CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208574Orig1s000
208574Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 122145

MEETING MINUTES

Teva Pharmaceuticals USA
Attention: Cory Wohlbach
Director, Regulatory Affairs, US Generics
425 Privet Road
Horsham, PA 19044

Dear Mr. Wohlbach:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Romidepsin Injection.

We also refer to the teleconference between representatives of your firm and the FDA on August 17, 2015. The purpose of the meeting was to discuss your proposed New Drug Application (NDA) table of contents for Romidepsin Injection, 10 mg/2 mL (5 mg/mL). We wish to draw your attention to the post meeting addendum.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alycia Anderson, Regulatory Project Manager, at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

Reference ID: 4576702

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	August 17, 2015; 3:00 p.m. - 4:00 p.m. (ET)
Meeting Location:	Teleconference
Application Number:	PIND 122145
Product Name:	Romidepsin Injection
Indication:	Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.
Sponsor/Applicant Name:	Teva Pharmaceuticals USA
Meeting Chair:	R. Angelo de Claro, MD, Clinical Team Leader
Meeting Recorder:	Alycia Anderson, CCRP

FDA ATTENDEES

Office of Hematology and Oncology Products/Division of Hematology Products
Ann T. Farrell, MD, Director
Edvardas Kaminskas, MD, Deputy Director
R. Angelo de Claro, MD, Clinical Team Leader
Hyon-Zu Lee, PharmD, Clinical Reviewer
Alycia Anderson, CCRP, Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology
Christopher Sheth, PhD, Pharmacology Toxicology Team Leader
Brenda Gehrke, PhD, Pharmacology Reviewer

Office of Pharmaceutical Quality/Office of New Drug Products
Olen Stephens, PhD, Acting Branch Chief, Branch II, Division of New Drug Products I

SPONSOR ATTENDEES

Rosario Lobrutto, PhD, Senior Director, R&D
Scott Tomsky, VP Generics Regulatory Affairs
Cory Wohlbach, Director, US Generics Regulatory Affairs
Todd Kays, PhD, Vice President, Biopharmaceutics
Ryan Hernandez, Manager, Regulatory Operations

Michael McGraw, PharmD, Director, Regulatory Affairs
Prakash Sunadaramurthi, PhD, Sr. Manager, Biologic CMC Development

1.0 BACKGROUND

Teva Pharmaceuticals USA submitted a pre-NDA meeting request on June 22, 2015. The purpose of this pre-NDA teleconference was to discuss the proposed NDA table of contents for Romidepsin Injection, 10 mg/2 mL (5 mg/mL).

The product name for this study is Romidepsin, which is used for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.

FDA sent Preliminary Comments to Teva Pharmaceuticals USA on August 7, 2015.

2. DISCUSSION

2.1.

Preamble
Before the meeting, please provide in a tabular format the comparative composition of your drug product and the listed drug in the vial and after dilution in 0.9% saline injection. Also include in your comparison, the pH of admixture and information on the admixture stability.

Discussion:
The Agency acknowledged that the Sponsor's response was acceptable.

Question 1:
Does FDA agree with the Romidepsin Injection, 10mg/vial (5mg/ml), ready to use formulation eCTD submission content plan?

FDA Response to Question 1:
From a technical standpoint (not content related), the proposed format for the planned NDA is acceptable. However, please see additional comments below:

- If you are utilizing the eCTD Backbone Files Specification For Module 1 v2.3, FDA Form 3674 should reside in m1.1.7 (not m1.1.6) and Generic Drug Fee Cover sheet, in m1.1.9 (not m1.1.2). If you are utilizing Module 1 Specification v1.3, both forms should be placed in m1.2 (cover letter section) with clear leaf titles, indicating the content.
- Do not provide duplicate heading element in m1.4.1, for each LOA. Instead, a single m1.4.1 section should be provided and all LOAs placed under the single heading element, with clear leaf titles. Same applies to m1.12.14, 1.14.1.3, etc.,
- Your approach to provide duplicate heading elements for m2.3 and 3.2.s is unacceptable. As there are a few ways to submit module 2 and 3, please make sure your approach fits the DTD and the "Granularity Annex", located at:-

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073261.pdf

Drug Product:
The eCTD content is acceptable provided that the following P.2 subsections are also included in your NDA submission.

P.2	Pharmaceutical Development [name, dosage form]
P.2.1	Components of the Drug Product
P.2.1.1	Drug Substance
P.2.1.2	Excipients
P.2.2	Drug Product
P.2.2.1	Formulation Development
P.2.2.2	(b) (4)
P.2.2.3	Physicochemical and Biological Properties
P.2.3	Manufacturing Process Development
P.2.4	Container Closure System
P.2.5	Microbiological Attributes
P.2.6	Compatibility

Discussion:
No discussion occurred.

Question 2:
Does the Agency require the inclusion of the following sections in the application content plan taking into account that this 505(b)(2) application is relying on the safety and efficacy of the RLD?

FDA Response to Question 2:
With a Biowaiver request along with justification and supportive information, the clinical and nonclinical sections do not need to be included in the NDA.

Discussion:
No discussion occurred.

Post Meeting Addendum:
The new dosage form that is being proposed triggers PREA, therefore an Initial Pediatric Study Plan (iPSP) is required and will need to be submitted to your IND as soon as possible.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an

assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on

FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Reference ID: 4576702

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues that required further discussion.

5.0 ACTION ITEMS

There were no issues that required further discussion.

6.0 ATTACHMENTS AND HANDOUTS

Teva Pharmaceuticals USA provided the Agency with a response to the Preamble and asked for clarification on two questions, one on the preamble and one on PREA, on August 14, 2015. Those responses are attached.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROMEO A DE CLARO
08/20/2015