CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208216Orig1s000

CHEMISTRY REVIEW(S)

Recommendation:
NDA: Approval

NDA 208216
Review #1

Drug Name/Dosage Form	Azacitidine/Injection
Strength	100 mg/vial
Route of Administration	Subcutaneous and Intravenous
Rx/OTC Dispensed	Rx
Applicant	Actavis LLC
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	OPQ/ONDP
Drug Product	Amit Mitra	OPQ/ONDP/DNDP 1/Branch 2
Process	David Anderson	Branch 3 Division 7
Microbiology	Nutan Mytle	Branch 2, DMA
Facility	Frank Wackes	
Biopharmaceutics	Banu Zolnik Okpo Eradiri	Branch 1/Division of Biopharmaceutics
Regulatory Business Process Manager	Rabiya Laiq	OPQ/OPRO/Branch 1
Application Technical Lead	Anamitro Banerjee	OPQ/ONDP/DNDP 1/Branch 2
Laboratory (OTR)		
ORA Lead		
Environmental Assessment (EA)		

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	10/18/2015	LoA provided Dt.: 5/18/2015.
	Type III			Adequate	Dr. J. S. Hathaway, Dated: 12-JUL-2004	Type 1 glass vials are not reviewed routinely
	Type III			Adequate	Dr. Z. F. Ge, Dated: 24-NOV-214	The information provided in the application along with the (b) (4) is adequate.
	Type V			Withdrawn		(b) (4)
	Type III			Withdrawn		(b) (4)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	050794	LD, Vidaza, 100 mg/vial , Azacitidine for injection
ANDA	201537	Azacitidine for injection, 100 mg/vial

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	None			
Pharmacology/Toxicology	Conducted separate review			
CDRH	N/A			

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval from the CMC point of view. No outstanding CMC deficiencies are identified at this time.

1. Summary of Complete Response issues
   None

2. Action letter language, related to critical issues such as expiration date
   The applicant has provided adequate stability data to support a 24 month shelf life.
3. Benefit/Risk Considerations
   None

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

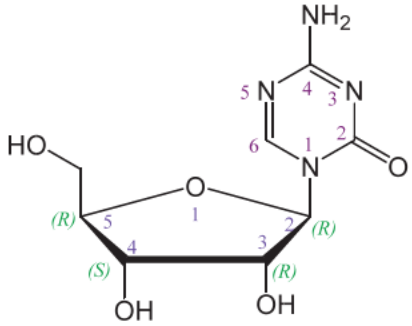
None

II. Summary of Quality Assessments

A. Drug Substance [USAN Name] Quality Summary

1. Chemical Name or IUPAC Name/Structure

1,3,5-Triazin-2(1*H*)-one, 4-amino-1-β-Dribofuranosyl



4-amino-1-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,3,5-triazin-2(1*H*)-one

Chemical Formula: $C_8H_{12}N_4O_5$

Molecular Weight: 244 (b) (4)

2. Properties/CQAs Relevant to Drug Product Quality

The API is a white to (b) (4) white powder with 4 stereocenters. (b) (4) The applicant lists the pKa to be (b) (4) but based on the molecular structure and solubility, this appears to be an error. (b) (4)

(b) (4)

3. List of starting materials

The applicant has referred to the DMF (b) (4) for drug substance information. The DMF is currently adequate to support this NDA.

4. Suppliers of starting materials (site)

The applicant has referred to the DMF (b) (4) for drug substance information. The DMF is currently adequate to support this NDA.

5. Summary of Synthesis

The applicant has referred to the DMF (b) (4) for drug substance information. The DMF is currently adequate to support this NDA.

6. Process

The applicant has referred to the DMF (b) (4) for drug substance information. The DMF is currently adequate to support this NDA.

7. Container Closure

The applicant has referred to the DMF (b) (4) for drug substance information. The DMF is currently adequate to support this NDA.

8. Retest Period & Storage Conditions

The applicant has referred to the DMF (b) (4) for drug substance information. The DMF is currently adequate to support this NDA.

B. Drug Product [Established Name] Quality Summary

1. Strength

100 mg/vial

2. Description/Commercial Image

The drug product Azacitidine for Injection is for subcutaneous (SC) and intravenous (IV). The (b) (4) powder is reconstituted as a suspension for SC and further diluted as a solution for IV administration. The drug product is supplied in a (b) (4) Type I clear glass vial closed with a (b) (4) stopper. The vial is capped with an (b) (4) The primary container is enclosed in a carton.

3. Summary of Product Design

The applicant used physical properties comparison to support the bioequivalence with the listed drug (LD) Vidaza (see below for Biopharmaceutics considerations). The applicant added (b) (4) (b) (4) While the LD contains mannitol, this product has sucrose and phosphate (b) (4). Additional specifications for elemental impurities are added per ICH Q3D.

As the API is sparingly soluble [redacted], For IV use, a more diluted solution [redacted] is further diluted with 0.9% sterile sodium chloride solution or sterile lactated ringer solution. The applicant conducted drug excipient compatibility studies to demonstrate stability at pH [redacted].

4. List of Excipients:

The excipients used in the manufacture of the drug product are disodium hydrogen phosphate dehydrate, USP, monosodium phosphate monohydrate, USP, [redacted], sucrose, USP, [redacted]

5. Process Selection (Unit Operations Summary)

a. Sterilization processes of the drug product, as applicable [redacted] The applicant provided lyophilization parameters for [redacted] kg commercial batch.

6. Container Closure

The primary container closure consists of a [redacted] USP Type I glass vial with a [redacted]

7. Expiration Date & Storage Conditions

The drug product may be stored at 25°C/60% RH with a shelf life of 24 months.

8. List of co-packaged components

None

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Azacitadine for Injection
Non Proprietary Name of the Drug Product	Azacitadine for Injection
Non Proprietary Name of the Drug Substance	Azacitadine
Proposed Indication(s) including Intended Patient Population	Treatment of patients with the following FAB myelodysplastic syndrome (MDS) subtypes: Refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL).
Duration of Treatment	Continue treatment as long as the patient continues to benefit
Maximum Daily Dose	NA

D. Biopharmaceutics Considerations

Background:
The listed drug product, Vidaza® (azacitidine suspension for subcutaneous injection), was approved under NDA 50794 on May 19, 2004. The intravenous route of administration (of the solution upon further dilution) was approved under the same NDA on January 7, 2007. Vidaza® is indicated for the treatment of patients with the following French-American-British (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia. The approval of intravenous route of administration was based on the results of a bioequivalence study evaluating the subcutaneous (SC) and intravenous (IV) routes of administration.

Submission:
The current 505(b)(2) NDA 208216 submission for Azacitidine for Injection, 100 mg/vial for the subcutaneous and intravenous routes of administration is relying on the FDA's findings of safety and efficacy for the listed drug, Vidaza®.

Review:
The Biopharmaceutics assessment is focused on the evaluation of the submitted information/data supporting the approval of the biowaiver requests for SC and IV routes of administration.

The overall supportive information is reviewed in the following sections:

- Comparison of injection site, and technique
- Effect of excipients on safety (sucrose vs. mannitol (b) (4))
- Comparison of physico-chemical characteristics and in vitro dissolution data
- Comparative assessment of the impact of mannitol and sucrose on the PK and renal elimination of azacitidine
- Pharmacokinetic information and literature data for the listed drug product (Vidaza®) following SC and IV administration

Reviewer's assessment of biowaiver request for the SC route of administration:
The Applicant provided comprehensive in vitro and literature data comparing the listed and the proposed azacitidine products in support of the biowaiver request for the SC route of administration.

In assessing the biowaiver request for the SC route, the following characteristics and factors for the listed and proposed drug products were evaluated and compared:

- Both drug products have the same concentration, injection volume, dosage form, the route of administration, and injection technique

- Comparative physico-chemical data such as viscosity, osmolality, pH, specific gravity, surface tension, and particle size data show that the listed and proposed drug products have similar properties. In addition, dissolution data of the listed drug (suspension) and the proposed drug product (suspension) are similar, indicating that the dissolution/release of drug from the suspension formulation in the injection site will be similar.
- When the suspension formulation in the finished product vials was submerged in (b) (4) complete dissolution occurred within (b) (4) (b) (4) the physical state of azacitidine is therefore expected to be similar for both, the listed drug product and the proposed drug product.
- Vidaza® label and published literature data show that azacitidine's absolute bioavailability is comparable between the SC and IV routes of administration, indicating that the route of administration is not a major factor on the PK of the drug.
- Both mannitol and sucrose (b) (4) in the formulation, and both are expected to be absorbed rapidly following SC administration due to their small molecular size.
- The published literature does not indicate any renal adverse effects or other concerns for sucrose at the levels present in the SC and IV formulations.

