Challenges Associated with Development of Generic PLGA/PLA Based Drug Products

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This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Outline

- Abbreviated New Drug Application (ANDA) or 505 (j) regulatory pathway

- Pharmaceutical equivalence and bioequivalence (BE) considerations of generic poly(lactide-co-glycolide) (PLGA)/poly (lactic acid) (PLA) based drug products

Abbreviated New Drug Applications (ANDA)

Drug products that are the same as the Reference Listed Drug:

- Are pharmaceutically equivalent
  - Same active ingredient(s), Identical in strength or concentration
  - Same dosage form
  - Same route of administration
- Are bioequivalent

Therapeutically equivalent

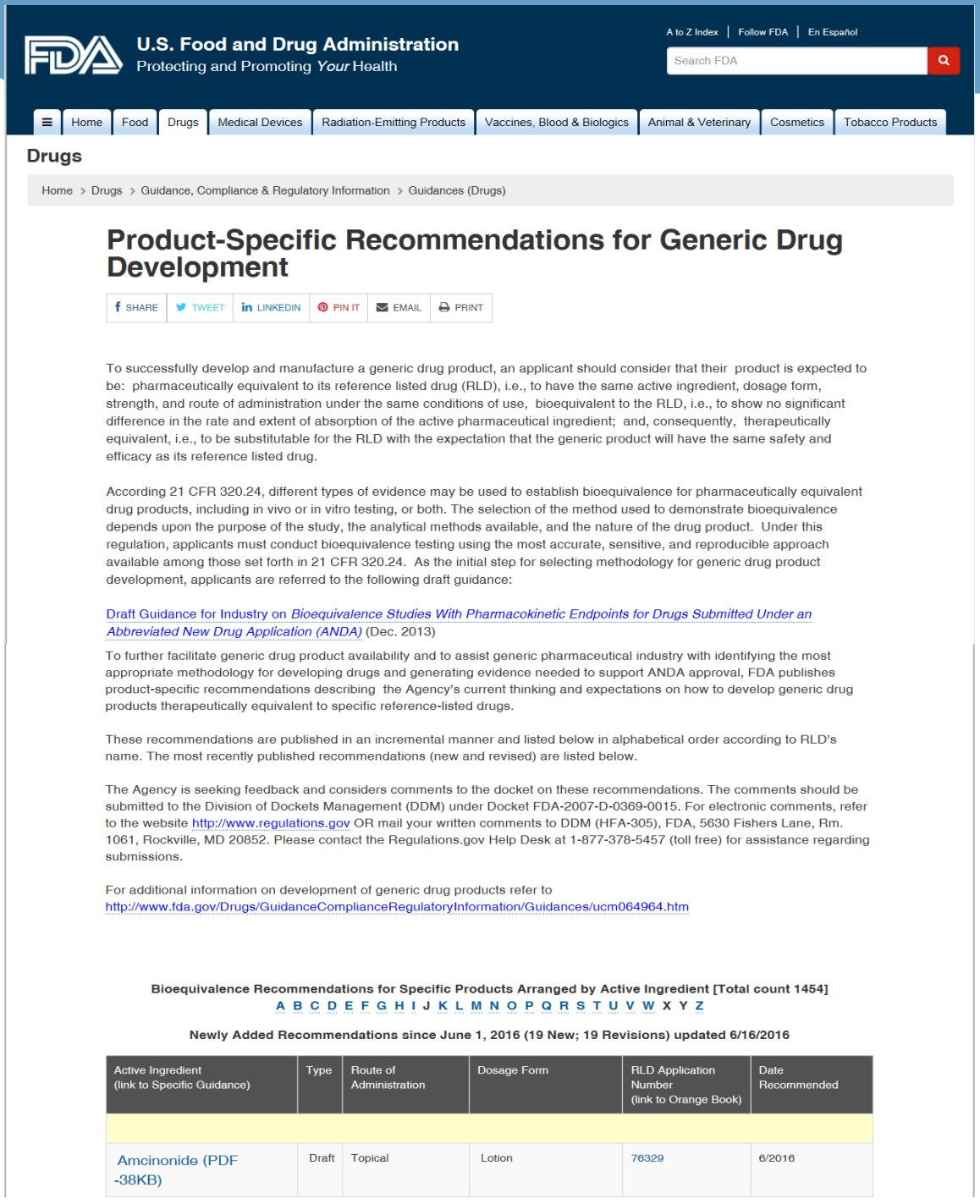
In addition, same labeling, including conditions of use.

