CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214120Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 214120
Review #1

Drug Name/Dosage Form	Azacitidine Tablets
Strength	200 mg and 300 mg
Route of Administration	Oral
Rx/OTC Dispensed	R_x
Applicant	Celgene Corporation, a wholly owned subsidiary of Bristol-Myers Squibb
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	03-Mar-2020	All
Amendment (SD)	15-May-2020	DP
Amendment (SD)	21-May-2020	Process/facilities
Amendment (SD)	28-May-2020	DP, Biopharm, Process/facilities
Amendment (SD)	22-Jun-2020	DP, Biopharm
Amendment (SD)	08-Jul-2020	DP
Amendment (SD)	06-Jul-2020	Process/facilities
Amendment (SD)	16-Jul-2020	DP
Amendment (SD)	06-Sept-19	Process/Facilities

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Karina Zuck	Haripada Sarker
Drug Product	Nina Ni	Anamitro Banerjee
Process and Facilities	Huiquan Wu	Bogdan Kurtyka
Microbiology	n/a	n/a
Biopharmaceutics	Min Kang	Om Anand
Regulatory Business Process Manager	Rabiya Haider	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a

Environmental	Raanan Bloom	n/a

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4)	Development of (b) (4)

2. **CONSULTS**
N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 214120 for Onureg® (azacitidine) tablets, 200 mg and 300 mg. As part of this action, OPQ grants a 30-month expiration period for the drug product when stored at "20°C to 25°C (68°F to 77°F) excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]." There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

NDA 214120 was submitted for Onureg® (azacitidine) tablets, 200 and 300 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Onureg® is a once daily, orally bioavailable, nucleoside metabolic inhibitor that is indicated as (b) (4) (b) (4) Azacitidine was originally approved under NDA 50794 in May of 2004 for the treatment of myelodysplastic syndrome (MDS). Azacitidine received orphan drug designation for the treatment of acute myeloid leukemia on 18 June 2008. The proposed product is an oral formulation of the approved product. The oral formulation was developed to allow sustained and extended administration of azacitidine.

Azacitidine drug substance is a small chiral molecule that is manufactured (b) (4) The drug product is supplied as a 200 or 300 mg, (b) (4) immediate-release, film-coated tablets for oral administration. The 200 mg dosage form is presented as a pink, oval tablet with debossed 200" on one side and "ONU" on the other side. The 300 mg tablet is presented as a brown, oval tablet with debossed "300" on one side and "ONU" on the other side.

The recommended (b) (4) dose for the drug product is 300 mg orally, once daily for the first 14 days of each 28-day cycle. The treatment should continue (b) (4) until unacceptable toxicity occurs.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 214120 and grants

a shelf life of 30 months for the drug product when stored in HDPE bottles at 20°C to 25°C (68°F to 77°F). Of note the original application included the drug product packaged in both bottles (b) (4) (b) (4)

Proposed Indication(s) including Intended Patient Population	(b) (4)
Duration of Treatment	(b) (4) (b) (4) until unacceptable toxicity.
Maximum Daily Dose	300 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Azacitidine drug substance is a white to off-white non-hygroscopic solid that is insoluble in acetone and ethanol; sparingly soluble in water and freely soluble in DMSO. Azacitidine is a ring analog of the naturally occurring pyrimidine nucleoside cytidine and differs from cytidine by having a nitrogen atom in the 5 position of the heterocyclic ring. Azacitidine exhibits polymorphic behavior. Polymorphic studies revealed (b) (4) (b) (4) (b) (4) Azacitidine may be classified as highly soluble and lowly permeable; however, the Applicant did not submit a request to designate a BCS class and the FDA has not designated the BCS class for this product.

The drug substance will be manufactured (b) (4) (b) (4) The applicant references NDA 50794 for the manufacture and control of the drug substance. NDA 50794 was approved in May of 2004 for the treatment of myelodysplastic syndrome (MDS).

The information included in the referenced NDA (NDA 050794) and the information submitted in this NDA are adequate to support the approval of NDA 214120.

Accordingly, NDA 214120 is recommended for approval from a drug substance perspective.

Drug Product

The drug product, Onureg® (oral azacitidine) is a 200 mg and 300 mg, (b) (4) immediate-release, film-coated tablets for oral administration. The 200 and 300 mg tablets are manufactured (b) (4) The drug product formulation includes the active and compendial excipients that are commonly used in solid oral dosage forms (croscarmellose sodium, magnesium stearate, mannitol, and silicified microcrystalline cellulose). The tablet coatings contain hypromellose, titanium dioxide, lactose monohydrate, polyethylene glycol/macrogol, and triacetin and either iron oxide red (for the 200 mg table) or iron oxide yellow, iron oxide red and black iron oxide (the 300 mg tablet). The 200 mg dosage form is presented as a pink, oval tablet with debossed 200" on one side and "ONU" on the other side. The 300 mg tablet is presented as a brown, oval tablet with debossed "300" on one side and "ONU" on the other side. The formulation contains no novel excipients and each of the excipients are below the maximum potency as reported in the IIG. Detailed descriptions of the quantitative and qualitative drug product formulation are provided in the submission.

The drug product is manufactured (b) (4)

(b) (4)

(b) (4) The applicant demonstrated the suitability of the manufacturing process for the drug product at the proposed commercial scale. The description of the manufacturing process includes appropriate in-process controls and operating parameters and is described in sufficient detail to support the approval of this NDA.

The drug product specifications include appearance, identification, uniformity of dosage units, assay, related substances, dissolution, microbial limits (b) (4) The applicant included a risk assessment for elemental impurities as per ICH Q3D/USP <232> and provided justification for the omission of tests for residual solvents. The results of the risk assessment were acceptable and therefore a test for an elemental impurity in the drug product release specifications was not proposed and is not required. The final drug product specifications are consistent with ICH Q6A and are based on batch analyses, manufacturing capability, and stability data. The drug product specifications are adequate to establish the drug product identity, potency and purity and provide adequate controls to ensure the quality of the drug product through the product expiry. The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

In support of the proposed 30-month expiry, the applicant included up to 18 months of long term (25°C/60% RH) and 6 months of accelerated (40°C/75% RH) data for four commercial scale batches per strength packaged in HDPE bottles (b) (4)

(b) (4). Three batches were manufactured (b) (4) (b) (4) All primary stability batches were manufactured at the commercial site according to the proposed commercial manufacturing process. Stability studies were executed in accordance with the ICH 1A and Q1B; and the available stability data shows consistency over time and supports the proposed expiry. Therefore, based on the 18 months of stability data included in this application for Onureg® (oral azacitidine) tablets, 200 and 300 mg, Celgene Corporation proposed and the FDA accepts the expiration dating period of **30 months** for the drug product when stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) and kept in the original bottle tightly closed with two 1g desiccant canisters. Of note, the applicant is not seeking approval (b) (4) (b) (4)

Post-Marketing Considerations:
The applicant plans to submit (b) (4) (b) (4)

NDA 214120 is recommended for approval from a drug product and drug process perspective.

