

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208216Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208216

SUPPL # N/A

HFD # 161

Trade Name N/A

Generic Name Azacitidine for Injection for SC or IV use, 100 mg/vial

Applicant Name Actavis LLC

Approval Date, If Known N/A

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The Actavis formulation, Azacitidine for Injection has the same qualitative and quantitative composition in terms of active ingredient (azacitidine), same dosage form, and route of administration and will be administered at the same dosage level for the same indications as the listed drug Vidaza®. The difference between the two products is the composition of the inactive ingredients (sucrose vs. mannitol) (b) (4) These differences are not expected to influence the amount of drug delivered to the site of action, since this is an injectable dosage form. Therefore, the Applicant proposes that in vivo bioavailability or bioequivalence of the drug product may be self-evident and requests a waiver for BA/BE studies.

To demonstrate high similarity between Actavis Azacitidine for Injection and RLD Vidaza, the Applicant provided quality data, as well as the bioequivalence, dissolution, and stability data. Quantitative and qualitative comparisons between the listed drug, Vidaza and Actavis' Azacitidine were submitted.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

N/A

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this

particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 050794 Vidaza (Azacitidine)

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new

clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Tracy Cutler
Title: Regulatory Health Project Manager
Date: April 29, 2016

Name of Office/Division Director signing form: DHP/Ann T. Farrell, MD
Title: Director, Division of Hematology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

TRACY L CUTLER
04/29/2016

ANN T FARRELL
04/29/2016

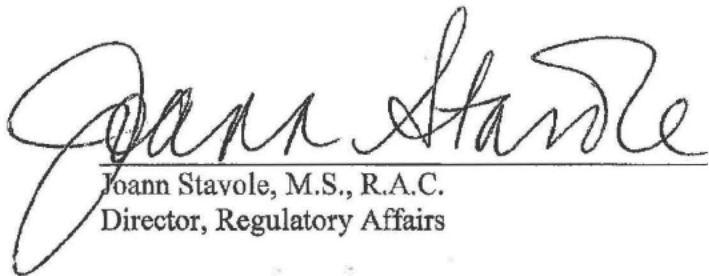
m1/1.3.3

GENERIC DRUG ENFORCEMENT ACT

**CERTIFICATION PURSUANT TO SECTION 306K
OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT, AS AMENDED:
PUBLIC LAW 102-282, MAY 13, 1992**

Actavis LLC hereby certifies that:

- (1) We did not, and will not use in any capacity, the services of any person debarred under subsection (a) or (b) of this section of the Act, in connection with this application;
- (2) That neither the applicant nor any affiliated person responsible for the development or submission of this application has been convicted within the past five (5) years of the offenses described in subsections (a) or (b) of this section of the Act.


Joann Stavole, M.S., R.A.C.
Director, Regulatory Affairs

06/23/2015
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208216 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: N/A Established/Proper Name: Azacitidine Dosage Form: Injection		Applicant: Actavis LLC Agent for Applicant (if applicable): N/A
RPM: Tracy Cutler		Division: Division of Hematology Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>) Date of check: _____</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>4/30/2016</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		N/A
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): -Nucleoside metabolic inhibitor
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

- | | |
|---|--|
| NDA: Subpart H | BLAs: Subpart E |
| <input type="checkbox"/> Accelerated approval (21 CFR 314.510) | <input type="checkbox"/> Accelerated approval (21 CFR 601.41) |
| <input type="checkbox"/> Restricted distribution (21 CFR 314.520) | <input type="checkbox"/> Restricted distribution (21 CFR 601.42) |
| Subpart I | Subpart H |
| <input type="checkbox"/> Approval based on animal studies | <input type="checkbox"/> Approval based on animal studies |
| <input type="checkbox"/> Submitted in response to a PMR | REMS: <input type="checkbox"/> MedGuide |
| <input type="checkbox"/> Submitted in response to a PMC | <input type="checkbox"/> Communication Plan |
| <input type="checkbox"/> Submitted in response to a Pediatric Written Request | <input type="checkbox"/> ETASU |
| | <input type="checkbox"/> MedGuide w/o REMS |
| | <input type="checkbox"/> REMS not required |