Some Key Components of Review Process: New Drug Applications (NDAs) vs. ANDAs

Brand-name drugs	Generic drugs
• Chemistry	• Chemistry
• Manufacturing	• Manufacturing
• Controls	• Controls
• Pharmaceutical Development	• Pharmaceutical Development
• Labeling	• Labeling
• Animal studies	• Bioequivalence
• Clinical studies	
• Bioavailability	

Bioequivalence

- Refers to the absence of a significant difference in the rate and extent to which the active ingredient in a pharmaceutically equivalent drug product becomes available at the site of action, when administered to subjects at the same molar dose under similar conditions



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Product-Specific Recommendations for Generic Drug Development

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To successfully develop and manufacture a generic drug product, an applicant should consider that their product is expected to be: pharmaceutically equivalent to its reference listed drug (RLD), i.e., to have the same active ingredient, dosage form, strength, and route of administration under the same conditions of use, bioequivalent to the RLD, i.e., to show no significant difference in the rate and extent of absorption of the active pharmaceutical ingredient; and, consequently, therapeutically equivalent, i.e., to be substitutable for the RLD with the expectation that the generic product will have the same safety and efficacy as its reference listed drug.

According 21 CFR 320.24, different types of evidence may be used to establish bioequivalence for pharmaceutically equivalent drug products, including in vivo or in vitro testing, or both. The selection of the method used to demonstrate bioequivalence depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Under this regulation, applicants must conduct bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in 21 CFR 320.24. As the initial step for selecting methodology for generic drug product development, applicants are referred to the following draft guidance:

Draft Guidance for Industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (ANDA)* (Dec. 2013)

To further facilitate generic drug product availability and to assist generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval, FDA publishes product-specific recommendations describing the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference-listed drugs.

These recommendations are published in an incremental manner and listed below in alphabetical order according to RLD's name. The most recently published recommendations (new and revised) are listed below.

The Agency is seeking feedback and considers comments to the docket on these recommendations. The comments should be submitted to the Division of Dockets Management (DDM) under Docket FDA-2007-D-0369-0015. For electronic comments, refer to the website http://www.regulations.gov OR mail your written comments to DDM (HFA-305), FDA, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Please contact the Regulations.gov Help Desk at 1-877-378-5457 (toll free) for assistance regarding submissions.

For additional information on development of generic drug products refer to http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm

Bioequivalence Recommendations for Specific Products Arranged by Active Ingredient [Total count 1454]

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Newly Added Recommendations since June 1, 2016 (19 New; 19 Revisions) updated 6/16/2016

Active Ingredient (link to Specific Guidance)	Type	Route of Administration	Dosage Form	RLD Application Number (link to Orange Book)	Date Recommended
Amcinonide (PDF -38KB)	Draft	Topical	Lotion	76329	6/2016

www.fda.gov

Product-Specific Recommendations for Generic Drug Development are available at:

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

Product-Specific Recommendations for Generic Drug Development

Drug Product	Active Ingredient	Dosage form	Bioequivalence Guidance
Vivitrol	**Naltrexone**	**Microsphere**	**Yes**
Zoladex	Goserelin acetate	Implant	No
Lupron Depot	**Leuprolide acetate**	**Microsphere**	**Yes**
Lupron Depot-PED	**Leuprolide acetate**	**Microsphere**	**Yes**
Lupron	**Leuprolide acetate**	**Microsphere**	**Yes**
Sandostatin LAR	**Octreotide**	**Microsphere**	**Yes**
Atridox	Doxycycline hyclate	In situ forming gel	No
Trelstar	**Triptorelin pamoate**	**Microsphere**	**Yes**
Arestin	**Minocycline HCl**	**Microsphere**	**Yes**
Eligard	Leuprolide acetate	In situ forming gel	No
Risperdal Consta	**Risperidone**	**Microsphere**	**Yes**
Ozurdex	Dexamethasone	Implant	No
Bydureon	Exenatide	Microsphere	No
Lupaneta Pack	Leuprolide acetate; Norethindrone acetate	Microsphere; Tablet	No

Contains Nonbinding Recommendations

Draft Guidance on Naltrexone

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Naltrexone

Dosage Form; Route: Extended-release suspension; intramuscular

Recommended Studies: One study

1. Type of study: In vivo single-dose fasting
   Design: Parallel
   Strength: 380 mg/vial (dose: 380 mg)
   Subjects: Healthy males and nonpregnant females, general population
   Additional comments: The 90% confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (C_{max}, AUC_{1-10}, AUC_{10-28}, and $AUC_{0-\infty}$) should fall within the limits of 80-125%

As per 21 CFR § 314.94(a)(9)(iii), the proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the reference product.

Changes in Inactive Ingredients

21 CFR 314.94 (a)(9)(iii) – *Inactive ingredient changes permitted in drug products intended for parenteral use.*

Generally, a drug product intended for parenteral use shall contain the same inactive ingredients (qualitatively the same – "Q1") and in the same concentration (quantitatively the same – "Q2") as the reference listed drug.