In conclusion, the provided overall information/data listed above supports the Applicant's request of a waiver for the requirement of the submission of in vivo bioavailability/ bioequivalence data for the SC route. Therefore, a biowaiver for the proposed Azacitidine for Injection product for **the subcutaneous route of administration is GRANTED**.

Reviewer's assessment of the biowaiver request for the IV route of administration:

The information/data submitted to demonstrate that; 1) the in vitro physico-chemical characterization on the listed and proposed drug products are comparable, 2) the presence of sucrose does not have an impact on the urinary excretion of azacitidine, and 3) the supportive PK information by the IV route is acceptable. Therefore, the Applicant's request for a waiver of the requirement to submit in vivo bioavailability/bioequivalence data for the proposed Azacitidine for Injection product **following IV administration is GRANTED.**

Additionally, it is noted that the suspension dissolves very rapidly; therefore, (b) (4) Since reconstitution time with an acceptance criterion of not more than (b) (4) is already one of the quality tests included in the specifications table of the drug product for batch release and stability testing, the Applicant was requested to (b) (4) . The Applicant provided an updated Specifications Table in an amendment (Seq.0010 dated 03/23/2016).

E. Novel Approaches

None

F. Any Special Product Quality Labeling Recommendations

None

G. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Anamitro Banerjee -S

Digitally signed by Anamitro Banerjee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000423276, cn=Anamitro Banerjee -S
Date: 2016.03.30 14:31:45 -04'00'

97 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

ASSESSMENT OF THE BIOPHARMACEUTICS

Background:
Azacitidine is a pyrimidine nucleoside analog of cytidine. Azacitidine is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. The listed drug product, Vidaza® (azacitidine suspension for injection) was approved under NDA 50794 on May 19, 2004 and the intravenous route of administration for the solution of the drug (after further dilution) was approved on January 7, 2007. Vidaza® is indicated for the treatment of patients with the following French-American-British (FAB) myelodysplastic syndrome (MDS) subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refactory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia. Note that the approval of the intravenous route of administration was based on the results of a bioequivalence study between the SC and IV routes of administration.

Drug Substance:
Azacitine is insoluble in acetone, ethanol/water (50/50), propylene glycol, and polyethylene glycol; sparingly soluble in water, water-saturated octanol, 5%, normal saline, and 5% Tween 80 in water; and soluble in dimethylsulfoxide (DMSO).

(b) (4)

Drug Product:
The drug product is a white- to almost white sterile (b) (4) powder in a single use vial. It was developed for subcutaneous (SC) injection after reconstitution as a suspension (at 25 mg/mL) and for intravenous (IV) infusion after reconstitution as a solution (at 10 mg/mL) with further dilution.

The listed drug (Vidaza®) and the proposed drug products are different in their respective inactive ingredients. Vidaza® contains mannitol whereas the proposed drug product contains sucrose, monosodium phosphate monohydrate and disodium hydrogen phosphate, dehydrate.

(b) (4)

Table 1: Formulation Comparison with Listed Drug Product

Components	Vidaza® 100 mg	Azacitidine for Injection 100 mg
	Formula/ unit dose	Formula/ unit dose
	Powder for solution for injection (100 mg /vial)	Powder for solution for injection (100 mg /vial)
Azacitidine	100.00 mg	100.00 mg
Mannitol	100.00 mg	Not applicable
Sucrose	Not applicable	170.00 mg
Monosodium phosphate monohydrate (MSP)	Not listed	(b) (4) mg
Disodium hydrogen phosphate, dihydrate (DSP)	Not listed	mg

Evaluation of Biowaiver Requests:

This review focuses on the evaluation of the information/data supporting the biowaiver request for both, the subcutaneous (SC) and intravenous (IV) routes of administration.

The Applicant stated that recruitment of patients with MDS and Chronic Myelomonocytic Leukemia is very difficult due to the rare and severe nature of the disease (average 24 months overall survival). Therefore, the Applicant provided a comprehensive assessment of the formulation differences between the listed and proposed drug products and their potential impact on the PK of azacitidine following SC and IV administration.

The Applicant's information/data provided to support the biowaiver requests for the SC and IV routes is reviewed in the following sections:

- Comparison of injection site, and technique
- Effect of excipients on safety (sucrose vs. mannitol (b) (4))
- Comparison of physico-chemical characteristics and in vitro dissolution data
- Assessment of the impact of mannitol and sucrose on the PK and renal elimination of azacitidine
- Pharmacokinetic information and literature data for the listed drug product, Vidaza® (azacitidine) following SC and IV administration

Reviewer's assessment of biowaiver request for the SC route of administration:

1. Factors Influencing Azacitidine PK Profile after SC Administration

- **Physiology of the SC environment**:

The Applicant provided the following information on the physiology of the SC environment.

"Drug administration by SC injection results in delivery to the interstitial area underlying the dermis of the skin. The interstitium consists of a fibrous collagen network supporting a gel-phase comprising negatively charged glycosaminoglycans (largely hyaluronan), salts, and plasma derived proteins. The proteins present within the interstitial space are essentially the same as those in plasma but are thought to be present at 50% lower concentration.

The small molecules (less than (b) (4)) are thought to be absorbed by the blood capillaries due to their largely unrestricted permeability across the vascular endothelium together with the high rate of filtration and reabsorption of fluid across the vascular capillaries (in the range of 20-40 L/day in comparison to approximately 2-4 L. By contrast, the absorption of particles (less than (b) (4) nm) and macromolecules into the blood is restricted by their limited permeability across the vascular endothelia and lymphatics provide an alternative absorption pathway from the interstitial space."

The Applicant submitted a published reference on the subcutaneous drug delivery and the role of lymphatics. The next figures illustrate the anatomy of the SC injection site and the absorption pathways (McLennan D.N et al., *Drug Discovery Today: Technologies*, Vol.2, No.1, 2005).

COPYRIGHT MATERIAL WITHHELD

Figure 1. A diagrammatic representation of the subcutaneous injection site. Adapted, with permission from Elsevier, from Moffett *et al.* [47].

COPYRIGHT MATERIAL WITHHELD

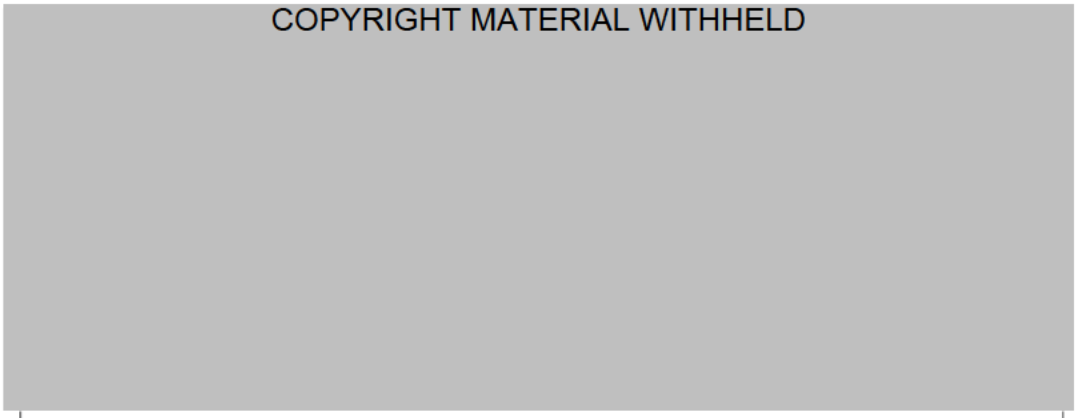


Figure 3. Generalised schematic representing SC absorption via the blood and lymphatic absorption pathways into the systemic circulation.