Biopharmaceutics

The biopharmaceutics review focused on (1) the acceptability of the proposed in vitro dissolution method and acceptance criterion for the routine quality control testing of the proposed drug product at batch release and on stability and (2) bridging of the pivotal clinical and commercial formulations and (3) the acceptability of biowaiver for the lower strength, 200 mg.

Dissolution Specification and Method: The dissolution method included a USP Apparatus 2 (Baskets) at 75 RPM in 500 mL of 0.05M Phosphate Buffer at 37°C. The proposed dissolution acceptance criterion was Q= (b) (4)% in 15 minutes. The dissolution method and acceptance criterion are acceptable as QC method for batch release and stability testing of the drug product.

Bridging of the Clinical Formulations: There were 9 different formulation investigated during the formulation development. Formulations F8 and intended commercialization formulation (ICF) F9 were used in the pivotal clinical trial and formulation F9 is the proposed commercial formulation. The F9 and F8 have been adequately bridged based on the following: (1) F8 and F9 showed bioequivalence via an in vivo BE Study (2) F9 and ICF F9 having minor differences (b) (4) and (3) F9 and ICF F9 showed similar in vitro dissolution profiles. For these reasons the registration batches of Azacitidine Tablets formulation ICF F9, 200 mg and 300 mg, are deemed adequately bridged with Azacitidine Tablets clinical formulation F8.

Biowaiver Request: The Applicant's submitted biowaiver request as per the 21 CFR 320.22(d)(2) and included the following evidence to support the approval of the proposed 200 mg strength: (1) the 200 mg and 300 mg Azacitidine Tablets are in same dosage form but in different strengths, (2) bioavailability of the 300 (3) evidence to support proportional similarity of the 200 mg and 300 mg in the active and inactive ingredients and (4) a comparison of the in vitro dissolution profiles for the 200 mg and 300 mg strengths. The Applicant's biowaiver request for the 200 mg is granted.

Based on the information provided (i.e. dissolution profile data for pivotal clinical batches and stability data), the proposed dissolution method and acceptance criterion, biowaiver request and bridging studies are deemed acceptable. The NDA 214120 is recommended for approval from biopharmaceutics perspective.

Facilities

This application includes 11 sites and all sites were listed as ready for inspection:

- (b) (4) **(FEI** (b) (4)**)**- Manufacture, analytical testing and stability testing of drug substance
- (b) (4) **(FEI** (b) (4)**)** – Manufacture, analytical testing and stability testing
- (b) (4) **(FEI** (b) (4)**)**- Analytical Testing and Biological Testing
- (b) (4) **(FEI** (b) (4)**)**- Biological Testing
- (b) (4) **(FEI** (b) (4)**)**- Particle Size Testing
- (b) (4) **(FEI** (b) (4)**)**- (b) (4) Testing
- (b) (4) **(FEI** (b) (4)**5)**- (b) (4) Testing
- (b) (4) **(FEI** (b) (4)**)**- Manufacture and testing
- (b) (4) **(FEI** (b) (4)**)**- Microbial Testing
- (b) (4) **(FEI** (b) (4)**)**- Packaging and Labeling
- (b) (4) **(FEI** (b) (4)**)**- Packaging and Labeling
- **Celgene International Sàrl (FEI 3006323509)**- Packaging and Labeling

At the conclusion of the review of NDA 214120, all facilities listed in were deemed acceptable for the responsibility listed in the application. This application is recommended for approval from the facilities perspective

Environmental Assessment

The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(e) and a statement of no extraordinary circumstances 21 CFR 25.15(d).

The request for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

Included at the beginning of the drug product review.

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

ONUREG® (azacitidine) tablets, for oral use
Initial U.S. Approval: 2004

DOSAGE FORMS AND STRENGTHS

Tablets: 200 mg and 300 mg (3).

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Onureg	Provided and adequate
Established name(s)	azacitidine	Provided and adequate
Route(s) of administration	For oral use	Provided and adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 200 mg and 300 mg	Provided and adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Tablets is not scored	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Instruct patients on the following:

- Do not split, crush or chew ONUREG tablets.
- Take a dose about the same time each day.
- If a dose of ONUREG is missed, or not taken at the usual time, take the dose as soon as possible on the same day, and resume the normal schedule the following day. Do not take 2 doses on the same day.
- If a dose is vomited, do not take another dose on the same day. Resume the normal schedule the following day.

TRADENAME is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	See above	Provided and adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

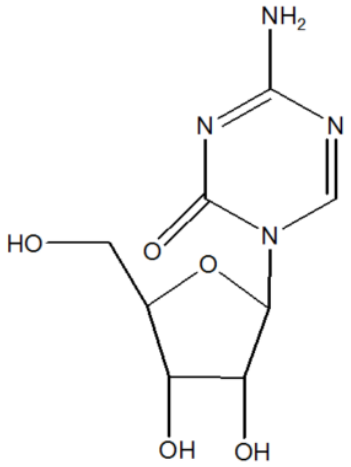
Tablets:

- 200 mg: pink, oval, film-coated tablet with debossed "200" on one side and "ONU" on the other side.
- 300 mg: brown, oval, film-coated tablet with debossed "300" on one side and "ONU" on the other side.

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets	Provided and adequate
Strength(s) in metric system	200 mg and 300 mg	Provided and adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	NA	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	See above	Provided and adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Tablets are not scored	Adequate
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Azacitidine is nucleoside metabolic inhibitor with a molecular formula of $C_8H_{12}N_4O_5$ and a molecular weight of 244 g/mol. The chemical name is: 4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one and the chemical structural is:



Azacitidine is a white to off-white solid. Azacitidine was found to be soluble in aqueous media across pH range from 1.0 to 7.0.