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	N/A
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified – no patent claim <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval – 4/29/2016
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	N/A
❖ Proprietary Name	N/A
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 9/8/2015 DMEPA: 9/17/2015 & 4/8/2016 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: 3/29/2016 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None DMPH: 3/29/2016
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	9/8/2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	4/13/2016
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ 	<p>N/A</p>
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<p>N/A</p>
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	<p>4/18/16 – Labeling IR 4/13/16 – Labeling IR 3/31/16 – Labeling IR 3/22/16 – CMC IR 3/7/16 – CMC IR 3/4/16 – CMC IR 3/2/16 – IR 2/23/16 – CMC IR 2/12/16 – IR 2/10/16 – CMC IR 12/17/15 – CMC IR 12/3/15 – CMC IR 11/12/15 – CMC IR 9/10/15 – Filing notification 9/10/15– Request for MV materials 8/3/15 – IR 7/14/15 – OSE IR 7/14/15 – Acknowledgment</p>
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	<p>Telecon memo – 3/15/16</p>
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	<p>N/A</p>

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	4/15/2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	4/15/2016
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	4/4/2016
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical review dated 4/4/2016
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input checked="" type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Pharmacology <input checked="" type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	N/A
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	4/1/2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	3/30/2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	Drug Substance 2/22/2016 Drug Product 3/23/2016 Process 3/10/2016 Facilities Inspection 3/28/2016 Biopharmaceutics 3/28/2016 Microbiology 3/17/2016
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	3/23/2016
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	N/A
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	N/A
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	N/A
❖ Ensure Pediatric Record is accurate	N/A
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

TRACY L CUTLER
04/29/2016

From: [Cutler, Tracy](#)
To: ["Regulatory Affairs US"](#)
Subject: NDA 208216 Azacitidine: Part 2 - Additional Labeling Revisions Requested
Date: Monday, April 18, 2016 8:45:11 AM
Attachments: [FDA Revised Labeling_041816_clean.doc](#)
[FDA Revised Labeling_041816_track.doc](#)

Good Morning Joann:

The proposed labeling submitted on 4/14/2016 for NDA 208216 Azacitidine has been reviewed. At this time, additional revisions are being requested. Please see the attached FDA revised labeling (dated 4/18/2016). **Please also ensure that all PLR formatting requirements are met.**

Please let me know if you are in agreement with the FDA revisions. If so, please provide a cover letter stating your agreement; in addition, provide a clean copy of the agreed labeling. If there are additional revisions, provide track changes, clean, and PDF versions of your annotated proposed labeling **no later than 10 am, Tuesday, April 19, 2016.** Please acknowledge receipt of this information request.

In order to facilitate review, respond directly to me via email. In addition, submit your documentation via the FDA electronic submissions gateway (ESG). Please contact me if you have any questions regarding this matter.

Best Regards,

Tracy

Tracy L. Cutler, MPH, CCRP, CIP
Regulatory Health Project Manager | Division of Oncology Products 1 (DOP1)
Office of Hematology and Oncology Products | OND | CDER | FDA
Phone: 301-796-9608 | Fax: 301-796-9845
Tracy.Cutler@fda.hhs.gov

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

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/s/

TRACY L CUTLER
04/18/2016

From: [Cutler, Tracy](#)
To: "Regulatory Affairs US"
Subject: NDA 208216 Azacitidine: Additional Labeling Revisions Requested
Date: Wednesday, April 13, 2016 12:17:59 PM
Attachments: [FDA Revised Labeling_0411316_clean.doc](#)
[FDA Revised Labeling_0411316_track.doc](#)
[FDA Revised Container label_041316.pdf](#)
[FDA Revised Carton Label_041316.pdf](#)
Importance: High

Good Afternoon Joann:

The proposed labeling submitted on 4/6/2016 for NDA 208216 Azacitidine has been reviewed. At this time, additional revisions are being requested. Please see the attached FDA revised labeling (dated 4/13/2016). **Please also ensure that all PLR formatting requirements are met.**

Please let me know if you are in agreement with the FDA revisions. If there are additional revisions, provide track changes, clean, and PDF versions of your annotated proposed labeling **no later than 1 pm, Friday, April 15, 2016.** Please acknowledge receipt of this information request.

In order to facilitate review, respond directly to me via email. In addition, submit your documentation via the FDA electronic submissions gateway (ESG). Please contact me if you have any questions regarding this matter.