- **Factors that may influence drug absorption from the SC administration**

The Applicant provided the following information on the factors that may influence drug absorption from SC administration: molecular size or particle size (in the case of injectable suspensions), pKa, pH of the product, solubility of the drug, drug solubility in the tissue fluids, viscosity of the formulation, drug concentration, age, body movement, blood supply at the injection site, injection volume, injection technique, and the site of injection.

- **Comparison of injection site, and technique**

The proposed and listed drug products have the same concentration, dosage form, route of administration, injection volume, and injection technique.

- **Excipients (sucrose vs. mannitol (b) (4)) on safety**

The Applicant provided information for the other FDA's approved drug products containing sucrose as excipient. The maximum expected amount of sucrose per day is within the limits of sucrose in the approved drug products. Therefore, subjects have been already exposed to the maximum expected amount of sucrose in the proposed drug product.

Table 6: FDA Approved SC Drug Products Containing Sucrose as excipient

SC inj products containing sucrose as excipient	How supplied	Sucrose dosage	The maximum recommended dose	The maximum expected dose of sucrose per day
ORENCIA® Abatacept	(b) (4)			(b) (4)
XOLAIR® Odalizumab				
PEGINTRON® peginterferon alfa-2b)				
AZACITIDINE ACTAVIS	**100 mg/4 ml**	**170 mg/vial**		

The Applicant also provided information showing that the amount of monosodium phosphate monohydrate and disodium hydrogen phosphate are below the amount used in the other FDA approved products (e.g., Somavert and Intron A) for the same route of administration.

➢ Comparison of Physico-Chemical Characteristics

The Applicant submitted comparative physico-chemical data such as viscosity, osmolality, pH, particle morphology, particle size and in vitro dissolution information between the listed drug and the proposed drug products. The in vitro tests were performed on ten samples from one lot of the test and one lot of the listed drug product.

(b) (4)

4 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

➢ Pharmacokinetic information and literature data for the listed drug product, Vidaza following SC and IV administration

According to the Vidaza® label, the pharmacokinetics of azacitidine was studied in 6 MDS patients following a single 75 mg/m^2 SC dose and a single 75 mg/m^2 IV dose. Azacitidine is rapidly absorbed following SC administration and maximum plasma concentration is reached in 30 minutes. The bioavailability of azacitidine following SC administration relative to IV is approximately 89%. The mean volume of distribution following IV dosing is 76±26 L, the mean apparent SC clearance is 167±49L/hour, and the mean half-life after SC administration is 41±8 minutes.

Published studies indicate that urinary excretion is the primary route of elimination of azacitidine and its metabolites. Following IV administration of radioactive azacitidine to 5 cancer patients, the cumulative urinary excretion was 85% of the radioactive dose. Fecal excretion accounted for less than 1% of the administered radioactive dose over 3 days. Mean excretion of radioactivity in urine following SC administration of ^{14}C-azacitidine was 50%. The mean elimination half-life of total radioactivity (azacitidine and its metabolites) was similar after IV and SC administration and was reported as approximately 4 hours.

➢ Additional Information submitted in the re-submission of the Biowaiver request for the Subcutaneous Route

➢ In Vivo Disposition of Mannitol

The Applicant stated that there is very limited data on the mannitol disposition following IV administration. However, in a three-way cross over PK study in healthy volunteers, plasma mannitol data showed that the inhalation route follows the IV route of administration after 2 hour post exposure (see figure below). It can be concluded that mannitol PK follows the same kinetics regardless of route of administration.

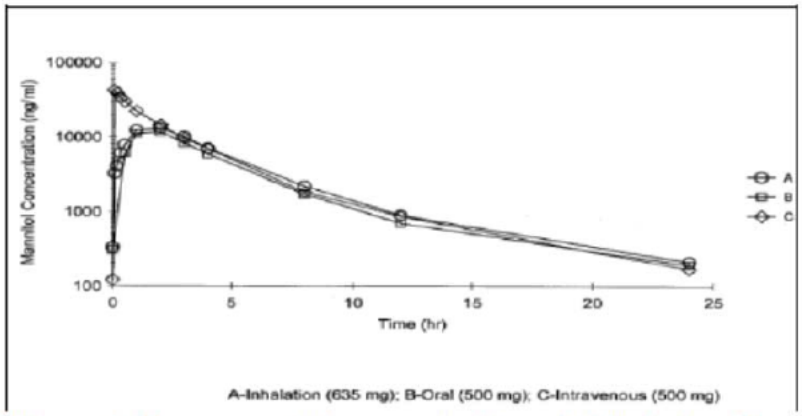


Figure 7: Mean mannitol concentrations: A-inhalation; B-oral; C-intravenous.

➢ **The effect of mannitol on the urinary flow:**

According to the literature data, mannitol administered in high doses (up to 150 fold of the amount in Vidaza®) is known to have an influence on the urinary flow and renal elimination of various chemicals. This process may theoretically occur for Vidaza®, however given the very low amount present in formulation ((b) (4) of the therapeutic dose), a linearity of dose-effect relationship and the differences in plasma availability (half-life) of azacitidine and mannitol, the increase of urinary excretion of Vidaza® and its metabolites due to mannitol presence will be negligible.

➢ **In Vivo Disposition of Sucrose**

- The Applicant stated that the published literature contains no evidence that sucrose produces renal adverse effects or other concerns at the levels present in the FDA's approved and marketed SC and IV drug products (e.g., Venofer, Actemra, Xolair).
- Significant metabolism of subcutaneously or intravenously administered sucrose is not expected, because subcutaneously administered sucrose is absorbed by simple diffusion (ref: Health Council of the Netherlands: Committee on Updating of OEL-Sucrose, 2004) and sucrose is not known to be converted to fructose and glucose outside the gastrointestinal tract or to be utilized in the synthesis of glycogen. Sucrose is eliminated mainly unchanged by renal excretion.
- The Applicant provided literature data on sucrose absorption following SC administration. It is stated that after SC administration of sucrose to the mouse, 50% of the compound is absorbed within 5-8 minutes, and the rate of disappearance after SC administration did not differ for sucrose of 6%, 10% and 14% (ref: Classen V., Neglected factors in Pharmacology and Neuroscience Research, Elsevier 1994, chapter 4, pg 36-38).
- According to the published data, sucrose administered in high doses is not known to have any impact on urinary flow, or renal elimination of other chemicals. No renal safety concerns in normal and impaired renal patients were triggered with other marketed IV products in the US (examples of FDA approved drug products containing sucrose in higher amounts are Actemra, Venofer or Xolair. From PK perspective, no influence of sucrose on excretion of azacitidine itself or its metabolites is expected.

➢ **Mannitol-Sucrose Comparative PK Data**

The Applicant stated that sucrose and mannitol have the same properties in the formulation, and both are expected to be absorbed rapidly due to their small molecular size. In addition, neither mannitol nor sucrose has the organic solvent characteristics that could alter the absorption of azacitidine from the injection site. In addition, no binding to plasma proteins is reported. The Applicant provided the following comparative PK table on sucrose and mannitol.

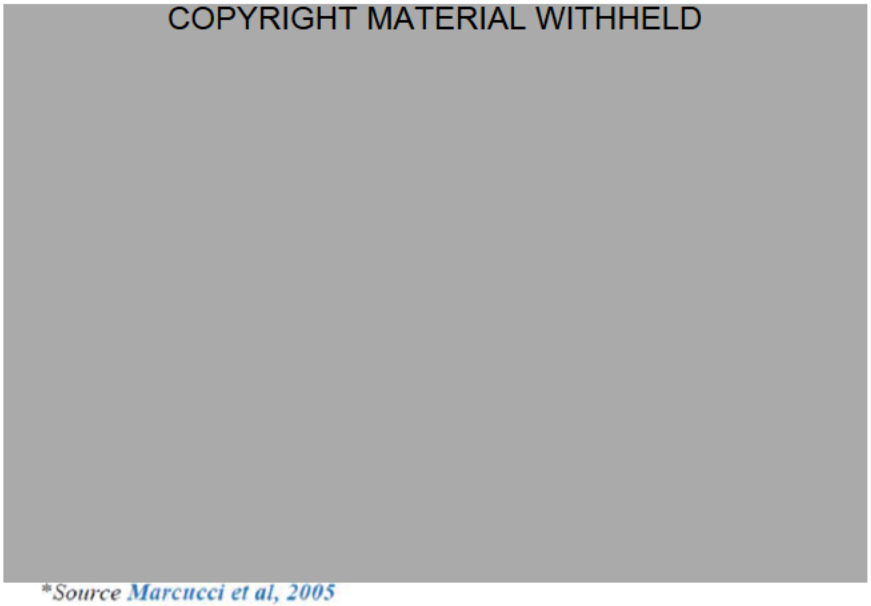
A short comparative table assessing their expected PK profiles is presented below:

	Mannitol	Sucrose
SC absorption	Facile (small m.w.), no specific transporter system	Facile (small m.w.), no specific transporter system
Influence of API absorption	Not expected (based on lack of interaction with the API); also, it lacks the characteristics of an absorption enhancer	Not expected (based on lack of interaction with the API); also, it lacks the characteristics of an absorption enhancer
Plasma distribution	Limited to intravascular space	Limited to intravascular space
Binding to plasmatic proteins	NO	NO
Pharmacological effect	None expected (at the proposed dose)	NO
Metabolism	NO	NO
Excretion	Renal mostly (unchanged)	Renal mostly (unchanged)

➢ **Additional Information on Azacitidine PK**

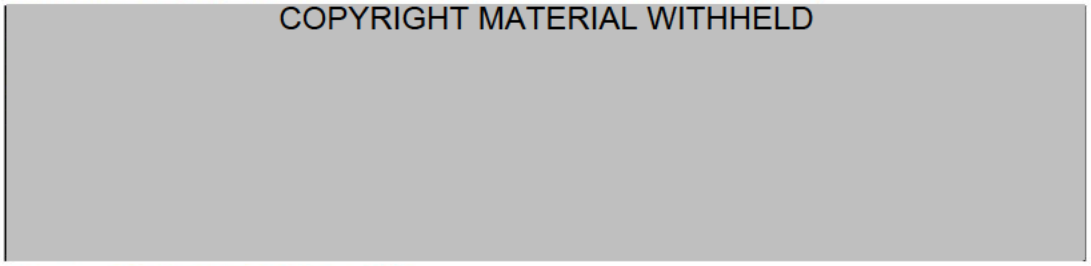
- The Applicant provided additional published information on the absorption kinetics of azacitidine following SC administration. The Applicant stated that only lipidic molecules are being absorbed from injection by passive diffusion through the cell membranes. Other molecules that are ionic in nature need either an active transporter, or facilitated diffusion, or diffusion through intercellular space (junctions). It is stated that that small molecules (b) (4) easily diffuse into blood following SC injection. It is also noted that additional factors such as local tissue perfusion, local temperature, depth, volume of injection, and binding interactions and catabolism in subcutaneous tissue impacts the absorption.
- The Applicant provided literature PK data (ref: Troetel WM., et al. Absorption, distribution and excretion of 5-azacytidine (NCS-102816) in man, Cancer Chemother Rep 1972; Jun 56(3):405-411) from early Phase 1 studies of Vidaza® given IV and SC routes. Similar to what has been reported in the Vidaza® label, absorption of azacitidine from the SC site was rapid with plasma levels within 2 hours equal to those patients treated with IV drug. The half-lives of 3.5 hours and 4.2 hours and 85% and 50% of the radioactivity was excreted in the urine with 48 hours following IV and SC injection, respectively. Subsequent study (ref: Von Hoff, DD., 5-Azacytidine A New Anticancer Drug with Effectiveness in Acute Myelogenous Leukemia, Annals of Internal Medicine, Volume 85, Number 2, pages 237-245) also confirmed the similar findings of rapid absorption and comparable half-lives between the IV and SC injections.
- Below are the concentration-time profiles and the summary PK parameters following SC and IV infusion in 6 MDS patients. The bioavailability based on AUCinf of the SC/IV ratio of the geometric leas square means was 89% with 90% CI between 70-112. Please note that this study was discussed above under the section on Azacitidine pharmacokinetic information.

Figure 1: Mean azacitidine concentration-time profile for subcutaneous (SC) and intravenous (IV) treatments.



*Source *Marcucci et al, 2005*

Table 2: Summary of Arithmetic Mean ± SD Pharmacokinetic Parameters Following Subcutaneous (SC) and Intravenous (IV) Dose Administration (n = 6)



*Source: *Marcucci et al study, 2005*

The Applicant also provided a literature reference regarding the PK of azacitidine evaluated in 53 Japanese patients receiving 75 mg/m^2 azacitidine SC or IV one daily for seven consecutive days on 28 day cycle.

Figure 2 Time-Course of Mean Plasma Concentrations of Azacitidine Following SC and IV administration (Source: **Uchida et al, 2011**)

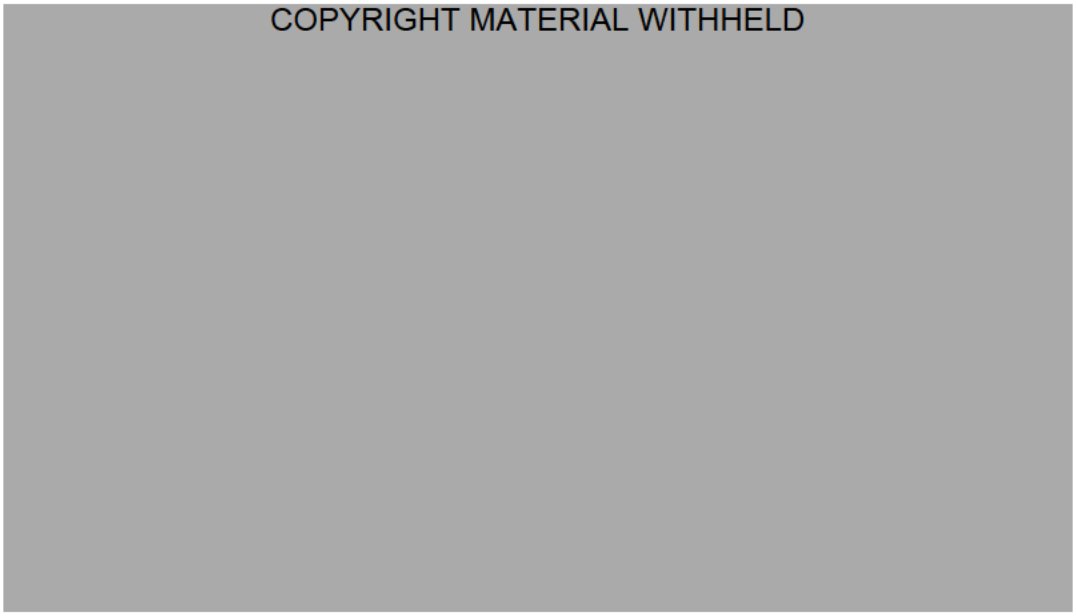
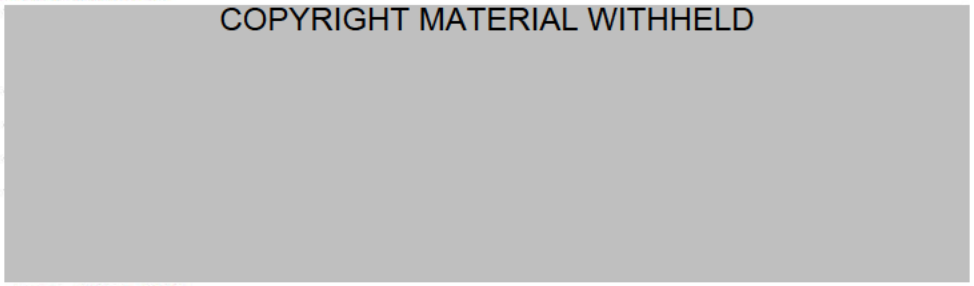


Table 3 Pharmacokinetic Parameters for Azacitidine after Subcutaneous and Intravenous Administration



Source: (Uchida, 2011)

➢ Additional in vitro dissolution data

The Applicant conducted an additional in vitro dissolution study comparing the dissolution of the proposed and listed drug products using (b) (4)). Below are the mean % dissolved values in table and figure formats. The Applicant reported an f2 similarity factor as (b) (4) indicating that the dissolution profiles of the proposed and listed drug products are similar.