ONUREG (azacitidine) is supplied as film-coated tablets containing 200 mg or 300 mg of azacitidine for oral use. Each core tablet contains the following inactive ingredients: croscarmellose sodium, magnesium stearate, mannitol, and silicified microcrystalline cellulose. The 200 and 300 mg tablet coating contains hypromellose, lactose monohydrate, polyethylene glycol, titanium dioxide, and triacetin. In addition, the 200 mg tablet coating contains iron oxide red and the 300 mg tablet coating contains black iron oxide, iron oxide red, and iron oxide yellow.

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	See above	Provided and adequate
Dosage form(s) and route(s) of administration	See above	Provided and adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	DS is not a salt	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	See above	Provided and adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ Therapeutic class	See above	Provided and adequate
Chemical name, structural formula, molecular weight	See above	Provided and adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)	See above	Provided and adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	NA	NA

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

How Supplied

TRADENAME tablets are available as:

- 200 mg: pink, oval, film-coated tablets with debossed "200" on one side and "ONU" on the other side.
- 300 mg: brown, oval, film-coated tablets with debossed "300" on one side and "ONU" on the other side.

Table 6 lists the package configurations and strengths.

Table 6: ONUREG Package Configurations and NDC Numbers

Package Configuration	Tablet Strength	NDC Number
Bottles of 14 with two desiccant cannisters	200 mg	59572-730-14
Bottles of 14 with two desiccant cannisters	300 mg	59572-740-14

Storage

Store bottles at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30° C (59°F to 86°F) [see USP Controlled Room Temperature]. Keep bottle tightly closed. Store and dispense in the original bottle (with two desiccant canisters).

Handling and Disposal

ONUREG is a hazardous drug. Follow applicable special handling and disposal procedures.[1] If powder comes in contact with skin, immediately and thoroughly wash with soap and water. If powder comes in contact with mucous membranes, immediately flush the area with water.

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	See above	Provided and adequate
Strength(s) in metric system	See above	Provided and adequate
Available units (e.g., bottles of 100 tablets)	See above	Provided and adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See above	Updated and adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	The tablets are not scored	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	NA	NA

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Keep bottle tightly closed. Store in the original bottle (with two desiccant canisters).	Protect the tablets from moisture to maintain stability.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	See above	"Do not eat" is included in both patient counseling information and patient information sections

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above	Provided and adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	NA	NA
Include information (b) (4) (b) (4)	(b) (4)	(b) (4)

1.2.5 Other Sections of Labeling

Patient counseling information

Storage Instructions

Advise patients to keep ONUREG in the original container (b) (4) (b) (4) advise patients to keep the container tightly closed with both desiccant canisters inside and to not eat the desiccant canisters *[see How Supplied/Storage and Handling (16.2)]*.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Manufactured by: Celgene Corporation
A Wholly Owned Subsidiary of Bristol-Myers Squibb
86 Morris Avenue
Summit, NJ 07901

ONUREG® is a registered trademark of Celgene Corporation.

Patent: www.celgene.com/therapies

ONUPI.001

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	See above	Provided and adequate

2.0 PATIENT LABELING

How should I store ONUREG?

(b) (4)

Keep ONUREG and all medicines out of the reach of children

What are the ingredients in ONUREG?
Active ingredient: azacitidine
Inactive ingredients:

(b) (4)

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Adequate

In the Amendment, SND 0022 (21), dated 07/16/2020, the applicant updated all pertinent sections of US packaging insert and patient information to remove

(b) (4)

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT." *None*

3.0 CARTON AND CONTAINER LABELING

(b) (4)

3.2 Carton Labeling

NA

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Provided	NA
Dosage strength	Provided	NA
Net contents	Provided	NA
"Rx only" displayed prominently on the main panel	Provided	NA
NDC number (21 CFR 207.35(b)(3)(i))	Provided	NA
Lot number and expiration date (21 CFR 201.17)	Provided	NA
Storage conditions	Provided	NA
Bar code (21CFR 201.25)	Provided	NA
Name of manufacturer/distributor	Provided	NA
And others, if space is available	NA	NA

Assessment of Carton and Container Labeling: Adequate

(b) (4), (b) (4) The following comments have been adequately addressed in the above updated bottle container labels. The bottle will not have a carton. It is not required to have a carton for the bottle presentation.

- Add "Each table contains 200 mg or 300 mg of azacytidine"

- Add “Keep out of reach of children”
- Add “Do not use if safety seal under cap is broken or missing” for bottle configuration only

Any deficiencies should be listed at the end in the “ITEMS FOR ADDITIONAL ASSESSMENT.” *None*

ITEMS FOR ADDITIONAL ASSESSMENT

NA

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: Nina Ni, Ph.D., 07/24/2020

Secondary Assessor Name and Date: Anamitro Banerjee, Ph.D., 07/24/2020

Nina Ni

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QUALITY A QUALITY ASSESSMENT
Chapter VII-Biopharmaceutics

NDA/ Type of Submission: NDA 214120-ORIG-1; 505(b)(1)
Applicant Name: Celgene Corporation, New Jersey, US
Drug Product Name/Strength: ONUREG (Azacitidine) Tablet/ 200 mg and 300 mg
Route of Administration: Oral
Applicant Name: Celgene Corporation, New Jersey, US
Submission Date: 3/3/2020 (Original Submission)

Background: The Applicant submitted this 505(b)(1) NDA seeking approval for ONUREG (Azacitidine) Tablets, 200 mg and 300 mg. Azacitidine is a nucleoside metabolic inhibitor indicated (b) (4) (b) (4) (b) (4) The proposed (b) (4) dose is 300 mg orally, once daily for the first 14 days of each 28-day cycle. This application is primarily supported by clinical safety and efficacy data obtained from the Pivotal Phase 3 Study (CC-486-AML-001).

The proposed two strengths, 200 mg and 300 mg, are compositionally proportional with respect to the active and inactive ingredients, differing only by the film coatings (b) (4) (b) (4)

Review Summary: This Biopharmaceutics Review focuses on evaluation of (1) the in vitro dissolution method and acceptance criterion as a quality control (QC) test for the proposed drug product, Azacitidine Tablets, 200 mg and 300 mg, (2) the bridging of the formulations between one used in the clinical (pivotal) study and the one intended for commercial production, and (3) the acceptability of biowaiver for the lower strength, 200 mg.