Best Regards,

Tracy

Tracy L. Cutler, MPH, CCRP, CIP
Regulatory Health Project Manager | Division of Oncology Products 1 (DOP1)
Office of Hematology and Oncology Products | OND | CDER | FDA
Phone: 301-796-9608 | Fax: 301-796-9845
Tracy.Cutler@fda.hhs.gov

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Recommendation to the Carton label

1. Remove the statement “Discard unused portion” from the side panel and replace with the statement “Dilute before intravenous infusion.” We recommend this revision to mitigate the risk of the undiluted product being administered intravenously. Additionally, the statement “Discard unused portion” is also present on the principal display panel; therefore, duplication of the statement is not necessary on the side panel.

Recommendation to the Container label

1. Include the statement “Sterile, Nonpyrogenic, Preservative-free” on the principal display panel. This statement was removed in the 4/6/2016 submission.

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/s/

TRACY L CUTLER
04/13/2016

From: [Cutler, Tracy](#)
To: "Regulatory Affairs US"
Subject: NDA 208216 Azacitidine: Labeling Revisions Requested
Date: Thursday, March 31, 2016 11:01:08 AM
Attachments: [FDA Revised Carton Label_033116.pdf](#)
[FDA Revised Container Label_033116.pdf](#)
[FDA Revised Labeling_033116_track.doc](#)
[FDA Revised Labeling_033116_clean.doc](#)
Importance: High

Good Morning Joann:

The proposed labeling (i.e. prescribing information and carton & container labels) for NDA 208216 Azacitidine has been reviewed. At this time, revisions are being requested. Please see the attached FDA revised labeling (dated 3/31/2016). **Please also ensure that all PLR formatting requirements are met.**

Please let me know if you are in agreement with the FDA revisions. If you are in agreement, accept the applicable change. If there are additional revisions, provide track changes, clean, and PDF versions of your annotated proposed labeling **no later than 1 pm, Thursday, April 7, 2016.** Please acknowledge receipt of this information request.

In order to facilitate review, respond directly to me via email. In addition, submit your documentation via the FDA electronic submissions gateway (ESG).

Please contact me if you have any questions regarding this matter.

Best Regards,

Tracy

Tracy L. Cutler, MPH, CCRP, CIP
Regulatory Health Project Manager | Division of Oncology Products 1 (DOP1)
Office of Hematology and Oncology Products | OND | CDER | FDA
Phone: 301-796-9608 | Fax: 301-796-9845
Tracy.Cutler@fda.hhs.gov

Recommendations

1. Consider revising the statement (b) (4) to “For subcutaneous use and intravenous infusion after reconstitution”. We recommend this to minimize the risk of administering the drug as an intravenous bolus.
2. Include the statement “Discard Unused Portion” after the revised statement “Single-Dose Vial” to bring prominence to this information and to minimize the risk of the entire contents of the vial being given as a single dose. The current display of the information “Discard Unused Portion” is on the side panel and is not prominent.

Recommendations

1. Consider revising the statement (b) (4) to “For subcutaneous use and intravenous infusion after reconstitution”. We recommend this to minimize the risk of administering the drug as an intravenous bolus.
2. Include the statement “Discard Unused Portion” after the revised statement “Single-Dose Vial” to bring prominence to this information and to minimize the risk of the entire contents of the vial being given as a single dose. The current display of the information “Discard Unused Portion” is on the side panel and is not prominent.
3. Consider reorienting all (b) (4) information, including “Cytotoxic Agent”, to the horizontal position to improve readability of these statements.
4. Relocate the statement “Cytotoxic Agent” to the PDP, if space permits. Relocation of this important information to the PDP will improve visibility.
5. Revise the statement (b) (4) to “Usual dosage: See prescribing information” given that the statement “Discard unused portion” will be relocated next to revised statement “Single-Dose Vial”.

Reference ID: 3910383

41 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

TRACY L CUTLER
03/31/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208216

INFORMATION REQUEST

Actavis LLC
Attention: Joann Stavole, M.S., R.A.C.
Director of Regulatory Affairs
400 Interpace Parkway
Parsippany, NJ 07054

Dear Ms. Stavole:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azacitidine.

We also refer to your June 30, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Biopharmaceutics:

The dissolution data for your proposed drug product indicate that approximately (b) (4)% azacitidine is released within (b) 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)

NDA 208216
Page 2

If you have any questions, please contact me, at (240) 402-6153. Please respond by COB March 23, 2016.