Table 15: Mean results of dissolution percentage, as time dependency

Time (min)	RLD Vidaza, F113C010	Sample Azacitidine NDA, FE14003A
0	0.0	0.0
3	49.8	40.6
6	77.1	69.3
9	88.6	84.5
12	93.0	91.9
15	95.0	95.0
20	96.0	96.6
30	96.7	97.2

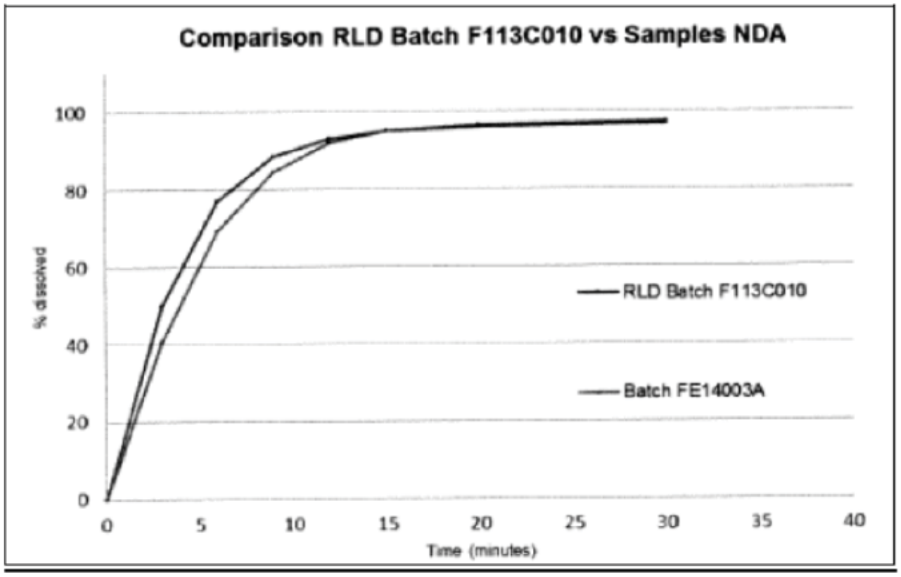


Figure 6: Dissolution profile comparison

Reviewer's Overall Assessment of the Biowaiver Request for the SC Route of Administration

The Applicant provided comprehensive in vitro and literature data comparing the listed and proposed drug products in support of the SC biowaiver request. The following characteristics and factors were compared in assessment of the biowaiver request.

- Both formulations have the same concentration, injection volume, dosage form, the route of administration, injection technique
- The comparative physico-chemical data such as viscosity, osmolality, pH, specific gravity, surface tension, and particle size data showed that the listed and proposed drug products have similar properties. In addition, the dissolution data of the

listed drug (suspension) and the proposed drug product (suspension) are similar indicating that the release (dissolution) of the drug from the formulation at the injection site will be similar.

- The results from an in vitro study in which drug product vials submerged in an (b) (4) ndicated that within (b) (4) min, the suspension will dissolve into solution, thereby the physical state of azacitidine is expected to be similar for both listed drug and the proposed drug.
- Vidaza® label and literature data indicated that azacitidine bioavailability is comparable between the SC and IV routes of administration.
- Both mannitol and sucrose (b) (4) in the formulation, and both are expected to be absorbed rapidly due to their small molecular size following SC administration
- The published literature does not include any information indicating that sucrose produces renal adverse effects or other concerns at the levels present in the SC formulation.

In conclusion, the overall information/data described above is acceptable and therefore supports the Applicant's request for a waiver of the requirement to submit in vivo bioavailability/bioequivalence data. The biowaiver request for the proposed Azacitidine for Injection product for the subcutaneous route of administration is **GRANTED.**

Reviewer's assessment of biowaiver request for the IV route of administration:

Factors Influencing Azacitidine PK Profile after IV Administration

The majority of the information supporting the biowaiver for the SC route of administration is also used to support the biowaiver for the IV route of the administration, because after the drug is rapidly absorbed from the subcutaneous site and reaches the systemic circulation, the drug's distribution/elimination pharmacokinetic profile is similar to that of the IV route of administration. Therefore, the following information also supports the biowaiver for the IV route of administration:

- Effect of excipients on safety (sucrose vs. mannitol and (b) (4))
- Comparison of physico-chemical characteristics and in vitro dissolution data
- Assessment of the impact of mannitol and sucrose on the PK and renal elimination of azacitidine
- Pharmacokinetic information and literature data for the listed drug product Vidaza® (azacitidine) following SC and IV administration

Reviewer's Overall Assessment of the Biowaiver Request for the IV Route of Administration

The Applicant provided sufficient data comparing the listed and proposed drug products in support of the IV biowaiver request. The following characteristics and factors were compared in assessment of the biowaiver request.

- Both formulations have the same concentration, injection volume, dosage form, the route of administration, injection technique
- The comparative physico-chemical data such as viscosity, osmolality, pH, specific gravity, surface tension, and particle size data showed that the listed and proposed drug products have similar properties.
- Vidaza® label and literature data indicate that azacitidine bioavailability is comparable between the SC and IV routes of administration.
- Both mannitol and sucrose (b) (4) in the formulation, and both are expected to have the similar disposition and elimination following IV administration.
- The published literature does not include any information indicating that sucrose produces renal adverse effects or other concerns at the levels present in the IV formulation.

In conclusion, the Applicant's assertion that sucrose will not impact on the urinary excretion of azacitidine is acceptable and the overall in vitro physico-chemical characterization and supportive PK information supports the Applicant's request for a waiver of the requirement to submit in vivo bioavailability/bioequivalence data. The biowaiver request for the proposed Azacitidine for Injection product for the intravenous route of administration is **GRANTED.**

Information Requests (IR) sent to the Applicant

IR letter dated December 3, 2015: The Applicant provided comprehensive physico-chemical data for the listed drug and the proposed drug products. However, adequate/sufficient information to support the biowaiver requests for SC and IV routes of administration was not provided in the original submission. Therefore, the following comments were conveyed to the Applicant in an IR letter dated December 3, 2015:

- *There are differences in the inactive ingredients between the proposed drug product and the listed drug that may impact the bioavailability of azacitidine following subcutaneous administration, therefore your request for waiver of the requirement for the submission of evidence demonstrating the in vivo*

bioequivalence of the proposed drug product per 21 CFR § 320.22 (b)(1) is not granted. You may either establish bioequivalence between the proposed drug product and listed drug to support the approval of subcutaneous administration of the proposed drug product, or withdraw the subcutaneous route of administration from the NDA.

- *For the intravenous route of administration, provide justification with supporting data (published literature, study data etc.) demonstrating that the replacement of mannitol with sucrose in the proposed drug product will not have any impact on the urinary excretion of azacitidine and its metabolites.*

Reviewer's evaluation of the Applicant's response provided in Seq.0004 dated 01/07/2016 for the IV route of administration - ADEQUATE

Reviewer's evaluation of the Applicant's response in Seq.0004 dated 01/07/2016 for the SC route of administration – NOT ADEQUATE
It is noted that the Applicant withdraw the subcutaneous route of administration from the NDA.

IR dated February 12, 2016: Although, the Applicant followed the FDA's advice of withdrawal of the SC administration from the NDA, during an internal meeting with the clinical team, it is became evident that approval of the subcutaneous route was needed to support Section 14 of the product's labeling, because the efficacy of the drug was established on the basis of clinical studies conducted with the SC route of administration. Therefore, the clinical review team sent the following IR comment to the Applicant 02/12/2016:

- *Clinical support for approval of azacitidine was based on use of the subcutaneous route of administration **not** the intravenous route. The innovator provided a study comparing subcutaneous route and intravenous route allowing an understanding of pharmacokinetic relationship between the various routes of administration. Provide clinical efficacy and safety data or literature references using your product via the intravenous route for review. Alternatively you could include the subcutaneous route of administration and establish bioequivalence between the proposed drug product and listed drug.*

IR dated March 3, 2016: The following information request was sent to the Applicant in preparation for the teleconference held on 3/3/2016, between Dr. Ann Farrell, Director of DHP and the Applicant.

