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RESEARCH**

*APPLICATION NUMBER:*  
**22-160**

**MEDICAL REVIEW(S)**

## Summary Review for Regulatory Action

<b>Date</b>	May 22, 2009
<b>From</b>	Robert L. Justice, M.D., M.S.
<b>Subject</b>	Division Director Summary Review of Complete Response #2
<b>NDA/BLA # Supplement #</b>	22-160
<b>Applicant Name</b>	Teva Parenteral Medicines, Inc.
<b>Date of Current Submission</b>	March 20, 2009, received March 23, 2009
<b>PDUFA Goal Date</b>	May 22, 2009
<b>Proprietary Name / Established (USAN) Name</b>	Oxaliplatin Injection/ oxaliplatin
<b>Dosage Forms / Strength</b>	50 mg/10 mL and 100 mg/20 mL
<b>Proposed Indication(s)</b>	1. Adjuvant treatment of stage III colon cancer patients in patients who have undergone complete resection of the primary tumor 2. Treatment of advanced colorectal cancer
<b>Action/Recommended Action for NME:</b>	<i>Tentative Approval</i>

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review	N/A
Statistical Review	N/A
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	X
Clinical Pharmacology Review	X
DDMAC	N/A
DSI	N/A
CDTL Review	N/A
OSE/DMEPA	X
OSE/DDRE	N/A
OSE/DSRCS	N/A
Other	N/A

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Errors Prevention and Analysis

DSI=Division of Scientific Investigations

DDRE= Division of Drug Risk Evaluation

DSRCS=Division of Surveillance, Research, and Communication Support

CDTL=Cross-Discipline Team Leader

# Signatory Authority Review

## 1. Introduction

This 505(b)(2) application seeks approval of Oxaliplatin Injection, 50 mg/10 mL and 100 mg/20 mL. This submission was received on March 23, 2009 and is a complete response to our action letter of March 2, 2009.

## 2. Background

This product differs from Eloxatin (oxaliplatin injection), the reference listed drug, by the addition of (b) (4) of lactose monohydrate/mL. The original Eloxatin formulation was a lyophilized formulation containing lactose but is no longer marketed. This 505(b)(2) application was originally submitted on February 9, 2007. The deficiencies in the December 4, 2007 action letter were as follows:

1. DMF 19,559 was deemed inadequate to support this NDA. A Letter of Deficiencies was sent to the DMF Holder on November 6, 2007. Satisfactory resolution of the Letter of Deficiencies is required for approval of this NDA.
2. Propose specifications for (b) (4), individual and total metallic impurities derived from platinum for the drug substance testing.
3. Reconcile a discrepancy in the proposed acceptance criteria for Impurity C in the drug product listed in "SPECIFICATION SHEET – CHECK USA", NMT (b) (4) to be consistent with the acceptance criteria for Impurity C at NMT (b) (4) in the "SPECIFICATION SHEET – RELEASE USA" and submit the revision to the NDA.

Regarding the carton/container labels:

4. Increase the prominence of the name of the drug "OXALIPLATIN INJECTION."
5. Provide a cautionary statement "Caution: contains cytotoxic agent" in the container and carton labels.
6. Provide separate NDC numbers for each of the vial configurations.
7. Submit a revised package insert identical to the attached version with the following additional revisions:
  - a. Remove the capitalization from all the "Oxaliplatin"s.
  - b. Provide separate NDC numbers for each of the vial configurations.

The applicant submitted a complete response to the action letter on August 29, 2008. The complete response letter of March 2, 2009 identified the following remaining deficiencies.

Your proposed acceptance criteria for (b) (4) Impurity A) and the (b) (4) (b) (4) Impurity B) currently exceed ICH Q3B(R2) for the Oxaliplatin Injection drug product. The proposed acceptance criteria for these impurities must be lowered to meet the current ICH Q3B(R2) guidance.

If these impurity specifications exceed the qualification limits, the impurities will need to be qualified preclinically or justifications for their levels should be provided based on appropriate literature citations.

### 3. CMC/Device

The Chemistry Review of the first complete response was signed on 2/24/09 and made the following recommendation and conclusion on approvability.

