for the reference medicinal product.
Patent information	In both country patent is granted for 20 years . In US patent information given in “orange book”.	

## CONCLUSION

A Reference Listed Drug (RLD) is an approved drug product to which new generic versions are compared to show that they are same as generic drugs. In For the USA, ANDAs have to refer to the RLD, which is authorised and listed in the Orange Book. In Europe, RLD is generally the innovator drug product (“Brand”) which is marketed on the basis of a full dossier (e.g., New Drug Application) that includes chemical, biological, safety, clinical efficacy, labeling, etc. and For the EU, the

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