Sincerely,

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Rabiya Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Rabiya Laiq -A,
0.9.2342.19200300.100.1.1=2001555007
Date: 2016.03.22 14:10:29 -04'00'

MEMORANDUM OF TELECONFERENCE

Teleconference Date: March 3, 2016

Application Number: NDA 208216

Product Name: Azacitidine

Applicant Name: Actavis

Subject: Inclusion of Intravenous & Subcutaneous Routes of Administration in NDA 208216

FDA Participants

Ann T. Farrell, MD, Director, Division of Hematology Products (DHP)

Tracy L. Cutler, MPH, Regulatory Health Project Manager, Division of Oncology Products 1 (DOP1)

Applicant Participants

Hafrun Fridriksdottir, Senior Vice President, Global R&D

Gregg DeRosa, Vice President Global Generics Clinical R&D

Cornelia Stancu, Executive Director R&D & Regulatory Affairs

Alina Aichimoaie, Director Clinical Pharmacology

Robert Cristian Dumitrescu, Clinical Pharmacology Specialist

Joann Stavole, Director, Regulatory Affairs – US

1.0 BACKGROUND:

NDA 208216 Azacitidine for Injection for IV use (a 505(b)(2) application) was submitted to FDA on June 30, 2015. The application is currently undergoing standard review with a PDUFA goal date of April 30, 2016.

In an information request (dated December 3, 2015), the Agency indicated that 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; thus the waiver of the requirement for the submission of evidence demonstrating the in vivo bioequivalence of the proposed drug product per 21CFR § 320.22 (b)(1) was not granted. In the response (dated January 7, 2016), the Applicant withdrew the subcutaneous route of administration from the application; intravenous only would be included in the application.

However with the withdrawal of the subcutaneous route of administration, there is no efficacy and safety data to support an intravenous only route of administration. In referencing the listed drug prescribing information, all clinical trials described in Section 14 describe the subcutaneous route of administration and efficacy results based on that usage.

FDA requested a conference call with Actavis to discuss the proposed application routes of administration (i.e., intravenous vs. subcutaneous) as well as the need for clinical support (i.e., efficacy & safety data) or justification of bioequivalence/biowaiver requests associated with each

route of administration. In preparation for the conference call, a FDA Information Request (dated March 2, 2016) was sent to the Applicant detailing the review team's concerns.

2.0 DISCUSSION:

- FDA provided background information and described concerns with removing the subcutaneous route of administration from the application.
- The Applicant discussed the current deficiencies associated with the biowaiver request for the subcutaneous route of administration.
- The Applicant inquired if other outside studies could be used to support bioequivalence. FDA answered that a bridge between the proposed drug and listed drug would need to be established. However, reviewing this clinical literature would be a complex and long process. The FDA noted that the NDA application is nearing the end of its review cycle.
- FDA indicated that this issue needs to be resolved quickly, as it may impede approval of the application.

3.0 ACTION ITEMS:

- The Applicant will revise the biowaiver request for the subcutaneous route of administration and attempt to address the current deficiencies. The Applicant response will be submitted no later than March 10, 2016.
- Following receipt of the Applicant's response, a teleconference will be scheduled, if needed, between the Applicant and FDA (biopharmaceutics) to discuss any additional deficiencies with that may impede the biowaiver request from being granted.

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/s/

TRACY L CUTLER
03/15/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208216

INFORMATION REQUEST

Actavis LLC
Attention: Joann Stavole, M.S., R.A.C.
Director of Regulatory Affairs
400 Interpace Parkway
Parsippany, NJ 07054

Dear Ms. Stavole:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azacitidine.

We also refer to your June 30, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Process:

In our information request dated September 10th, 2015 we conveyed that the lyophilization operating parameters to be employed at commercial scale must be adequately defined with development data to justify their selection. We acknowledge that you have provided more specific details regarding the planned (b)(4) scale lyophilization process for commercial production in your February 29th, 2016 communication; (b)(4)

For example, (b)(4)

(b)(4) You have not provided adequate development data and discussion of scalability issue to support the proposed changes in lyophilization process parameters. Please provide additional data to support the proposed parameters for (b)(4) and address scalability issue. We remind you that process validation is to confirm the process design and demonstrate that the commercial manufacturing process performs as expected (Guidance for Industry Process

NDA 208216
Page 2

Validation: General Principles and Practices (2011)), rather than develop and finalize the commercial manufacturing process.