- *Vidaza was originally approved based on the subcutaneous route of administration. All clinical trials described in section 14 of the Vidaza labeling describe the subcutaneous route of administration and efficacy results based on that usage. A single PK/bioavailability study was conducted comparing single administration subcutaneous route with the intravenous route. This information was included in the Clinical Pharmacology section of the labeling (12.3). No efficacy or safety information was provided with intravenous use. You originally*

submitted an NDA with a proposal for subcutaneous as well as intravenous use. Due to issues with your biowaiver request for subcutaneous use, you requested withdrawal of the subcutaneous use. Thus, your application is left with only the intravenous use, for which there is no efficacy and safety data. Provide the justification that allows the use of the efficacy and safety data obtained with the subcutaneous route for an intravenous use only presentation or resubmit a biowaiver request for the subcutaneous route with supportive data for review. In your justification, explain why the observed differences in PK with the intravenous use compared with the subcutaneous use, do not impact with the observed efficacy and safety effect seen with the subcutaneous route.

Reviewer's evaluation of the Applicant's response provided in Seq.0006 dated 02/18/2016 and Seq.0009 dated 03/10/2016 for SC administration -ADEQUATE

It is noted that the Applicant re-submitted the biowaiver request in the amendment dated 3/10/2016 and submitted **new information** to support the SC biowaiver request in the amendments S006 and S009.

IR dated March 22, 2016: Since the proposed drug product for the SC route is a suspension, (b) (4) Since the proposed drug product dissolves very rapidly, (b) (4) In addition, a reconstitution time with an acceptance criterion of not more than (b) (4) seconds is already a test in the specifications table of the drug product for batch release and stability testing. Therefore, the following IR comment was conveyed to the Applicant on March 22, 2016:

- *The dissolution data for your proposed drug product indicate that approximately (b) (4) azacitidine is released within (b) (4) minutes. The FDA therefore considers the Reconstitution Time Test as a more appropriate test for batch release and stability. Provide a revised Specifications Table in which the (b) (4)*

Reviewer's evaluation of the Applicant's response provided in Seq. 0010 dated 3/23/2016 to the IR Comment -ADEQUATE

The Applicant (b) (4) provided an updated Specifications Table.

BIOPHARMACUETICS OVERALL ASSESSMENT AND SIGNATURES:

The Biopharmaceutics assessment was focused on the evaluation of the submitted information/data supporting the approval of the biowaiver requests for SC and IV routes of administration.

- ***SC Route Biowaiver:*** Comprehensive in vitro and literature data comparing the listed and the proposed azacitidine products were submitted in support of the biowaiver request for the SC route of administration. In assessing the biowaiver request for the SC route, the following characteristics and factors for the listed and proposed drug products were evaluated and compared; **1)** both drug products have the same concentration, injection volume, dosage form, the route of administration, and injection technique**, 2)** Comparative physico-chemical data such as viscosity, osmolality, pH, specific gravity, surface tension, and particle size data showed that the listed and proposed drug products have similar properties. In addition, the dissolution data indicated similar release for the listed and proposed drug products, **3)** Vidaza® label and published literature data show that azacitidine's absolute bioavailability is comparable between the SC and IV routes of administration, indicating that the route of administration is not a major factor on the PK of the drug, **4)** both mannitol and sucrose have similar properties in the formulation, and both are expected to be absorbed rapidly following SC administration due to their small size, and **5)** the published literature does not indicate any renal adverse effects or other concerns for sucrose at the levels present in the SC and IV formulations. Therefore, the overall information/data listed above supports the Applicant's request of a waiver for the requirement to submit in vivo bioavailability/bioequivalence data for the SC route and the biowaiver for **the subcutaneous route of administration** is **GRANTED**.

- ***IV Route Biowaiver:*** The overall submitted information/data demonstrated that; **1)** the in vitro physico-chemical characterization of the listed and proposed drug products are comparable, **2)** the presence of sucrose does not have an impact on the urinary excretion of azacitidine, and **3)** the PK information supports the IV route. Therefore, the Applicant's request for a waiver of the requirement to submit in vivo bioavailability/ bioequivalence data for the proposed Azacitidine for Injection product **following IV administration** is **GRANTED.**

- ***Dissolution Test:*** Since the SC suspension dissolves very rapidly, (b) (4) . Therefore, the Applicant was requested to (b) (4) However, it is noted that the reconstitution test with an acceptance criterion of not more than (b) (4) seconds is one of the tests included in the specifications controlling the quality of the proposed drug product.

Reviewer's Assessment and Signature:
From the Biopharmaceutics perspective, the Applicant's biowaiver requests for the both the SC and IV routes of administration are granted and **APPROVAL** is recommended for NDA 208216 for Azacitidine for Injection for SC and IV use, 100 mg/vial.

3/22/2016
Banu Sizanli Zolnik, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Review Comments and Concurrence:

I concur with Dr. Zolnik's assessment and approval recommendation for NDA 208216.

3/28/2016
Okpo Eradiri, Ph.D.
Biopharmaceutics Lead (Acting)
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

Tertiary Review Comments and Concurrence:

I concur with Drs. Zolnik and Eradiri's overall assessment of the information supporting the granting of the biowaiver request for the SC and IV routes of administration, as well as the recommendation for approval of NDA 208216 for Azacitidine for Injection.

Angelica Dorantes, Ph.D./March 28, 2016
Biopharmaceutics Branch Chief (Acting)
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality

ASSESSMENT OF MICROBIOLOGY

23. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

Reviewer's Assessment: P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** (3.2.P.1-description and composition of the drug product.pdf, page 1/7)
  Drug product is white, (b) (4) powder in a single use vial.
  Table -Drug product composition (Reproduced from submission-3.2.P.1-description and composition of the drug product.pdf, page 2/7)

Components of the drug product	(b) (4)	(b) (4) Product Quantity/vial	Role in Actavis formulation	Quality reference
Azacitidine	(b) (4)	100.00 mg (b) (4)	Active substance	USP
Mannitol		N/A	N/A	N/A
Sucrose		170.00 mg	(b) (4)	USP
Monosodium phosphate monohydrate		(b) (4) mg		USP
Disodium hydrogen phosphate, dihydrate		mg		USP
				(b) (4)
(b		N/A	(b) (4)	USP
		N/A		USP

Reconstitution: (3.2.P.1-description and composition of the drug product.pdf, page 6/7)

Lyophilized powder in a single use vial	Volume of diluent to be added to vial	Nominal concentration per mL
100 mg for SC use	4 mL WFI	25 mg/mL
100 mg for IV use	10 mL WFI	10 mg/mL

- **Description of container closure system –**
  (3.2.P.7-container closure system.pdf, page 1/8)

Packaging material	Type	Commercial name	Supplier

40 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

The results showed that after inoculation of reconstituted solution with microorganisms were within the proposed acceptance criteria (increase < (b) (4)) even after (b) (4) hours after their inoculation.

Acceptable

Reviewer's Assessment: Acceptable

2.3.P.7 Container/Closure System

24. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

Reviewer's Assessment: Please see response in section 'container closure system' under Q40.
The information provided in support of drug product quality microbiology for NDA 208216 is acceptable.

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

25. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

Applicant's Response:

Reviewer's Assessment: No materials are obtained or derived from animal sources.

26. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

Applicant's Response:

Reviewer's Assessment: NA

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: There were no quality microbiology deficiencies identified in the information provided. The application is recommended for approval from a quality microbiology perspective.