In Vitro Dissolution Method and Acceptance Criterion: ACCEPTABLE

The proposed in vitro dissolution method and dissolution acceptance criterion shown in the table below are approved for the Quality Control (QC) testing of Azacitidine Tablets, 200 mg and 300 mg, for batch release and stability testing:

Apparatus	Speed	Volume/ Temp	Medium	Acceptance Criterion
USP 2 (Paddle)	75 rpm	500 mL/ 37 °C	0.05M Phosphate Buffer (pH 6.8)	Q= (b) (4)% at 15 minutes

Biowaiver Request: ACCEPTABLE

The Applicant's submitted biowaiver request as per the 21 CFR 320.22(d)(2) to support the approval of the proposed 200 mg strength is based on the following: (1) The 200 mg and 300 mg Azacitidine Tablets are in same dosage form but in different strengths, (2) Bioavailability of the 300 mg has been measured (Pivotal Study: CC-486-AML-002, PK Linearity: AZA-PH-US-2007-CL-005), (3) Evidence to support proportional similarity of the 200 mg and 300 mg in the active and inactive ingredients, and (4) The in vitro dissolution

profiles of the 200 mg and 300 mg strengths are similar. The Applicant's biowaiver request for the lower strength (200 mg) is granted.

Formulation Bridging: ACCEPTABLE

The registration batches, the Intended for Commercialization Formulation (ICF) F9 and the interim formulation F9 as well as the clinical formulation F8 (used in the Pivotal Study, CC-486-AML-001) have been adequately bridged, on the basis of (1) F8 and F9 showing bioequivalence via an in vivo BE Study (CC-486-CAGEN-001), (2) F9 and ICF F9 having minor differences (b) (4) (b) (4) between the registration batches formulation ICF F9 and F9, and (3) F9 and ICF F9 showing similar in vitro dissolution profiles. Therefore, the registration batches of Azacitidine Tablets formulation ICF F9, 200 mg and 300 mg, are deemed adequately bridged with Azacitidine Tablets clinical formulation F8, (b) (4) mg.

Overall Recommendation: From the Biopharmaceutics perspective, NDA 214120 for the proposed ONUREG (Azacitidine) Tablets, 200 mg and 300 mg, is **Adequate** and recommended for Approval.

BIOPHARMACEUTICS ASSESSMENT

1. List of Submissions Reviewed:

eCTD sequence #	Received date	Document
01	3/3/2020	Original NDA submission
011	5/28/2020	Quality/Response to Quality/Biopharmaceutics IR #1
017	6/22/2020	Quality/Response to Quality/Biopharmaceutics IR #2

2. BCS Designation:

Solubility: Azacitidine is highly soluble (≥ 1.2 mg/mL) in aqueous media across physiologic pH (pH 1-7.7) range, as described in Table 1. At 5°C, the two pKa values of Azacitidine were determined to be pKa1= 2.85±0.04 (basic) and pKa2=10.19±0.02 (acidic), further supporting highly ionizable characteristic of Azacitidine as a drug substance.

Table 1: Solubility vs. pH at 5°C

pH	Experimental Solubility / (mg/mL)	Volume (mL) Needed to Dissolve Highest Strength 300 mg
1.0[a]	77.4	4
2.6	16.9	18
3.9	6.25	48
5.3	5.85	51
6.7	7.75	39
7.7	6.17	49

[a] Calculated value

Permeability: The intrinsic permeability and the interaction of azacitidine with xenobiotic transporter P-glycoprotein (P-gp) as a substrate and as an inhibitor were determined using control cell monolayers over 30 and 60 min and human P-gp expressing LLC-PK1 cell lines. The mean cumulative (60 min) azacitidine Papp value was 0.45 x 10^{-6} cm/sec. Azacitidine (with intrinsic permeability of 20 µM) was determined to have low permeability based on the apparent permeability (Papp) values measured in the control cell line as compared to Papp values measured for the low permeability comparator mannitol and the high permeability comparator propranolol.

Reviewer's comments: Based on the above information, Azacitidine may be classified as highly soluble and lowly permeable. However, the Applicant did not submit a request to designate a BCS class to this drug product. The FDA has not designated the BCS class for this drug product.

3. Formulation

The two strengths (200 mg and 300 mg) of the proposed immediate-release oral tablets are manufactured (b) (4) The formulations of the

two strengths are compositionally proportional with respect to the active and inactive ingredients (b) (4)
(b) (4)

Table 2: Composition of Azacitidine) Tablets, 200 mg and 300 mg (Formulation F9 and Intended Commercial Formulation (ICF))

Component	Function	Quantity per Unit Tablet (% w/w)		
		Formulation F9	Intended Commercial Formulation	
		(b) (4) 200 mg 300 mg	200 mg	300 mg
Tablet Core				
Azacitidine	Drug Substance	(b) (4)		
Mannitol				
Silicified microcrystalline cellulose				
Croscarmellose Sodium				
Magnesium Stearate				
(b) (4)				
Film Coating				
(b) (4)				
Coated tablet weight (Strength)				(b) (4)

Table 3: Composition of (b) (4) Film Coating for 200 mg Tablet

Component	Quality Reference	Quantity (%w/w)	Amount per tablet (mg)
Hypromellose (b) (4)	USP/Ph. Eur.		(b) (4)
Titanium Dioxide (b) (4)	USP/Ph. Eur.		
Lactose Monohydrate	NF/Ph. Eur.		
Polyethylene Glycol / Macrogol (b) (4)	USP/Ph. Eur.		
Triacetin	USP/Ph. Eur.		
Iron Oxide Red (b) (4)	NF		

Table 4: Composition of (b) (4) Film Coating for 300 mg Tablet

Component	Quality Reference	Quantity (%w/w)	Amount per tablet (mg)
Hypromellose (b) (4)	USP/Ph. Eur.	(b) (4)	(b) (4)
Titanium Dioxide (b) (4)	USP/Ph. Eur.		
Lactose Monohydrate	NF/Ph. Eur.		
Polyethylene Glycol / Macrogol (b) (4)	USP/Ph. Eur.		
Triacetin	USP/Ph. Eur.		
Iron Oxide Yellow (b) (4)	NF		
Iron Oxide Red (b) (4)	NF		
Ferrosoferric Oxide / Black Iron Oxide (b) (4)	NF		