If you have any questions, please contact me, at (240) 402-6153. Please respond by March 8, 2016.

Sincerely,

Rabiya
Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Rabiya Laiq -A,
0.9.2342.19200300.100.1.1=2001555007
Date: 2016.03.07 10:30:59 -0500

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208216

INFORMATION REQUEST

Actavis LLC
Attention: Joann Stavole, M.S., R.A.C.
Director of Regulatory Affairs
400 Interpace Parkway
Parsippany, NJ 07054

Dear Ms. Stavole:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azacitidine.

We also refer to your June 30, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance:

During the recent pre-approval inspection, multiple mass spectrometry data files from the R&D laboratories for samples described as Azacitidine drug substance were observed to contain an ^{(b) (4)}

^{(b) (4)} Please confirm with data from the same mass spectrometry method if this unknown peak is present in the Azacitidine drug substance lots used in the registration batch manufacturing (Batch # 71107AR007 and 71384AA001). If detected at qualification levels, confirm the identity and quantity of this impurity with validated method.

NDA 208216
Page 2

If you have any questions, please contact me, at (240) 402-6153. Please respond by March 8, 2016 or sooner.

Sincerely,

Rabiya Laiq -

A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Rabiya Laiq -A,
0.9.2342.19200300.100.1.1=2001555007
Date: 2016.03.04 19:44:52 -05'00'

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: [Cutler, Tracy](#)
To: ["Regulatory Affairs US"](#)
Subject: NDA 208216 Azacitidine: Information Request
Date: Wednesday, March 02, 2016 5:36:20 PM
Importance: High

Good Afternoon Ms. Stavole:

At this time please address the following information request regarding NDA 208216 Azacitidine. **Respond no later than 3 pm, Thursday, March 10, 2016.** Please acknowledge receipt of this information request.

NOTE: This information request will be discussed at the teleconference scheduled for Thursday, March 3rd.

- 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.

-
Please provide your response to this information request directly to me via email. In addition, please also submit your response via the FDA Electronic Submissions Gateway (ESG). Please contact me if you have any questions regarding this matter.

Best Regards,

Tracy

Tracy L. Cutler, MPH, CCRP, CIP
Regulatory Health Project Manager | Division of Oncology Products 1 (DOP1)
Office of Hematology and Oncology Products | OND | CDER | FDA
Phone: 301-796-9608 | Fax: 301-796-9845
Tracy.Cutler@fda.hhs.gov

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/s/

TRACY L CUTLER
03/02/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208216

INFORMATION REQUEST

Actavis LLC
Attention: Joann Stavole, M.S., R.A.C.
Director of Regulatory Affairs
400 Interpace Parkway
Parsippany, NJ 07054

Dear Ms. Stavole:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azacitidine.

We also refer to your June 30, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Process:



If you have any questions, please contact me, at (240) 402-6153. Please respond by February 29, 2016.

Sincerely,

Rabiya Laiq -
A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Rabiya Laiq -A,
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Date: 2016.02.23 20:06:58 -0500'

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

From: [Cutler, Tracy](#)
To: [Regulatory Affairs US](#)
Subject: NDA 208216 Azacitidine: Information Request
Date: Friday, February 12, 2016 11:09:44 AM
Importance: High

Good Morning Ms. Stavole:

At this time please address the following information request regarding NDA 208216 Azacitidine. **Respond no later than 11 am, Friday, February 19th**. Please acknowledge receipt of this information request.

- Clinical support for approval of azacytidine 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.

-
Please provide your response to this information request directly to me via email. In addition, please also submit your response via the FDA Electronic Submissions Gateway (ESG). Please contact me if you have any questions regarding this matter.

Best Regards,

Tracy

Tracy L. Cutler, MPH, CCRP, CIP
Regulatory Health Project Manager | Division of Oncology Products 1 (DOP1)
Office of Hematology and Oncology Products | OND | CDER | FDA
Phone: 301-796-9608 | Fax: 301-796-9845
Tracy.Cutler@fda.hhs.gov

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/s/

TRACY L CUTLER
02/12/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208216

INFORMATION REQUEST

Actavis LLC
Attention: Joann Stavole, M.S., R.A.C.
Director of Regulatory Affairs
400 Interpace Parkway
Parsippany, NJ 07054

Dear Ms. Stavole:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azacitidine.