#### **Recommendation and Conclusion on Approvability**

From a Chemistry, Manufacturing and Controls standpoint, this New Drug Application is recommended for approval pending acceptable submission of acceptable carton and container labeling. Also note that the review from DMEPA, OSE is still pending. On 24-FEB-2009, applicant agreed to have an (b) (4) expiration date for the Oxaliplatin Injection as supported by their updated stability data and they have provided updated container/carton labeling. The package insert was found acceptable on 17-FEB-2009. Microbiology review recommended approval on 04-DEC-2007. The Office of Compliance recommended an overall acceptable on 05-FEB-2009. The responses to our comments for DMF 19,559 (Oxaliplatin, Sicor de Mexico) were determined to be acceptable on 20-FEB-2009.

SICOR Pharmaceuticals, Inc. requests a waiver for evidence of bioavailability/bioequivalence in accordance with 21 CFR §320.22(b)(1). SICOR's drug product meets the required criteria:

- 1) Oxaliplatin Injection, 5 mg/mL is a parenteral drug product intended for administration by intravenous infusion.
- 2) SICOR's proposed drug product has the same active pharmaceutical moiety, dosage form, strength, route of administration, and conditions of use as Sanofi Aventis' Eloxatin® Injection (oxaliplatin injection), previously approved under NDA No. 21-759.
- 3) The only difference between the proposed drug product and Eloxatin® Injection is that SICOR's product contains lactose as an excipient. However, Sanofi Aventis' Eloxatin® for Injection also contained lactose.

From a CMC standpoint, waiver for evidence of bioequivalence is recommended. Also refer to the Clinical Pharmacology review dated 30-NOV-2007 for further information.

In an update of the Chemistry Review dated 3/2/09 it was noted that all of the DMEPA comments regarding container and carton labeling have been addressed by the applicant and that "approval is recommended from a CMC perspective."

The Chemistry Review of the current submission provides the following summary of the complete response to our March 2, 2009 action letter.

In the current submission, Teva proposes to lower the release and stability acceptance criteria for Impurity A and Impurity B to meet the current ICH Q3B (R2) criteria. The proposed specifications are as follows:

Impurity A NMT	(b) (4)
Impurity B NMT	

Based on the previous stability data package and the new proposals for acceptance criteria, the Agency can now grant a 12-month expiration dating period for the drug product (Oxaliplatin Injection). This expiration dating period is consistent with the observed levels for Impurity A and Impurity B, which both occur at levels of (b) (4) at the 12-month time point under long term conditions (25°C/60% RH). These levels exceed the proposed specifications at the (b) (4) time point under the same conditions. Refer to the previous Chemistry Review by Josephine Jee, dated 24-FEB-2009 for additional information.

The carton and vial labels are found adequate by CMC and DMEPA. Refer to the 24-FEB-2009 Chemistry Review for additional information.

The review concluded that “Based on the provided data at 25°C/60% RH of Oxaliplatin Injection, an expiration dating period of 12 months is the maximum that can be granted.”

*Comment: I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. With an expiration dating period of 12 months the impurity levels are acceptable and do not require further qualification (see below).*

## 4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review signed 2/25/09 addressed the issues of impurities.

### **Toxicology Issues and Recommendations:**

The Teva/Sicor NDA 22,160 differs from the current reference listed drug (RLD) formulation by an addition of (b) (4) of lactose monohydrate/mL. The original Sanofi-Aventis oxaliplatin formulation (RLD) was a lyophilized formulation containing lactose (NDA 21,492, marketed 2002-2004) to be administered in combination with 5-FU/LV. Thousands of patients were treated with the oxaliplatin/lactose formulation in clinical trials at doses ranging from 0.45-200 mg/m<sup>2</sup>. The Sanofi Aventis formulation changed to an aqueous solution (N21,759) in 2005; the lactose formulation was discontinued at this time.

In 2006/2007, Sanofi-Aventis petitioned that the Agency require all applicants for approval of generic and 505(b)(2) formulations referencing Eloxatin solution, containing an acid (other than oxalic acid), a conjugate base, or added sugars such as lactose, to demonstrate that any new compound or impurity resulting from such formulations, do not compromise the safety or efficacy of the drug product.

If impurities are identified which are not within the qualification limit (0.2% for drug product), as described in ICH Q3B(R), or within the end-of-shelf-life specification levels for these impurities in the RLD, the impurities will require further qualification using preclinical studies, or reduction to below qualification limits.

The following impurities of concern were identified in NDA 21,492/21,759 (Sanofi Aventis) and NDA 22,160 (Teva/Sicor):

The chemistry review team has provided a comparison of the end-of-shelf-life specifications of these impurities from the current NDA at (b) (4) and the Sanofi Aventis specification for the same impurity profile for Eloxatin (see below). The reference citation for these Eloxatin impurity limits was not documented.