4. Dissolution Method Development

The Applicant's proposed dissolution method is summarized in Table 5 below:

Table 5: Proposed dissolution method parameters for Azacitidine Tablets

Apparatus	Speed	Volume/ Temp	Medium	Sampling Times (min)	Acceptance Criterion
USP 2 (Paddle)	**75 rpm**	**500 mL/ 37 °C**	**0.05M Phosphate Buffer (pH 6.8)**	**5, 10, 15, 20, 30, 45**	**Q= (b) (4) % at 15 minutes**

During the early development stages (IND 074618; CC-486) of Azacitidine, a Type C meeting with CMC was held where the Applicant was recommended by FDA to follow the dissolution method as described under the FDA's Guidance on *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances (August 2018)*. However, the Applicant proposed a slightly different dissolution method [Apparatus 2 (Paddle), 500 mL in 0.05 M Phosphate Buffer (pH 6.8) at 75 rpm].

4.1 Selection of dissolution medium: The Applicant noted that the Azacitidine (b) (4)
(b) (4)

(b) (4)

[redacted]

4.2 Selection of dissolution paddle speed: While using (b) (4) rpm paddle rotation speed, the Applicant noted

(b) (4)

[redacted]

4.3 Discriminating ability: The Applicant claimed that the pH 6.8 buffer medium demonstrates better discriminating ability towards the particle size (API PSD), tablet hardness, and excipient variations (e.g., (b) (4)).

Figure 2: Azacitidine Tablet Dissolution in (b) (4)

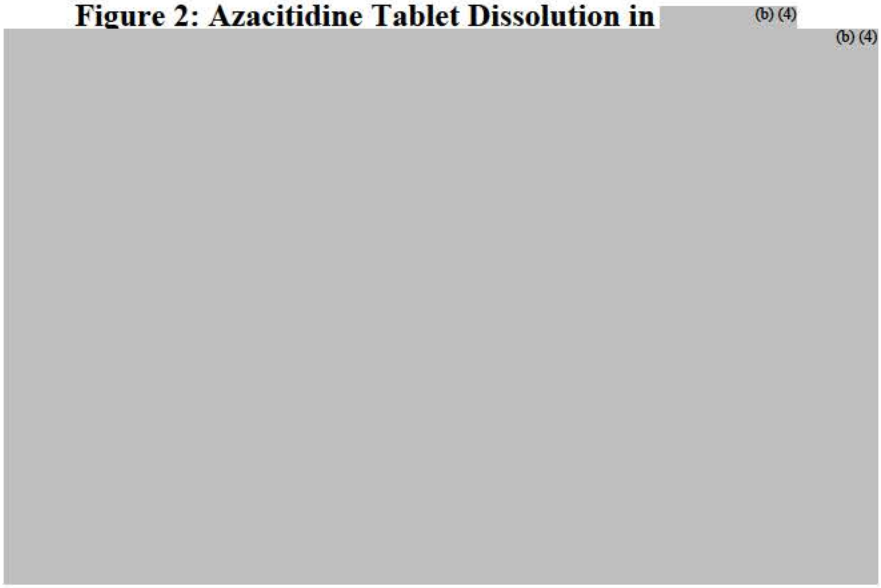


Figure 3: Azacitidine Tablet Dissolution in pH (b) (4) Medium

Figure 4: Azacitidine Tablet Dissolution in pH (b) (4) Medium

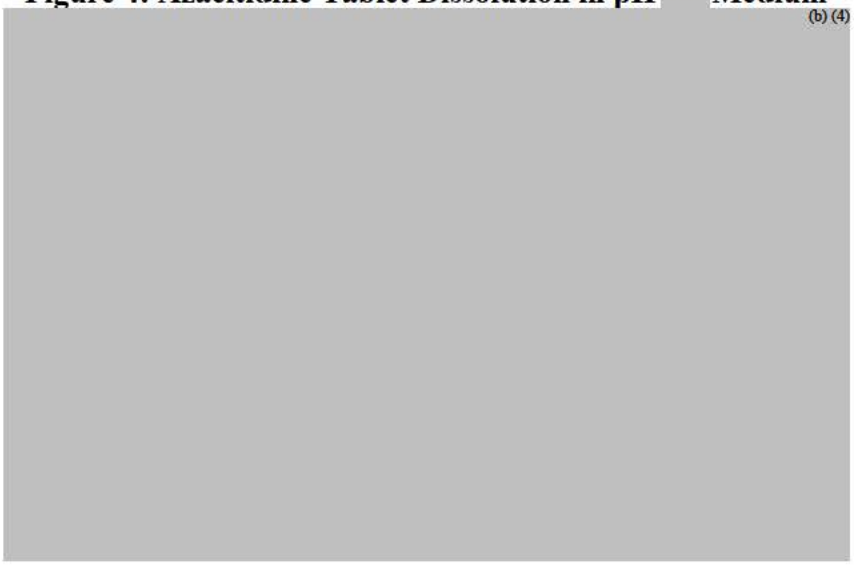
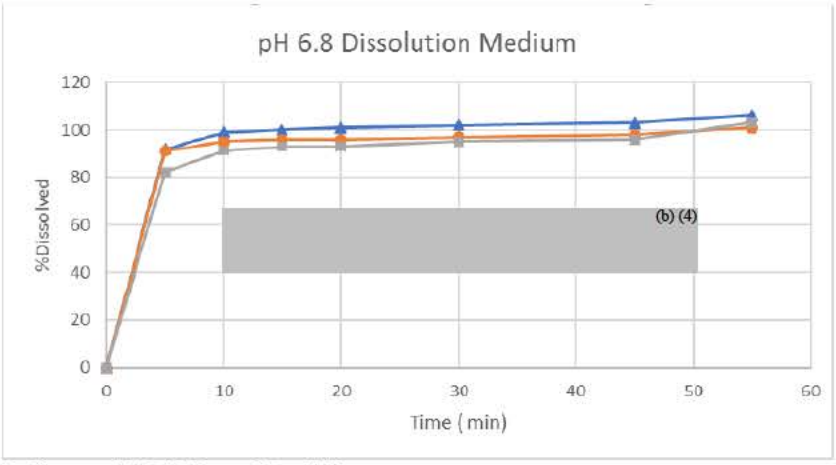


Figure 5: Azacitidine Tablet Dissolution in pH 6.8 Medium



Reference: NB 6218 pg. 33 and 40

However, as can be seen in Figures 2-5, the submitted data does not clearly validate the Applicant's claims that pH 6.8 buffer media shows better discriminating ability compared to the pH (b) (4) as only minimal difference is observed. However, this Reviewer notes that it is generally difficult to show discriminating ability for drug products containing highly soluble drug substances like Azacitidine.