We also refer to your June 30, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Micro:



If you have any questions, please contact me, at (240) 402-6153. Please respond by February 17, 2016.

Sincerely,

Rabiya Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Rabiya Laiq -A,
0.9.2342.19200300.100.1.1=2001555007
Date: 2016.02.10 16:04:11 -05'00'

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208216

INFORMATION REQUEST

Actavis LLC
Attention: Joann Stavole, M.S., R.A.C.
Director of Regulatory Affairs
400 Interpace Parkway
Parsippany, NJ 07054

Dear Ms. Stavole:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azacitidine.

We also refer to your June 30, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

(b) (4)

If you have any questions, please contact me, at (240) 402-6153. Please respond by January 7, 2016.

Sincerely,

Rabiya Laiq -A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Rabiya Laiq -A,
0.9.2342.19200300.100.1.1=2001555007
Date: 2015.12.17 13:06:28 -05'00'

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208216

INFORMATION REQUEST

Actavis LLC
Attention: Joann Stavole, M.S., R.A.C.
Director of Regulatory Affairs
400 Interpace Parkway
Parsippany, NJ 07054

Dear Ms. Stavole:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azacitidine.

We also refer to your June 30, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.



If you have any questions, please contact me, at (240) 402-6153. Please respond by January 7, 2016.

Sincerely,

Rabiya Laiq

-A

Digitally signed by Rabiya Laiq -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Rabiya Laiq -A,
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Date: 2015.12.03 16:10:03 -05'00'

Rabiya Laiq, Pharm.D.
Regulatory Business Process Manager
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208216

INFORMATION REQUEST

Actavis LLC
Attention: Joann Stavole, M.S., R.A.C.
Director of Regulatory Affairs
400 Interpace Parkway
Parsippany, NJ 07054

Dear Ms. Stavole:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Azacitidine.

We also refer to your June 30, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

(b) (4)



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If you have any questions, please contact me, Rabiya Laiq, Pharm.D., Regulatory Business Process Manager, at (240) 402-6153. Please respond by December 4, 2015.

Sincerely,

Digitally signed by Janice T. Brown -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=1300101685,
cn=Janice T. Brown -A
Date: 2015.11.12 10:39:57 -05'00'

Janice Brown, M.S.
Quality Assessment Lead, Branch II
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



NDA 208216

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Actavis LLC
Attention: Joann Stavole, MS, RAC
Director, Regulatory Affairs
400 Interpace Parkway, Morris Corporate Center III, Building D, 3rd Floor
Parsippany, NJ 07054

Dear Ms. Stavole:

Please refer to your New Drug Application (NDA) dated June 30, 2015, received June 30, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Azacitidine for Injection for subcutaneous or intravenous use, 100 mg/vial.