Comparative specifications for impurities:

Impurity	Teva/Sicor NDA 22-160	Sanofi Aventis NDAs 21-492/21-759
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(b) (4)

(b) (4)

All other impurities are within the qualification threshold, as described in ICH Q3B(R), or within the end-of-shelf-life specification levels for these impurities in the RLD.

The amended pharmacology/toxicology review of March 4, 2009 concluded the following.

Nonclinical Safety Issues Relevant to Clinical Use: The proposed acceptance criteria for (b) (4) (Impurity A) and the (b) (4) (Impurity B) currently exceed ICH Q3B(R2) for the Oxaliplatin Injection drug product. The proposed acceptance criteria for these impurities must be lowered to meet the current ICH Q3B(R2) guidance. If these impurity specifications exceed the qualification limits, the impurities will need to be qualified preclinically or justifications for their levels should be provided based on appropriate literature citations.

Adverse clinical reactions associated with Oxaliplatin Injection are expected to be comparable to those reported for Eloxatin.



The pharmacology toxicology review of the second complete response stated the following.

**Response from Sponsor:**

On March, 25, 2009, Teva accepted our requirement to lower release and shelf-life acceptance criteria for impurities A and B to meet ICH Q3B(R2) of 0.2% (as stated above). In addition, Teva is currently conducting a pre-clinical bridging study for impurity qualification.

**Recommendations:**

There are no additional pharmacology/toxicology concerns at this time.

*Comment: I concur that the impurity issue has been resolved by the change in release and shelf-life acceptance criteria for impurities A and B and that there are no other pharmacology/toxicology issues that would preclude approval.*

## **5. Clinical Pharmacology/Biopharmaceutics**

The Clinical Pharmacology Review of this complete response dated 2/23/09 noted that there is no new clinical pharmacology information in this submission.

## **6. Clinical Microbiology**

Not applicable.

## **7. Clinical/Statistical-Efficacy**

Not applicable. No clinical efficacy data were submitted.

## **8. Safety**

Not applicable. No clinical safety data were submitted.

## **9. Advisory Committee Meeting**

Not applicable.

## **10. Pediatrics**

A full pediatric waiver was granted by the PeRC.

## **11. Other Relevant Regulatory Issues**

There are no other unresolved relevant regulatory issues that would preclude a tentative approval.

## **12. Labeling**

- Proprietary name: Oxaliplatin Injection
- Physician labeling: The package insert was reviewed for consistency with the RLD label.
- Carton and immediate container labels: On 2/25/09 DMEPA made recommendations for revisions to the carton and container labels. The applicant submitted revised labels which were found to be acceptable to the chemistry reviewers.
- Patient labeling: The patient labeling was reviewed for consistency with the RLD label.

## **13. Decision/Action/Risk Benefit Assessment**

- Regulatory Action

Tentative approval

- Risk Benefit Assessment

The risk benefit relationship for Oxaliplatin Injection is the same as that for the RLD.

- Recommendation for Postmarketing Risk Management Activities
- None

- Recommendation for Other Postmarketing Study Commitments

None

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Robert Justice  
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MEDICAL OFFICER

## Summary Review for Regulatory Action

<b>Date</b>	March 2, 2009
<b>From</b>	Robert L. Justice, M.D., M.S.
<b>Subject</b>	Division Director Summary Review of Complete Response
<b>NDA/BLA # Supplement #</b>	22-160
<b>Applicant Name</b>	Teva Parenteral Medicines, Inc.
<b>Date of Submission</b>	August 29, 2008, received September 2, 2008
<b>PDUFA Goal Date</b>	March 2, 2009
<b>Proprietary Name / Established (USAN) Name</b>	Oxaliplatin Injection/ oxaliplatin
<b>Dosage Forms / Strength</b>	50 mg/10 mL and 100 mg/20 mL
<b>Proposed Indication(s)</b>	1. Adjuvant treatment of stage III colon cancer patients in patients who have undergone complete resection of the primary tumor 2. Treatment of advanced colorectal cancer
<b>Action/Recommended Action for NME:</b>	<i>Complete Response</i>

<b>Material Reviewed/Consulted</b>	
OND Action Package, including:	
Medical Officer Review	N/A
Statistical Review	N/A
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	X
Clinical Pharmacology Review	X
DDMAC	N/A
DSI	N/A
CDTL Review	N/A
OSE/DMEPA	X
OSE/DDRE	N/A
OSE/DSRCS	N/A
Other	N/A

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DSRCS=Division of Surveillance, Research, and Communication Support

CDTL=Cross-Discipline Team Leader

# Signatory Authority Review

## 1. Introduction

This 505(b)(2) application seeks approval of Oxaliplatin Injection, 50 mg/10 mL and 100 mg/20 mL. This submission is a complete response to our approvable letter of December 4, 2007.