Reviewer's comments: The Applicant proposed to use a dissolution method [Apparatus 2 (Paddle), 500 mL in 0.05 M Phosphate Buffer (pH 6.8) at 75 rpm] which is slightly different from the dissolution conditions . described under the FDA's Guidance on *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances (August 2018)*. The Applicant scientifically justified the use of pH 6.8 buffer medium and paddle speed of 75 rpm (b) (4) (b) (4) (b) (4) Follow up requests (see below) [1] [2] were made to the Applicant to further clarify the provided justifications. A summary of the FDA IRs, the Applicant's responses and the Reviewer's assessment are presented as follows:

Summary of FDA's IR # 1 Comments (dated 5/13/20): FDA asked Applicant (b) (4) (b) (4)

Summary of Applicant's Response to IR # 1 (dated 5/29/20): In their response, the Applicant (b) (4)

Reviewer's Comment: Although, this Reviewer notes that (b) (4) (b) (4) overall information provided, the proposed dissolution method is considered acceptable to this Reviewer provided that the Acceptance Criterion is tightened from "Q= (b) (4)% in (b) (4) minutes" to "Q= (b) (4)% in 15 minutes". The Applicant was requested to revise the dissolution acceptance criterion, the Applicant's responses and the Reviewer's assessment are presented as follows:

[1] Applicant's Response to IR #1 (received on 5/28/20): \\cdsesub1\evsprod\nda214120\0011\m1\us\resp-to-fda-corr-dated-13may2020.pdf
[2] Applicant's Response to IR #2 (received on 6/22/20): \\cdsesub1\evsprod\nda214120\0017\m1\us\resp-to-fda-corr-dated-09jun2020.pdf

Summary of FDA's IR # 2 Comments (dated 6/9/20): FDA (1) agreed to the Applicant's proposed dissolution method but requested that the Acceptance Criterion be tightened from "Q= (b)(4)% in (b)(4) min" to "Q= (b)(4)% in 15 min", and (2) requested additional supporting information for the Biowaiver such as (i) Comparative Dissolution Profile in Multimedia, (ii) Compositional Similarity in different strengths drug products, and (iii) dose-dependent PK linearity data.

Summary of Applicant's Response to IR # 2 (dated 6/22/20): In their response, the Applicant (1) tightened the Acceptance Criterion to "Q= (b)(4)% in 15 min" and updated the Specifications Report, (2) provided all of the required Biowaiver's supporting materials as per the 21 CFR 320.22(d)(2).

Reviewer's Comment: The drug substance is highly soluble, and the dissolution is very rapid using the proposed dissolution method. Although the Applicant did not use the standard conditions as described in the FDA Dissolution Guidance *(August 2018)*, the Applicant justified the use of pH 6.8 as the dissolution medium and a slightly higher rotational speed. The Applicant also attempted to demonstrate the discriminating ability of the dissolution method regarding a few formulation variables. However, the method was demonstrated to be not discriminating. This Reviewer considers it acceptable because the drug substance is highly soluble, and the drug product is designed to disintegrate and dissolve rapidly. Therefore, given the high solubility of Azacitidine, the dissolution risk from biopharmaceutics perspective is low, the proposed dissolution method is acceptable.

5. Dissolution Data and Acceptance Criterion:

Table 10: In Vitro Dissolution Data of 200 mg ICF Batches

Tablet Strength	200 mg	200 mg	200 mg	200 mg
Batch No.	1715624	1715625	1715626	1715627
Batch size	(b)(4) Kg	(b)(4) Kg	(b)(4) Kg	(b)(4) Kg
Manufacturer/date	(b)(4) Dec 2017	(b)(4) Dec 2017	(b)(4) Dec 2017	(b)(4) Dec 2017
Drug Substance Manufacturer /Lot Number	(b)(4) CA17-0851(1715160[1]) CA17-0255 (1714603[1])	(b)(4) CA17-0255 (1714603[1]) CA17-0852 (1715161[1])	(b)(4) CA17-0255 (1714603[1]) CA17-0854 (1715162[1])	(b)(4) 33002423 (1712405[1]) 34002976 (1713620[1])
Use	Registration Stability	Registration Stability	Registration Stability	Registration Stability
Dissolution by HPLC (%dissolved[a])	Min Max Mean RSD	Min Max Mean RSD	Min Max Mean RSD	Min Max Mean RSD
5 min	(b)(4) 91 4	(b)(4) 91 3	(b)(4) 89 3	(b)(4) 89 3
10 min	95 3	95 3	94 2	93 2
15 min	97 3	96 2	95 2	94 2
20 min	98 3	97 2	96 2	95 2
30 min	99 3	98 2	98 2	96 2
45 min	100 3	100 2	99 1	97 2

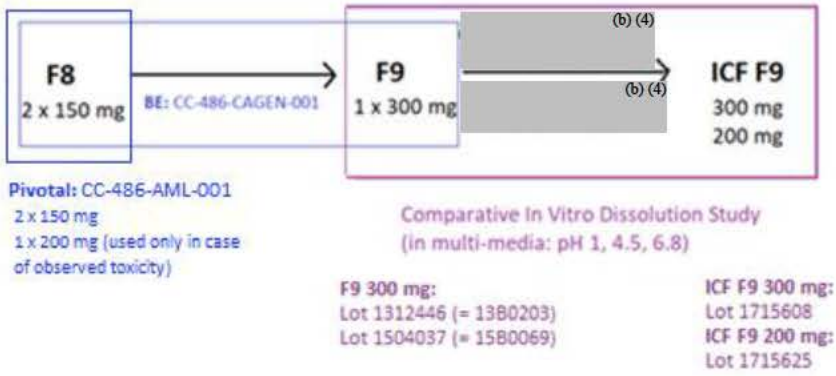
Table 11: In Vitro Dissolution Data of 300 mg ICF Batches