An applicant may seek approval of a drug product that differs from the reference listed drug in **preservative, buffer, or antioxidant** provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

A formulation which contains an excipient not contained in the RLD and not considered to be an "exception excipient" cannot be submitted as an ANDA.

Q1/Q2 Equivalent Formulations

- All inactive ingredients – **including preservative, buffer, and antioxidant**– are the same as that in the RLD and in the same concentration
- The Test does not contain an inactive ingredient not contained in the RLD
- The difference in amounts of inactive ingredients between Test and RLD are less than 5%

Bioequivalence Studies of PLGA/PLA Based Drug Products

- Establishment of Q1/Q2 sameness prior to conducting a BE study
- Below are the studies that have been recommended for demonstration of bioequivalence of microspheres:
  - Single-dose, parallel PK study (partial AUC and Cmax)
  - Multiple-dose, steady-state, crossover PK study (AUC and Cmax) in combination with in vitro drug release testing
  - Clinical endpoint study

Establishment of Q1/Q2

The main challenge associated with establishment of Q1/Q2 sameness between the test and reference products is the evaluation of Q1 sameness of PLA/PLGA.

PLA/PLGA are random copolymers with inherent heterogeneity and are available with various physicochemcial properties which may vastly change product performance.

Establishment of Q1/Q2

Some key physicochemcial properties of PLA/PLGA include:

- Polymer composition (L to G ratio)
- Molecular weight and weight distribution
- Polymer architecture (linear vs star-shaped)
- Intrinsic viscosity
- Glass transition temperature
- Polymer end-cap
- Crystallinity

The effect of each parameter on the product performance is product specific. Therefore, the key physicochemical properties that are necessary for evaluation of Q1 sameness is on a case-by-case basis.

Establishment of Q1/Q2

- The key physicochemical properties of PLA/PLGA could be altered during manufacturing process. Therefore, in addition to the characteristics of the raw PLA/PLGA materials, it is critical to characterize PLA/PLGA using the finished product.

- The Q1/Q2 sameness of PLA/PLGA between the test and reference products should be determined using the finished microspheres rather than the raw materials.

Single-dose, Parallel PK Study

Posted draft guidances:

- Naltrexone microspheres
  - Subjects: in healthy males and nonpregnant females.
  - PK parameters: $AUC_{1\text{-}10}$, $AUC_{10\text{-}28}$, $AUC_{0\text{-}\infty}$, and C_{max}
- Triptorelin pamoate microspheres
  - Subjects: Advanced prostate cancer male patients.
  - PK parameters: Log-transformed $AUC_{7\text{-}t}$, AUC_t, $AUC_{0\text{-}\infty}$, and C_{max}

Single-dose, Parallel PK Study

Posted draft guidances:

- Octreotide acetate microspheres
  - Subjects: Healthy males and nonpregnant females.
  - PK parameters: Log-transformed $AUC_{0\text{-}28}$, $AUC_{28\text{-}56}$, $AUC_{t,}$ $AUC_{0\text{-}\infty,}$ and C_{max}
- Leuprolide acetate microspheres
  - Subjects: Prostatic carcinoma patients undergoing initial therapy.
  - PK parameters: Log-transformed $AUC_{7\text{-}t}$, AUC_t, $AUC_{0\text{-}\infty,}$ and C_{max}

Multiple-Dose, Crossover PK Study In Combination With In Vitro Drug Release Testing

Posted draft guidances:

- Risperidone microspheres
  - In vitro drug release at both 37°C and 45°C (water bath):
    - Parameters to measure: Cumulative drug release at days 1 and 21 at 37°C and at day 8 at 45°C as well as T50% at 45°C
  - In vivo steady state PK study:
    - Subjects: Patients who are already receiving a stable regimen of risperidone long-acting injection via the intramuscular route.
    - PK parameters: Log-transformed C_{max} and AUC

Clinical Endpoint Studies

- Posted draft guidances:
  - Minocycline HCl microspheres
- Randomized, double-blind, parallel, three-arm, vehicle-controlled in vivo study in male and nonpregnant female adults with generalized, moderate-to-advanced periodontitis
- Primary endpoint: The change of within-subject average pocket depth from the baseline (day 1) visit to the month 6 (study day 180 ± 14) visit

Summary

- Characterization studies on PLA/PLGA for demonstration of Q1/Q2 sameness between the test and reference products are on a case by case basis.
- Q1/Q2 sameness of PLA/PLGA between the test and reference products should be determined using the finished drug products.
- A variety of studies can be performed to demonstrate bioequivalence for PLA/PLGA based microspheres submitted in an ANDA.
- Product-specific bioequivalence recommendations are posted publicly on FDA's website and give information on the type of bioequivalence study that should be conducted.

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