## 2. Background

This product differs from Eloxatin (oxaliplatin injection), the current reference listed drug by the addition of (b) (4) of lactose monohydrate/mL. The original Eloxatin formulation was a lyophilized formulation containing lactose but is no longer marketed. This 505(b)(2) application was originally submitted on February 9, 2007. The deficiencies were as follows:

1. DMF 19,559 was deemed inadequate to support this NDA. A Letter of Deficiencies was sent to the DMF Holder on November 6, 2007. Satisfactory resolution of the Letter of Deficiencies is required for approval of this NDA.
2. Propose specifications for (b) (4), individual and total metallic impurities derived from platinum for the drug substance testing.
3. Reconcile a discrepancy in the proposed acceptance criteria for Impurity C in the drug product listed in "SPECIFICATION SHEET – CHECK USA", NMT (b) (4) to be consistent with the acceptance criteria for Impurity C at NMT (b) (4) in the "SPECIFICATION SHEET – RELEASE USA" and submit the revision to the NDA.

Regarding the carton/container labels:

4. Increase the prominence of the name of the drug "OXALIPLATIN INJECTION."
5. Provide a cautionary statement "Caution: contains cytotoxic agent" in the container and carton labels.
6. Provide separate NDC numbers for each of the vial configurations.
7. Submit a revised package insert identical to the attached version with the following additional revisions:
  - a. Remove the capitalization from all the "Oxaliplatin"s.
  - b. Provide separate NDC numbers for each of the vial configurations.

### 3. CMC/Device

The Chemistry Review of this complete response was signed on 2/24/09 and made the following recommendation and conclusion on approvability.

#### **Recommendation and Conclusion on Approvability**

From a Chemistry, Manufacturing and Controls standpoint, this New Drug Application is recommended for approval pending acceptable submission of acceptable carton and container labeling. Also note that the review from DMEPA, OSE is still pending. On 24-FEB-2009, applicant agreed to have an (b)(4) expiration date for the Oxaliplatin Injection as supported by their updated stability data and they have provided updated container/carton labeling. The package insert was found acceptable on 17-FEB-2009. Microbiology review recommended approval on 04-DEC-2007. The Office of Compliance recommended an overall acceptable on 05-FEB-2009. The responses to our comments for DMF 19,559 (Oxaliplatin, Sicor de Mexico) were determined to be acceptable on 20-FEB-2009.

SICOR Pharmaceuticals, Inc. requests a waiver for evidence of bioavailability/bioequivalence in accordance with 21 CFR §320.22(b)(1). SICOR's drug product meets the required criteria:

- 1) Oxaliplatin Injection, 5 mg/mL is a parenteral drug product intended for administration by intravenous infusion.
- 2) SICOR's proposed drug product has the same active pharmaceutical moiety, dosage form, strength, route of administration, and conditions of use as Sanofi Aventis' Eloxatin® Injection (oxaliplatin injection), previously approved under NDA No. 21-759.
- 3) The only difference between the proposed drug product and Eloxatin® Injection is that SICOR's product contains lactose as an excipient. However, Sanofi Aventis' Eloxatin® for Injection also contained lactose.

From a CMC standpoint, waiver for evidence of bioequivalence is recommended. Also refer to the Clinical Pharmacology review dated 30-NOV-2007 for further information.

In an update of the Chemistry Review dated 3/2/09 it was noted that all of the DMEPA comments regarding container and carton labeling have been addressed by the applicant and that "approval is recommended from a CMC perspective."

*Comment: I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. The issue of impurity specifications is discussed below.*

### 4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review signed 2/25/09 addressed the issues of impurities. The toxicology issues and recommendations are quoted in detail below because of their significance to this action.