Tablet Strength	300 mg	300 mg	300 mg	300 mg
Batch No.	1715608	1715609	1715610	1715611
Batch size	(b) (4) Kg	(b) (4) Kg	(b) (4) Kg	(b) (4) Kg
Manufacturer/date	(b) (4) Dec 2017	(b) (4) Dec 2017	(b) (4) Dec 2017	(b) (4) Dec 2017
Drug Substance Manufacturer /Lot Number	(b) (4) CA17-0246 (1713042[1]) CA17-0251 (1713816[1])	(b) (4) CA17-0253 (1714602[1]) CA17-0256 (1714604[1])	(b) (4) CA17-0256 (1714604[1]) CA17-0851 (1715160[1])	(b) (4) 34002976 (1713620[1])
Use	Registration Stability	Registration Stability	Registration Stability	Registration Stability

Dissolution by HPLC (%dissolved[4])		Mean	Min	Max	RSD	Mean	Min	Max	RSD	Mean	Min	Max	RSD	Mean	Min	Max	RSD
	5 min	91	(b) (4)		2	91	(b) (4)		2	92	(b) (4)		2	93	(b) (4)		1
	10 min	94			2	94			1	95			2	95			1
	15 min	94			2	95			1	96			2	96			1
	20 min	95			2	96			1	96			2	97			2
	30 min	96			2	97			2	97			2	98			2
	45 min	97			2	98			2	98			2	99			2

Reviewer's Comments: The in vitro dissolution data of the registered batches using the proposed dissolution method showed that the Azacitidine Tablets, are rapidly dissolving (≥ (b) (4)% in 15 minutes). Therefore, the FDA requested that the Applicant tighten the proposed Acceptance Criterion from "Q= (b) (4)% in (b) (4) minutes" to "Q= (b) (4)% in 15 minutes" in an IR dated 6/9/20. In the Applicant's response dated 6/22/20, the Acceptance Criterion was accepted and revised to "Q= (b) (4)% in 15 minutes". As can be seen in Table 10 and 11 above, the Applicant's registered ICF batches for both 200 mg and 300 mg are able to adequately meet the tightened Acceptance Criterion at "Q= (b) (4)% in 15 minutes", and the specifications have also been updated accordingly in M.3.2.P.5.1.

6. Formulation Bridging:



There have been several versions of formulations used throughout the drug development. Specifically, the formulation used in the Pivotal Study (CC-486-AML-001) was F8, while the formulation intended for commercialization is ICF F9. Formulation 9 (F9) is similar to the intended commercial formulation (ICF), with the only difference between F9 and ICF (b) (4) Therefore, F8 is first bridged to F9, then to ICF F9.

The formulation F8, used in was developed in three dosage strengths, 100, 150 and 200 mg. This formulation was used in the phase 3 pivotal clinical study CC-486-AML-001 and AZA-MDS-003. In addition, the formulation F8 was used in Phase 2 [CC-486-GEN-001, CC-486-NPC-001, CC-486-MDS-006 and CC-486-AML-002] and a few Phase 1 [CC-486-CAGEN-001, CC-486-MDS-001 and AZA-MDS-004] clinical studies.

First, in order to bridge **F8** (used in the Pivotal Study, CC-486-AML-001) to **F9**, which is different in the formulation composition, an in vivo BE study (CC-486-CAGEN-001) was conducted by the Applicant. This in vivo BE study (CC-486-CAGEN-001) compared 1 x 300 mg tablet (**F9**) to 2 x 150 mg tablets (**F8**). Although at the time of Biopharmaceutics Review, the OCP's review was not finalized, OCP's primary reviewer for this application (Dr. Meng Li) provided confirmation via Email that the BE study (CC-486-CAGEN-001) used to bridge **F8** and **F9** formulations has been found to be acceptable. Then, to bridge formulations **F9** to **ICF F9**, the comparative in vitro dissolution study was conducted. **F9** is same as the to-be-marketed/commercial formulation **ICF F9** with no change in manufacturing process, equipment, and site. The only change made from **F9** to **ICF F9** was (b) (4)

(b) (4)

In the comparative in vitro dissolution study in multimedia (USP Apparatus 2 [Paddle], 500 mL of 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer dissolution media, 50 rpm (and 200 rpm between 46 and 60 min), a fast dissolution was observed in all tested batches of **F9** and **ICF F9** ((b) (4)% in ≤15 min).

Figure 6: Multi-media Dissolution Profiles of Formulation F9 300 mg (Lot 1312446 and Lot 1504037) and ICF 300 mg (Lot 1715608) and 200 mg (Lot 1715625) in pH 1.0

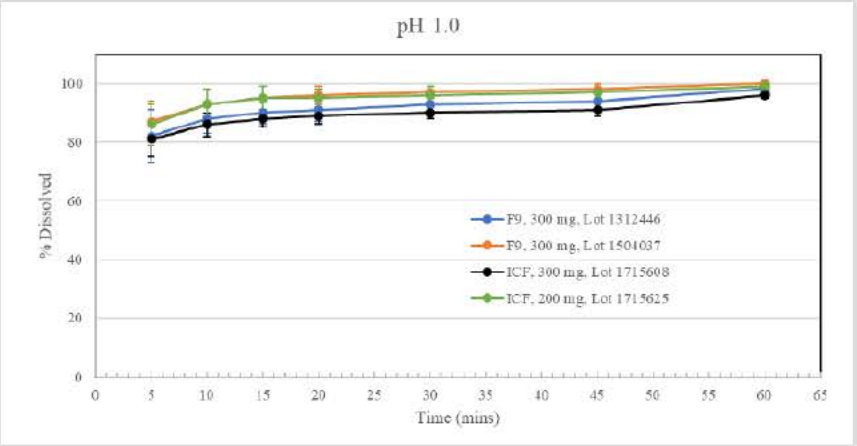


Figure 7: Multi-media Dissolution Profiles of Formulation F9 300 mg (Lot 1312446 and Lot 1504037) and ICF 300 mg (Lot 1715608) and 200 mg (Lot 1715625) in pH 4.5