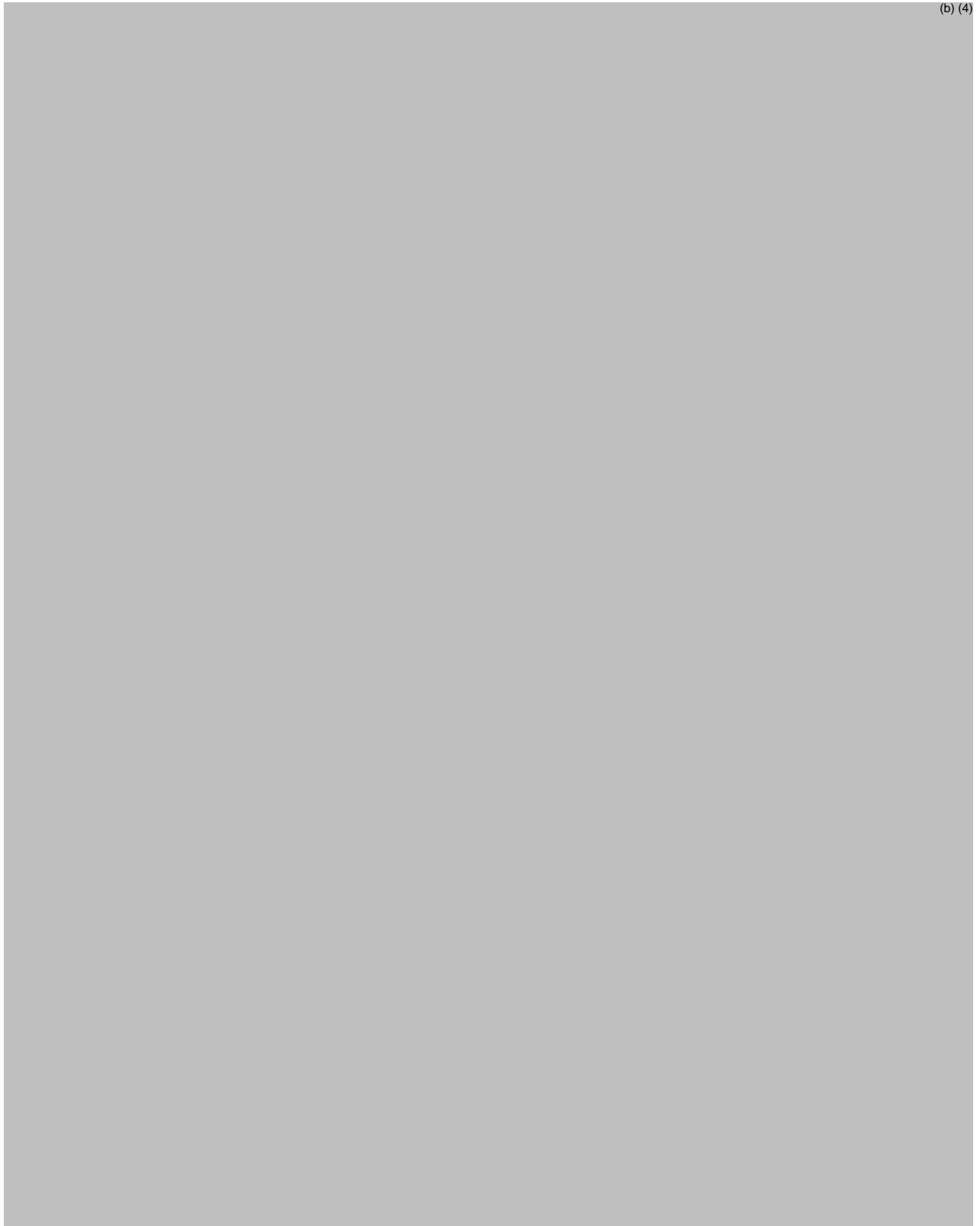
We also refer to your amendment dated August 17, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 30, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 2, 2016.

At this time, we are notifying you that, we have identified some product quality review issues. There are no clinical review issues at this time. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:



(b) (4)

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

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

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above request for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, please contact Tracy Cutler, Regulatory Health Project Manager, at (301) 796-9608 or Tracy.Cutler@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ann Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
09/10/2015



**REQUEST FOR METHODS
VALIDATION MATERIALS**

NDA 208216

September 10, 2015

Actavis LLC
Attention: Joann Stavole, M.S., R.A.C.
400 Interpace Parkway
Morris Corporate Center III
Building D, 3rd Floor
Parsippany, NJ

Dear Joann Stavole:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Azacitidine for Injection and for Suspension, 100 mg/vial.

We will be performing methods validation studies on Azacitidine for Injection and for Suspension, 100 mg/vial, as described in NDA 208216.

In order to perform the necessary testing, we request the following sample materials and equipments:



Please include the **MSDSs** and the **Certificates of Analysis** for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this email. You may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

LAURA POGUE
09/10/2015

From: Cutler, Tracy
To: ["RegulatoryAffairsUS@actavis.com"](mailto:RegulatoryAffairsUS@actavis.com)
Subject: NDA 208216 Azacitidine: Information Request
Date: Monday, August 03, 2015 1:48:00 PM
Importance: High

Good Afternoon Ms. Stavole:

At this time please address the following information request regarding NDA 208216. Please provide your response no later than 2 pm, Monday, August 17th.

1. Submit the packet insert with the Pregnancy and Lactation Labeling Rule (PLLR) format incorporated.

-
Please provide your response to this information request directly to me via email. In addition, please also submit your response via the FDA Electronic Submissions Gateway (ESG). Please contact me if you have any questions regarding this matter.