**Toxicology Issues and Recommendations:**

The Teva/Sicor NDA 22,160 differs from the current reference listed drug (RLD) formulation by an addition of (b) (4) of lactose monohydrate/mL. The original Sanofi-Aventis oxaliplatin formulation (RLD) was a lyophilized formulation containing lactose (NDA 21,492, marketed 2002-2004) to be administered in combination with 5-FU/LV. Thousands of patients were treated with the oxaliplatin/lactose formulation in clinical trials at doses ranging from 0.45-200 mg/m<sup>2</sup>. The Sanofi Aventis formulation changed to an aqueous solution (N21,759) in 2005; the lactose formulation was discontinued at this time.

In 2006/2007, Sanofi-Aventis petitioned that the Agency require all applicants for approval of generic and 505(b)(2) formulations referencing Eloxatin solution, containing an acid (other than oxalic acid), a conjugate base, or added sugars such as lactose, to demonstrate that any new compound or impurity resulting from such formulations, do not compromise the safety or efficacy of the drug product.

If impurities are identified which are not within the qualification limit (0.2% for drug product), as described in ICH Q3B(R), or within the end-of-shelf-life specification levels for these impurities in the RLD, the impurities will require further qualification using preclinical studies, or reduction to below qualification limits.

The following impurities of concern were identified in NDA 21,492/21,759 (Sanofi Aventis) and NDA 22,160 (Teva/Sicor):

The chemistry review team has provided a comparison of the end-of-shelf-life specifications of these impurities from the current NDA at (b) (4) and the Sanofi Aventis specification for the same impurity profile for Eloxatin (see below). The reference citation for these Eloxatin impurity limits was not documented.



Comparative specifications for impurities:

Impurity	Teva/Sicor NDA 22-160	Sanofi Aventis NDAs 21-492/21-759
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(b) (4)

(b) (4)

All other impurities are within the qualification threshold, as described in ICH Q3B(R), or within the end-of-shelf-life specification levels for these impurities in the RLD.

*Comment: I discussed the conclusions reached by the pharmacology/toxicology reviewers with FDA legal counsel. I was informed that this 505(b)(2) application cannot refer to impurity data in the RLD NDA unless it was included in product labeling or the applicant has right of reference. Since this information is not in the Eloxatin labeling and the applicant does not have right of reference, the applicant must either lower the specifications for impurities A and B to meet the current ICH Q3B(R2) guidance, qualify them preclinically, or provide justifications for their levels based on appropriate literature citations.*

## **5. Clinical Pharmacology/Biopharmaceutics**

The Clinical Pharmacology Review of this complete response dated 2/23/09 noted that there is no new clinical pharmacology information in this submission.

## **6. Clinical Microbiology**

Not applicable.

## **7. Clinical/Statistical-Efficacy**

Not applicable. No clinical data was submitted.

## **8. Safety**

Not applicable. No clinical data was submitted.

## **9. Advisory Committee Meeting**

Not applicable.

## **10. Pediatrics**

A full pediatric waiver was granted by the PeRC.

## **11. Other Relevant Regulatory Issues**

There are no other unresolved relevant regulatory issues.

## **12. Labeling**

Includes:

- Proprietary name: Oxaliplatin Injection
- Physician labeling: The package insert was reviewed for consistency with the RLD label.
- Carton and immediate container labels: On 2/25/09 DMEPA made recommendations for revisions to the carton and container labels. The applicant submitted revised labels which were found to be acceptable to the chemistry reviewers.
- Patient labeling: The patient labeling was reviewed for consistency with the RLD label.

## **13. Decision/Action/Risk Benefit Assessment**

- Regulatory Action

Complete response. The following deficiency will be communicated in the letter.

Your proposed acceptance criteria for (b) (4) (Impurity A) and the (b) (4) (Impurity B) currently exceed ICH Q3B(R2) for the Oxaliplatin Injection drug product. The proposed acceptance criteria for these impurities must be lowered to meet the current ICH Q3B(R2) guidance.

If these impurity specifications exceed the qualification limits, the impurities will need to be qualified preclinically or justifications for their levels should be provided based on appropriate literature citations.

- Risk Benefit Assessment

The risk benefit relationship for Oxaliplatin Injection is the same as that for the RLD.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for Other Postmarketing Study Commitments

None

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Robert Justice  
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MEDICAL OFFICER

Deputy Division Director Summary Review of NDA 22-160

Drug: oxaliplatin

Applicant: Sicor Pharmaceuticals

Date: December 2, 2007

On February 9, 2007, Sicor Pharmaceuticals submitted a 505(b) (2) NDA for oxaliplatin. The Agency first approved Eloxatin® (oxaliplatin) on August 9, 2002 in a lyophilized dosage form containing lactose. Subsequently Sanofi-Aventis submitted an NDA for a liquid dosage form which did not contain lactose. The latter NDA was approved on January 31, 2005. Sanofi-Aventis has discontinued marketing the lyophilized dosage form.