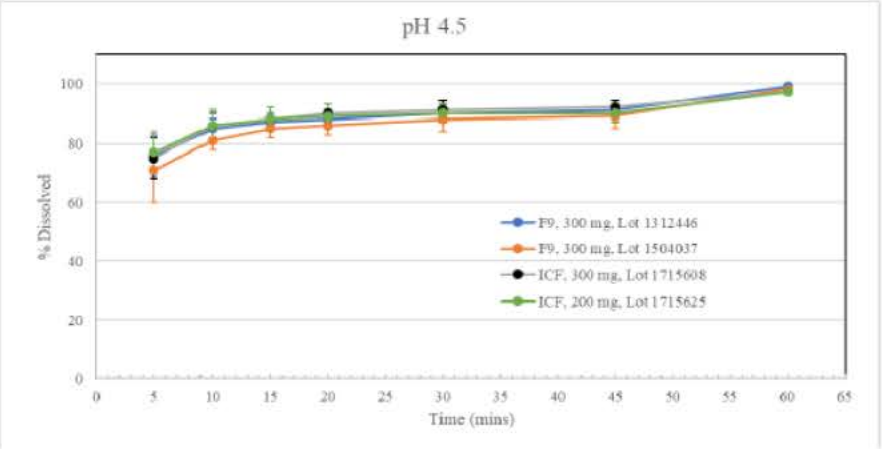
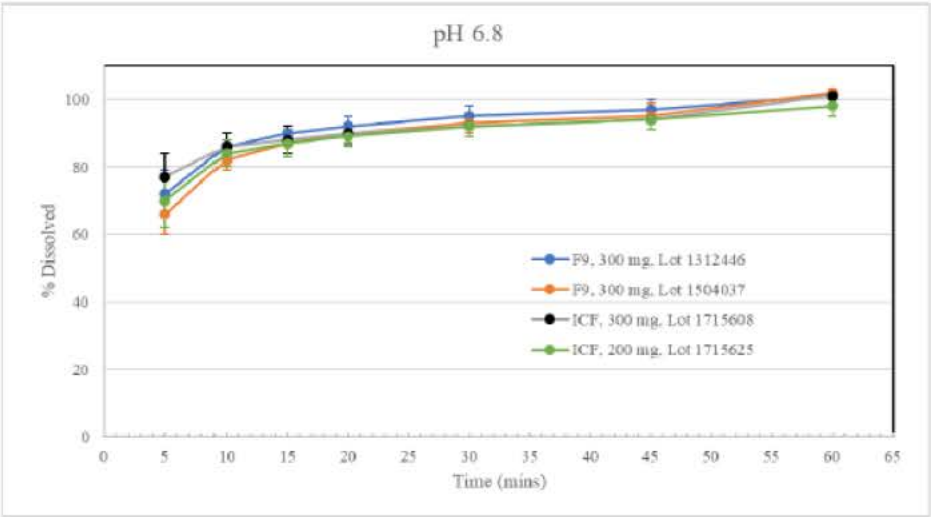


Figure 8: Multi-media Dissolution Profiles of Formulation F9 300 mg (Lot 1312446 and Lot 1504037) and ICF 300 mg (Lot 1715608) and 200 mg (Lot 1715625) in pH 6.8



Reviewer's comments: In general, no additional in vivo bridging BE studies are needed (b) (4) (b) (4) The bioequivalence study (CC-486-CAGEN-001) is adequate with both ratio (%) of geometric means of Azacitidine's AUC and Cmax within 90% CI (within bioequivalence limits of (b) (4) %) as described below. Therefore, no additional in vivo bridging BE studies were needed between the clinical (F8) and the to-be-marketed/commercial (ICF F9) formulations.

Table 21: Statistical Comparisons of Azacitidine Plasma Pharmacokinetics Parameters - AUC and C_{max} (Stage 1 [BE]) (Study CC-486-CAGEN-001)

Parameter	Formulation	N	Geometric Mean	Ratio (%) of Geometric Means (F9/F8)	90% CI of Ratio (%) of Geometric Means (F9/F8)	Intra-subject CV%
AUC_t (ng*h/mL)	8	30	225.0	106.27	(95.213, 118.622)	25.4
	9	30	239.1			
AUC_∞ (ng*h/mL)	8	30	228.5	105.71	(95.012, 117.619)	24.7
	9	30	241.6			
C_{max} (ng/mL)	8	30	143.0	101.52	(89.868, 114.676)	28.3
	9	30	145.1			

AUC_t = area under the concentration time curve from time zero to the last quantifiable time point, calculated by the linear trapezoidal rule; AUC_∞ = area under the plasma concentration time curve from time zero extrapolated to infinity; BE = bioequivalence; C_{max} = observed maximum concentration; CV% = % coefficient of variation; PK=Pharmacokinetics.
Source: Report CC-486-CAGEN-001Table 13

Table 22: Statistical Comparisons of Azacitidine Plasma Pharmacokinetics Parameters - T_{max} (Stage 1 [BE]) (Study CC-486-CAGEN-001)

Parameter	Formulation	N	Median	Median Difference	90% CI of Median Difference (F9-F8)	p-value
t_{max} (h)	8	30	1.0	-0.017	(-0.25, 0.03)	< 0.710
	9	30	1.0			

BE = bioequivalence; PK=Pharmacokinetics; t_{max} = observed time to first maximum concentration.
Source: Report CC-486-CAGEN-001Table 14

From a Biopharmaceutics standpoint, formulation bridging is deemed adequately established between the registration batches and the batches studied in the pivotal clinical trials.

7. Biowaiver Request [3]:

The Applicant submitted the biowaiver for the lower strength of Azacitidine Tablets, 200 mg, and the supporting materials are as the following: (i) same dosage form but in different strength, (ii) bioavailability of the other strength (300 mg) has been measured [Pivotal Study: CC-486-AML-002, PK Linearity: AZA-PH-US-2007-CL-005], (iii) both products (300 mg and 200 mg) meet an appropriate in vitro test approved by FDA [comparative in vitro dissolution study in multimedia in M.1.12.13, presented above in Figures 6-8], and (iv) evidence showing that the different strengths are proportionally similar in their active and inactive ingredients [drug product formulation compositions].

Based on the Applicant's submitted information that adequately supports the biowaiver requirements as required by the 21 CFR 320.22(d)(2), the biowaiver is granted for Azacitidine 200 mg strength.

* M.12.13 (Request for Waiver for In Vivo Studies): \\cdsesub1\evsprod\nda214120\0017\m1\us\req-waiv-inviv.pdf

Min (Sammie) Kang

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