Best Regards,

Tracy

Tracy L. Cutler, MPH, CCRP, CIP
Regulatory Health Project Manager | Division of Oncology Products 1 (DOP1)
Office of Hematology and Oncology Products | OND | CDER | FDA
Phone: 301-796-9608 | Fax: 301-796-9845
Tracy.Cutler@fda.hhs.gov

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/s/

TRACY L CUTLER
08/03/2015

Wright, Kevin

From: Wright, Kevin
Sent: Tuesday, July 14, 2015 2:15 PM
To: 'Regulatory Affairs US'
Cc: Kang, Sue
Subject: RE: NDA 208216 Azacitidine: Proprietary Name Request

Ms. Stavole,

I am confirming receipt of this communication. Thank you for your prompt response.

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 kevin.wright@fda.hhs.gov

 Thinking green when printing

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PREDECISIONAL, PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW.

If you are not the named addressee, or if this message has been addressed to you in error, you are directed not to read, disclose, reproduce, disseminate, or otherwise use this transmission. If you have received this document in error, please immediately notify me by email or telephone.

From: Regulatory Affairs US [<mailto:RegulatoryAffairsUS@actavis.com>]

Sent: Tuesday, July 14, 2015 2:02 PM

To: Wright, Kevin

Cc: Kang, Sue; Regulatory Affairs US

Subject: RE: NDA 208216 Azacitidine: Proprietary Name Request

Dear Dr. Wright,

Actavis is not requesting to have a proprietary name for this 505b2 application and intends to market it under its generic name.

Kind regards,
Joann

Joann Stavole, MS, RAC
Director, Regulatory Affairs

Actavis
Morris Corporate Center III
400 Interpace Parkway
Parsippany, NJ 07054
United States
T 862-261-7735
C  (b) (6)
E JOANN.STAVOLE@actavis.com



From: Wright, Kevin [<mailto:Kevin.Wright@fda.hhs.gov>]
Sent: Tuesday, July 14, 2015 9:42 AM
To: Regulatory Affairs US
Cc: Kang, Sue
Subject: NDA 208216 Azacitidine: Proprietary Name Request
Importance: High

Ms. Stavole,

This email is to notify you that Division of Medication Error and Prevention Analysis (DMEPA) is requesting you submit a request for proprietary name review to NDA 208216 azacitidine if you intend to market this product with a proprietary name.

The request for proprietary name review should include FDA Form 356h, and a cover letter stating “REQUEST FOR PROPRIETARY NAME”, on the first page of the submission. Also, this submission should contain the proposed labels and labeling or a reference to the submission containing the labels and labeling.

A complete request for proprietary name review should include the primary proprietary and where applicable the alternate proprietary name, intended pronunciation, derivation of proprietary name, and/or intended meaning of any modifiers (e.g. prefix, suffix) contained in the proprietary name.

Additionally, your request should include the following product characteristics: established name, prescription status, dosage form, product strength, proposed indication for use, route of administration, usual dosage, frequency of administration, dosing in specific populations, instructions for use, setting of use, storage requirements and the intended package configuration.

As a reference for future proprietary name submissions, attached is a copy of the guidance document.

If you have any questions or comments regarding this email, please contact me.

Best regards,

Kevin Wright, PharmD

Safety Regulatory Project Manager | OSE | CDER | FDA | 301.796.3621 kevin.wright@fda.hhs.gov

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This e-mail, including any attachments, is meant only for the intended recipient of the transmission, and may be a confidential or privileged communication. If you received this e-mail in error, any review, use, dissemination, distribution, or copying of this e-mail is strictly prohibited. Please notify us immediately of the error by return e-mail and please delete this message from your system. Thank you in advance for your cooperation.

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/s/

KEVIN WRIGHT
07/14/2015



NDA 208216

NDA ACKNOWLEDGMENT

Actavis LLC
Attention: Joann Stavole, MS, RAC
Director, Regulatory Affairs
400 Interpace Parkway
Morris Corporate Center III, Building D, 3rd Floor
Parsippany, NJ 070504

Dear Ms. Stavole:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of DrugProduct: Azacitidine for Injection for SC or IV use, 100 mg/vial

Date of Application: June 30, 2015

Date of Receipt: June 30, 2015

Our Reference Number: NDA 208216

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 29, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please contact me at (301) 796-9608 or Tracy.Cutler@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tracy L. Cutler, MPH, CCRP, CIP
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

TRACY L CUTLER
07/14/2015