Sicor based the filing of this application as a 505 (b) (2) based on the prior NDAs for oxaliplatin submitted by Sanofi-Aventis. The following text is from the submission:

*Our proposed drug product, Oxaliplatin Injection, 5 mg/mL, has the same active ingredient, dosage form, strength, route of administration, and conditions of use as of Sanofi Aventis's listed liquid drug product. However, the proposed drug product also contains lactose, which was present at this concentration in Sanofi-Aventis's previously marketed lyophilized dosage form of Eloxatin® (oxaliplatin for injection). SICOR's liquid formulation of the drug was developed to match the assay and impurity profiles of the innovator's discontinued lyophilized drug after reconstitution. In accordance with 314.54(a)(1)(iii), SICOR identifies Sanofi-Aventis's Eloxatin® as the previously approved drugs under NDA Nos. 021-759 and 021-492, for which FDA has made a finding of safety and effectiveness. SICOR relies on these findings of safety and effectiveness in seeking approval of our proposed drug product, Oxaliplatin Injection, 5 mg/mL.*

Sicor submitted a Chemistry Manufacturing, and Controls section which included information on manufacturing process, stability, proposed labeling including carton and container labeling. Sicor's submitted labeling was in PLR format.

Sicor requested a waiver for bioavailability and a request for a categorical exclusion.

Dr. Brian Booth, deputy director and clinical pharmacology team leader agreed with the applicant that a waiver for bioavailability studies was appropriate.

The Chemistry Review Team agreed with the request for categorical exclusion. However, during their review they identified the following deficiencies which are copied from the review:

CMC Deficiencies

1. DMF 19,559 was deemed inadequate to support this NDA. A Letter of Deficiencies was sent to the DMF Holder on November 06, 2007. Satisfactory resolution of the Letter of Deficiencies is required for the approval of this NDA.
2. Propose specifications for (b) (4), individual and total metallic impurities derived from platinum for the drug substance testing.
3. Reconcile a discrepancy in the proposed acceptance criteria for Impurity C in the drug product listed in "SPECIFICATION SHEET – CHECK USA", NMT (b) (4) to be consistent to the acceptance criteria for Impurity C at NMT (b) (4) in the "SPECIFICATION SHEET –RELEASE USA" and submit the revision to the NDA.

Labels:

4. Increase the prominence of the name of the drug "OXALIPLATIN INJECTION."
5. Provide a cautionary statement "Caution: contains cytotoxic agent" in the container and carton labels.
6. Provide separate NDC numbers for each of the vial configurations.

Package Insert:

7. Submit a revised packaged insert
  - a. Remove the capitalization from all of the Oxaliplatins.
  - b. Provide separate NDC numbers for each of the vial configurations.

During the review process, the Microbiology review team identified the following deficiency:

*The validation of the (b) (4) used to (b) (4) employed as holding vessels in the (b) (4) manufacturing process was not provided in the application.*

The applicant responded to the above deficiency. A second review by the Microbiology team found the response adequate and recommended approval.

The Office of Compliance EES report was found acceptable.

The labeling was submitted in PLR format and reviewed by the SEALD team. The SEALD team recommendations were incorporated into the labeling.

A regulatory concern that would interfere with any approval action is the submission of a Citizen's Petition by Sanofi-Aventis. The Petition requests that the FDA to require all petitioners for approval of generic formulations referencing Eloxatin solution (ANDAs), containing an added acid, or conjugate base, to demonstrate safety and efficacy through preclinical and/or clinical testing and to require all petitioners for approval of generic formulations referencing Eloxatin solution (ANDAs) containing added sugars (e.g. lactose), to demonstrate that Pt(DACH) complexes do not form under anticipated storage and use conditions through preclinical and/or clinical testing, and that any new by-products have been shown to be safe and retain the same tumor specificity and efficacy. Since

there are CMC deficiencies at this time, a discussion of the implications of the Citizen's Petition on this product is not necessary.

**Conclusion:**

I concur with the above recommendation by the CMC review team that the application cannot be approved. The applicant will need to address the deficiencies before an approval can be granted. Therefore an approvable letter will be sent listing the deficiencies.

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Ann Farrell  
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MEDICAL OFFICER