Reviewer's Signature
Nutan Mytle, Ph.D.
Microbiology Reviewer
Branch II
Division of Microbiology Assessment/OPF
3/16/2015

Secondary Review Comments and Concurrence:
I concur

Nandini Bhattacharya, Ph.D.
CDER/OPQ/OPF/DMA/Branch II
3.17.2016

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

27. Is the applicant's claim for categorical exclusion acceptable?

28. Is the applicant's Environmental Assessment adequate for approval of the application?

Applicant's Response:

Reviewer's Assessment:

The applicant requested a categorical exclusion based on 21CFR §25.31(a). Since the NDA is submitted as a 505(b) (2) application, the EA may be waived according to the CFR provision.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

Satisfactory, Amit K. Mitra, Ph.D/ 3/22/2016

Secondary Review Comments and Concurrence:

I concur
Anamitro Banerjee, Ph.D. March 23, 2016
Acting Branch Chief, ONDP, Branch 2

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

For NDA only

1. Package Insert

(a) "Highlights" Section (21CFR 201.57(a))

(Attach proposed text)

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Not provided Established Name: Azacitidine for injection	Proprietary name not needed for marketing approval Satisfactory, Established name same as LD
Dosage form, route of administration	Dosage: 1) Injections (Powder for injection) Route: Intraveous infusion; 2) For subcutaneous injection of suspension	Satisfactory
Controlled drug substance symbol (if applicable)	None	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Azacitidine for Injection is supplied as lyophilized powder in 100 mg single-(b)(4) vials.	Satisfactory (same as LD)

Conclusion:

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

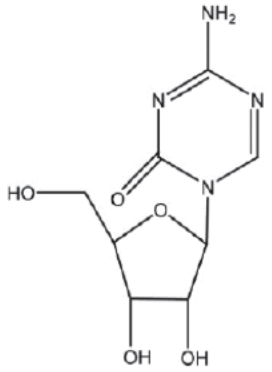
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	For injection: Azacitidine for Injection is supplied as lyophilized powder in 100 mg single-(b)(4) vials.	Satisfactory
Strengths: in metric system	100 mg	Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	None	Dosage form is not a tablet. Therefore, identifying marks as recorded in the Item are not valid.

Conclusion:

This section will be modified according to PLR, if needed.

#11: Description (21CFR 201.57(c)(12))

Azacitidine for Injection contains azacitidine, which is a pyrimidine nucleoside analog of cytidine. Azacitidine is 4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one. The structural formula is as follows:



The molecular formula is $C_8H_{12}N_4O_5$. The molecular weight is 244. Azacitidine is a white to almost white powder. Azacitidine was found to be insoluble in acetone, ethanol, and methyl ethyl ketone; slightly soluble in ethanol/water (50/50), propylene glycol, and polyethylene glycol; sparingly soluble in water, water saturated octanol, 5% dextrose in water, N-methyl-2-pyrrolidone, normal saline and 5% Tween 80 in water; and soluble in dimethylsulfoxide (DMSO).

The finished product is supplied in a sterile form for reconstitution as a suspension for subcutaneous injection or reconstitution as a solution with further dilution for intravenous infusion. Vials of Azacitidine for Injection contain 100 mg of azacitidine, 170 mg sucrose, monosodium phosphate monohydrate and disodium hydrogen phosphate, dihydrate as a sterile lyophilized powder.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Proprietary name: Not provided Established name: Azacitidine for injection.	Satisfactory
Dosage form and route of administration	Injections, Intravenous administration by infusion or subcutatneous administration for the suspension.	Satisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)	(b) (4)	Satisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	Sucrose USP (170 mg), monosodium phosphate monohydrate, USP, and disodium hydrogen phosphate dehydrate, USP	Satisfactory
Statement of being sterile (if applicable)	"The finished product is supplied in a sterile form for reconstitution	Satisfactory

	as a suspension for subcutaneous injection or reconstitution as a solution with further dilution for intravenous infusion. Vials of Azacitidine for Injection contain 100 mg of azacitidine, 170 mg sucrose, monosodium phosphate monohydrate and disodium hydrogen phosphate, dihydrate as a sterile lyophilized powder "	
Pharmacological/ therapeutic class	Anticancer (see label)	Satisfactory
Chemical name, structural formula, molecular weight	Yes	Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Yes	Satisfactory

Conclusion:

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Store unreconstituted vials at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Discard unused portion.

Handling and Disposal

(b) (4)

Sterile, Nonpyrogenic, Preservative-free.

This vial stopper is not made with natural rubber latex.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	100 mg azacitidine per vial	Satisfactory
Available units (e.g., bottles of 100 tablets)	Single use vial in cartons	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC number is provided	Dosage form is not a tablet. Therefore, identifying marks as recorded in the Item are not valid.
Special handling (e.g., protect from light, do not freeze)	(b) (4)	Satisfactory
Storage conditions	Store unreconstituted vials at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].	Satisfactory

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured by: Sindan Pharma SRL 11 Ion Mihalache Blvd. Bucharest 1, Romania 011171 and Distributed by: Actavis Pharma, Inc. Parsippany, NJ 07054 USA	Satisfactory

Conclusion:
Satisfactory (This section may be revised according to PLR).

2. Container and Carton Labeling

1) Immediate Container Label

(b) (4)

Reviewer's Assessment:

The applicant provided the following required items: Established name, dose strength, route of administration, single use sterile vial, reference to prescribing information for dosing and administration, prescription only, name and quantitiy of inactive ingredient, lot #, and expiration date. The immediate container label is satisfactory. DMEPA may have additional comments. These comments will be assessed during labeling review.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name: not provided Established name: Satisfactory	
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	None	Satisfactory
Net contents (21 CFR 201.51(a))	None	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
Storage (not required)	None	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	None	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

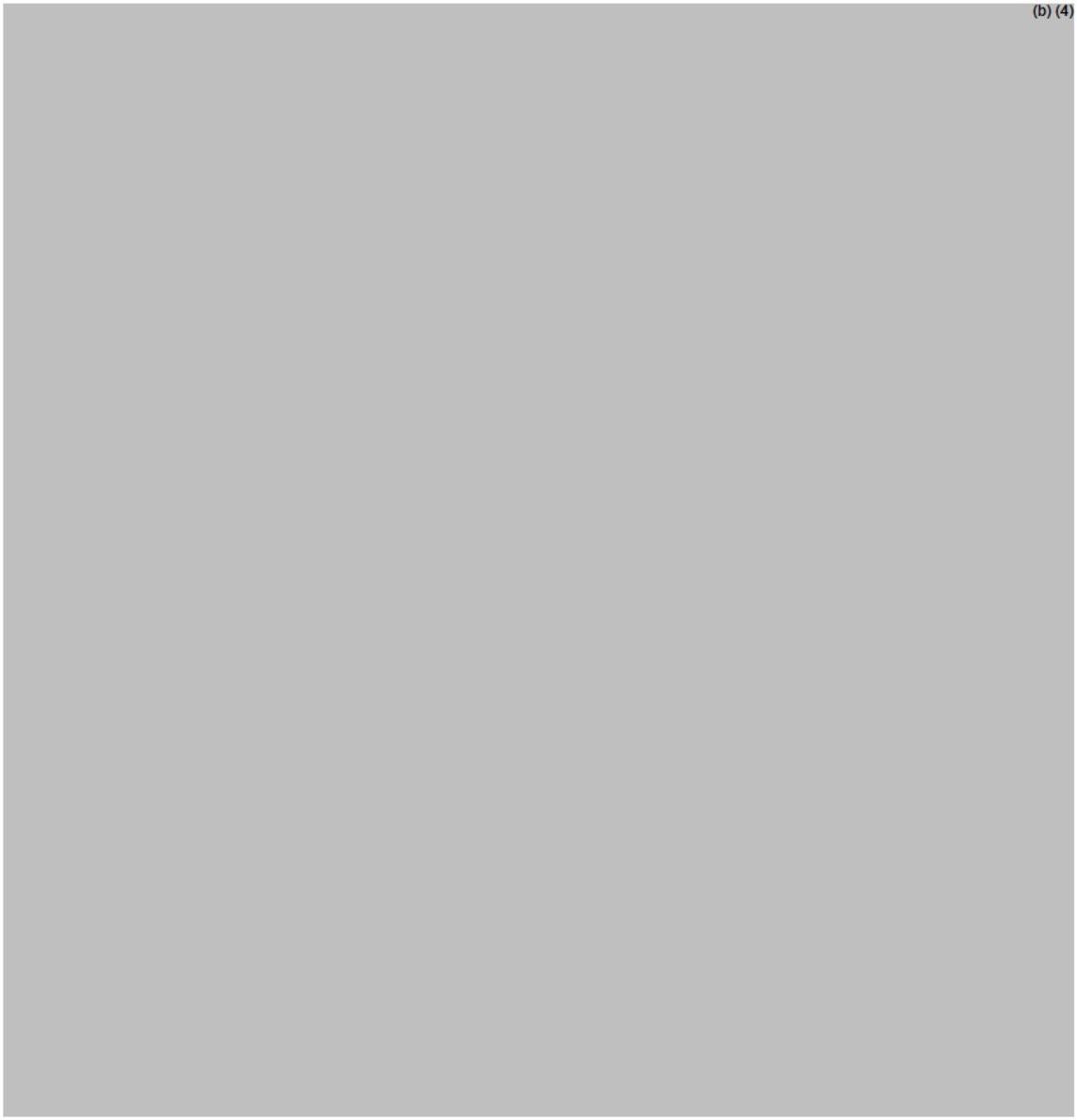
**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion:
May be revised according to PLR during labeling review.

