Liposomal Doxorubicin Call for Clarity

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Cytori Therapeutics
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Drug Shortage History

DEPARTMENT OF HEALTH & HUMAN SERVICES

SEP 0 5 2014

Food and Drug Administration
10903 New Hampshire Ave
Building 51
Silver Spring, MD 20993

Paul A. Braier, Ph.D, Esq.
Greenblum & Bernstein, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191

Re: Docket No. FDA-2014-P-0417

Dear Dr. Braier:

This letter responds to your April 8, 2014, Citizen Petition (the Petition) submitted on behalf of Sun Pharma Global FZE (Sun) pursuant to section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. § 355(q)). The Petition requests that the Food and Drug Administration (FDA or Agency) withdraw its "designation" of Sun's doxorubicin hydrochloride (HCl) liposome injection product (the Sun product) approved under abbreviated new drug application (ANDA) 203263 as the reference listed drug (RLD)[1] and reject any application referring to the Sun product as the RLD.[2]

In the alternative, the Petition requests that for any drug application (pending or future) that references the Sun product as the RLD, the Agency require a demonstration of bioequivalence to the Sun product with statistically enhanced confidence.[3]

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Orange Book Changes

☑ RX ☑ OTC ☑ DISCN

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Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code	RLD	RS	Applicant Holder
RX	DOXORUBICIN HYDROCHLORIDE	DOXIL (LIPOSOMAL)	N050718	INJECTABLE, LIPOSOMAL	INJECTION	20MG/10ML (2MG/ML)	AB	RLD		JANSSEN RESEARCH AND DEVELOPMENT LLC
RX	DOXORUBICIN HYDROCHLORIDE	DOXIL (LIPOSOMAL)	N050718	INJECTABLE, LIPOSOMAL	INJECTION	50MG/25ML (2MG/ML)	AB	RLD		JANSSEN RESEARCH AND DEVELOPMENT LLC
RX	DOXORUBICIN HYDROCHLORIDE	DOXORUBICIN HYDROCHLORIDE (LIPOSOMAL)	A208657	INJECTABLE, LIPOSOMAL	INJECTION	20MG/10ML (2MG/ML)	AB			DR REDDYS LABORATORIES LTD
RX	DOXORUBICIN HYDROCHLORIDE	DOXORUBICIN HYDROCHLORIDE (LIPOSOMAL)	A203263	INJECTABLE, LIPOSOMAL	INJECTION	20MG/10ML (2MG/ML)	AB		RS	SUN PHARMA GLOBAL FZE
RX	DOXORUBICIN HYDROCHLORIDE	DOXORUBICIN HYDROCHLORIDE (LIPOSOMAL)	A208657	INJECTABLE, LIPOSOMAL	INJECTION	50MG/25ML (2MG/ML)	AB			DR REDDYS LABORATORIES LTD
RX	DOXORUBICIN HYDROCHLORIDE	DOXORUBICIN HYDROCHLORIDE (LIPOSOMAL)	A203263	INJECTABLE, LIPOSOMAL	INJECTION	50MG/25ML (2MG/ML)	AB		RS	SUN PHARMA GLOBAL FZE

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January 2017 FDA Guidance

Referencing Approved Drug Products in ANDA Submissions

Guidance for Industry

DRAFT GUIDANCE

Ref. Standard is the BE Comparitor

C. Reference Standard

1. *Selection of a Reference Standard*

As discussed above, the FD&C Act requires an applicant to provide "information to show that the new drug is bioequivalent" to its RLD.[32] 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.[33]

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 the ANDA.[34] To facilitate generic drug development, FDA generally selects a single reference standard that ANDA applicants must use in any in vivo testing conducted to support a demonstration of bioequivalence. FDA selects a single reference standard to ensure the greatest level of consistency between a generic drug and its RLD and among generic drugs. Ordinarily, the reference standard selected by FDA will be the RLD.[35] FDA usually selects as the reference standard the highest strength available for drug products with multiple approved strengths.[36] If

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Ref. Std. Remains if RLD Returns

3. Requesting Selection of a Reference Standard

There are circumstances in which a potential ANDA applicant may ask FDA to select a reference standard. These circumstances include, for example, if FDA has not selected a reference standard, if a potential ANDA applicant believes a reference standard other than the one selected by FDA is appropriate, or if a reference standard is moved to the Discontinued Section and FDA has not selected a new reference standard for the same drug product. If there is no reference standard in the Active Section of the Orange Book for a drug product the applicant intends to duplicate, the potential applicant may submit controlled correspondence to FDA asking FDA to select a reference standard for that drug product. If there is a reference standard in the Active Section of the Orange Book but there are limited or no quantities of the reference standard 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 under 21 CFR 10.25(a) and 10.30 to request that FDA select that different listed drug also as a reference standard. If the Agency selects a new reference standard, that product generally will remain the reference standard even if the original reference standard (e.g., the discontinued RLD) resumes marketing.

April 2017 FDA Guidance

Contains Nonbinding Recommendations

Draft Guidance on Doxorubicin Hydrochloride

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:	Doxorubicin hydrochloride
Dosage Form; Route:	Injectable, liposome; Injection
Recommended Studies:	Two studies

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RS or RLD for BE Studies

The following clinical and in vitro studies are recommended to demonstrate bioequivalence:

In Vivo Bioequivalence Study:

1. Type of study: Fasting*
   Design: Single-dose, two-way crossover in vivo
   Strength: 50 mg/vial or 20 mg/vial
   Dose: 50 mg/m^2
   Subjects: Ovarian cancer patients whose disease has progressed or recurred after platinum-based chemotherapy and who are already receiving or scheduled to start therapy with the reference listed drug (RLD) or the reference standard product.
   Additional comments:

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Points for Clarity

- History of Liposomal Doxorubicin
  - Doxil RLD replaced with a new Lipodox Ref. Standard in 2014
  - Doxil RLD reappears in March 2017
  - New Liposomal Guidance in April 2017
  - No discussion on the 2017 Orange Book changes

Points For Clarity

- Generic Drug Guidance indicates Ref. Standard is the BE study comparator
- Liposomal Guidance indicates Ref. Standard **or** RLD can be used for BE study
- Creates an inherent Conflict with no explanation

Points for Clarity

- Liposomal Guidance only applies to 3 products
- April 2017 Guidance appears in same time period as new RLD Orange Book listing
- New Guidance could list RS and RLD by name, for clarity, given the tumultuous history of liposomal doxorubicin
- New Guidance could list equivalence of Doxil and Caelyx for additional clarity given the identical nature of their chemical and manufacturing formulation

THANK YOU!

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