2) Carton Labeling

(b) (4)



Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	None Established name is satisfactory	Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	None	Satisfactory
Net contents (21 CFR 201.51(a))	None	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	None	**Satisfactory**
Sterility Information (if applicable)	None	**Satisfactory**
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
Storage Conditions	None	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	None	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory

Name of manufacturer/distributor	None	Satisfactory
"See package insert for dosage information" (21 CFR 201.55)	None	Satisfactory
"Keep out of reach of children" (optional for Rx, required for OTC)	None	
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	None	Satisfactory.

Conclusion:
The labeling section is satisfactory. However, the labeling may be revised according to the PLR format.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
May be further revised in PLR format/Amit K. Mitra, Ph.D/3/22/2016

Secondary Review Comments and Concurrence:

I concur
Anamitro Banerjee, Ph.D. March 23, 2016
Acting Branch Chief, ONDP, Branch 2

II. List of Deficiencies To Be Communicated

None

III. Attachments

A. Lifecycle Knowledge Management

A. Facility

OVERALL RECOMMENDATION:
DRUG SUBSTANCE

FUNCTION	SITE INFORMATION	DUNS/FEI NUMBER	INITIAL RISK IDENTIFICATION	FINAL RECOMMENDATION
DRUG PRODUCT				
FUNCTION	**SITE INFORMATION**	**DUNS/FEI NUMBER**	**INITIAL RISK IDENTIFICATION**	**FINAL RECOMMENDATION**

B. Lifecycle Knowledge Management

a) Drug Substance

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Initial Risk Ranking***	**Justification**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments****
	H, M, or L			Acceptable or Not Acceptable	

b) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments****
Sterility	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	H	(b) (4)		Continue stability monitoring post approval
Endotoxin Pyrogen	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M			Continue stability monitoring post approval
Assay	• Formulation	L		The drug	Continue

(API)	• Container/closure • Process parameter • Scale/equipment • Site			product is unstable at high temperature and in the presence of water	stability monitoring post approval
Physical Stability (solid state)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	L	(b) (4)	The drug product is reconstituted with with water for injection leading to a solution	None
Uniformity of dose (Fill volume/deliverable volume)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M			Fill volume is kept the same as that of the LD (see pharmaceutical development report)
Osmolality	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M			None
pH (high)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	L			Monitor stability
pH (low)	• Formulation • Container/closure • Process	L			Monitor stability

	• parameter • Scale/equipment • Site				
Particulate matter	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M			Monitor stability
Leachable Extractable	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	L			
Redispersibility/reconstitution time	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M	(b) (4)		
Moisture content	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	L			Monitor stability
Appearance (caking)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	M			

Appearance(color/turbidity)	• Formulation • Container/closure • Process parameter • Scale/equipment • Site	L	(b) (4)		Monitor stability

*Risk ranking applies to product attribute/CQA
**For example, critical controls, underlying control strategies assumptions, post marketing commitment, knowledge management post approval, etc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VERIFICATION REPORT SUMMARY

TO: Amit Mitra, CMC Reviewer
David Anderson, Process Reviewer
Janice Brown, CMC Lead
Olen Stephens, Branch Chief
Rabiya Laiq, MVP Manager
ONDP
E-mail Address: amit.mitra@fda.hhs.gov; david.anderson@fda.hhs.gov; janice.brown@fda.hhs.gov
Phone: 301-796-1420, 240-402-8885, 301-796-1652

FROM: FDA
Division of Pharmaceutical Analysis
Laura C. Pogue, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-2155

Through: David Keire, Ph.D., Lab Chief, Branch I
Phone: (314) 539-3850

SUBJECT: Methods Verification Report Summary

Application Number: 208216

Name of Product: Azacitidine for Injection and for Suspension, 100 mg/vial

Applicant: Actavis LLC

Applicant's Contact Person: Joann Stavole, M.S., R.A.C.

Address: 400 Interpace Parkway, Morris Corporate Center III, Building D, 3rd Floor, Parsippany, NJ

Telephone: 862-261-7735 Email: RegulatoryAffairsUS@actavis.com

Date Methods Validation Consult Request Form Received by DPA: 09/04/2015

Date Methods Validation Package Received by DPA: 11/19/2015

Date Samples Received by DPA: 11/19/2015

Date Analytical Completed by DPA: 1/14/2016

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments: See attached summary for analyst comments and results.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis, Missouri 63110
Telephone (314) 539-2135
FAX (314) 539-2113

Date: January 14, 2016

To: Amit Mitra, CMC Reviewer
Janice Brown, CMC Lead

Through: David Keire Ph.D., Lab Chief, Branch I, CDER/OPQ/OTR/DPA

From: Anjanette Smith, Chemist, CDER/OPQ/OTR/DPA

Subject: Method Verification of NDA 208216: Azacitidine for Injection and Suspension, Actavis LLC

The following method was verified (as written) and is acceptable for quality control and regulatory purposes:

1) Degradation products by (b) (4) ((b) (4)

Analysis to address reviewer concerns presented in Appendix A:

The Division of Pharmaceutical Analysis has the following comments:
Degradation products by (b) (4) (b) (4)

(b) (4)

4 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

LAURA POGUE
01/14/2016

DAVID A KEIRE
01/14/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REQUEST FORM

TO: **FDA**
Division of Pharmaceutical Analysis
Attn: Laura C. Pogue, Ph.D.
645 S. Newstead Avenue
St. Louis MO 63110

FROM: Amit Mitra, CMC Reviewer
David Anderson, Process Reviewer
Janice Brown, CMC Lead
Office Name: ONDP
E-mail Address: amit.mitra@fda.hhs.gov; david.anderson@fda.hhs.gov; janice.brown@fda.hhs.gov
Phone: 301-796-1420, 240-402-8885, 301-796-1652

Through: Olen Stephens, Branch Chief
Phone: (301)-796-3901
and
Rabiya Laiq, Methods Validation Project Manager
Phone: (240)-402-6153

SUBJECT: Methods Validation Request

Application Number: NDA 208216

Name of Product: Azacitidine for Injection and for Suspension, 100 mg/vial

Applicant: Actavis LLC

Applicant's Contact Person: Joann Stavole, M.S., R.A.C.

Address: 400 Interpace Parkway, Morris Corporate Center III, Building D, 3rd Floor, Parsippany, NJ

Telephone: 862-261-7735 Email: RegulatoryAffairsUS@actavis.com

Date NDA Received by CDER: **6/30/2015**
Submission Classification/Chemical Class: 6
Date of Amendment(s) containing the MVP: **NA**
Special Handling Required: No
DATE of Request: **8/28/2015**
DEA Class: N/A
Requested Completion Date: **12/1/2015**
Format of Methods Validation Package (MVP)
User Fee Goal Date: **4/30/2016**
☐ Paper ☒ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the Methods Validation Requestor and the Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the Methods Validation Requestor and the Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The CMC Reviewer, Methods Validation Project Manager, and CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

ATTACHMENT(S): *Methods Validation Request Sheet*, A/NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	**METHODS VALIDATION REQUEST**	NDA # 208216

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION

⇒ ITEM 2: **Contents of Attached Methods Validation Package**	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	3.2.P.1
Specifications/Methods for New Drug Substance(s)	3.2.S.4.1
Specifications/Methods for Finished Dosage Form(s)	3.2.P.5.1
Supporting Data for Accuracy, Specificity, etc.	DS: 3.2.S.4.3 DP: 3.2.P.5.3
Applicant's Test Results on NDS and Dosage Forms	
Other:	

⇒ ITEM 3: **REQUESTED DETERMINATIONS**
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.

Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
(b) (4)	DEGRADATION PRODUCTS ((b) (4)	3.2.P.5.3	6	See below

Additional Comments: **Please confirm that method (b) (4) can adequately resolve the drug product (**

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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

/s/

RABIYA LAIQ
09/04/2015