CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219249Orig1s000

PRODUCT QUALITY REVIEW(S)

Title:	NDA IQA Template Title Page-EXEC SUMMARY
Document ID:	OPQ-ALL-TEM-0040
Effective Date:	26 Sep 2023 Revision: 00
Total Pages:	4

Template Revision: 03

Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	219249		
Applicant Name	GENENTECH INC		
Drug Product Name	Inavolisib		
Dosage Form	Tablet		
Proposed Strength(s)	3 mg and 9 mg		
NDA Classification	Type 1 - NME		
Route of Administration	Oral		
Maximum Daily Dose	9 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	(b) (4)		
Drug Product Description	Film-coated tablets: • 3 mg: red and round convex-shaped with an “INA 3” (b) (4) on one side. • 9 mg: pink and oval-shaped with an “INA 9” (b) (4) on one side.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F) [see USP Controlled Room Temperature].		
Review Team	**Discipline**	**Primary**	**Secondary**

	Drug Substance	Kabir Shahjahan	Haripada Sarker
	Drug Product/ Labeling	Olen Stephens	Xing Wang/ David Claffey (labeling)
	Manufacturing	Diane Goll	Zhaoyang Meng
	Biopharmaceutics	Payal Agarwal	Anitha Govada
	Microbiology	Diane Goll	Zhaoyang Meng
	Other (specify)	N/A	
	RBPM	Utkarsh Desai	
	ATL	Xing Wang	
Consults	None		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

An expiration dating period of 24 months may be granted when stored at the proposed storage conditions.

b. Additional Comments for Action

N/A

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities were deemed acceptable based on prior history, file review and district recommendation. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends APPROVAL of NDA 219249 for Inavolisib tablets, for oral use.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate

Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: Yes

Comments:

A product lifecycle management (PLCM) document was submitted to detail proposed plans about Established Conditions (ECs), non-Established Conditions (non-ECs), and Post-Approval Change Management Protocols (PACMP). The applicant confirmed via IR response (06/25/2024) "that changes to the established conditions identified in the Product Lifecycle Management (PLCM) document will be operating under regulations and guidance, as stated in Section 2 Identification of the Established Conditions in the PLCM: "Changes will be reported to the regulatory agency in accordance with the applicable regulation depending on the type of change to ECs and the impact to product quality."". Per Mary Manibusan (OQS), a PQS assessment will not be required for this application as all Established Conditions listed in the PLCM will be operating under regulations and guidance. OPQ assessment of ECs focused on whether the applicant has scientific justification for the proposed ECs, and to exclude things that FDA might normally consider ECs. The Applicant agreed (08/22/2024) to update the established conditions in Module 3.2, Table R-5 in Product Lifecycle Management (b) (4) (b) (4)

Comparability Protocols (PACMP): Yes

Comments:

PACMP includes the proposal to change the packaging configuration in tablet count from 30 to 28 tablets per bottle to align with the 28-day dosing cycle. The bottle remains unchanged. The Applicant intends to submit a CBE-0 for a 28-table bottle package configuration. The applicant's proposal is reasonable, and the change is low risk. The comparability protocol to change the tablet count, associated labeling, and data package to support the change are acceptable.

Additional Lifecycle Comments: None

Application Technical Lead Name and Date:

Xing Wang, Ph.D. *08/28/2024*

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CHAPTER IV: LABELING

NDA Number	219249
Assessment Cycle Number	1
Drug Product Name	TRADENAME (inavolisib) tablets, for oral use

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	**0001**
Patient Information	Adequate	**0001**
Instruction for Use (IFU)	N/A	
Container Labels	Adequate	**0001**
Carton Labeling	Adequate	**0001**

Brief Description of Outstanding Issues:

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0001	3/27/2024	Original submission

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

TRADENAME (inavolisib) tablets, for oral use

Initial U.S. Approval: YYYY

(b) (4) tablets: 3 mg and 9 mg

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

Item	Item in Proposed Labeling	Assessor's Comments
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	Change to 'Tablets'
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)
[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).
[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>
[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)

Item	Item in Proposed Labeling	Assessor's Comments
For injectable drug products for parenteral 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.[8]	N/A	

Assessment: *Adequate*

Minor change recommended for dosage form.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

The recommended dose of TRADENAME is 9 mg taken orally once daily with or without food.

Item	Item in Proposed Labeling	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	
Important administration instructions supported by product quality information (e.g., do not	N/A	

[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments

Item	Item in Proposed Labeling	Assessor's Comments
crush or chew extended-release tablets, instructions for mixing with food).		
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: *Adequate*

No special instructions

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(b) (4) tablets:

- 3 mg: red and round convex-shaped with an "INA 3" (b) (4) on one side.

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition
[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

- 9 mg: pink and oval-shaped with an "INA 9" (b) (4) on one side.

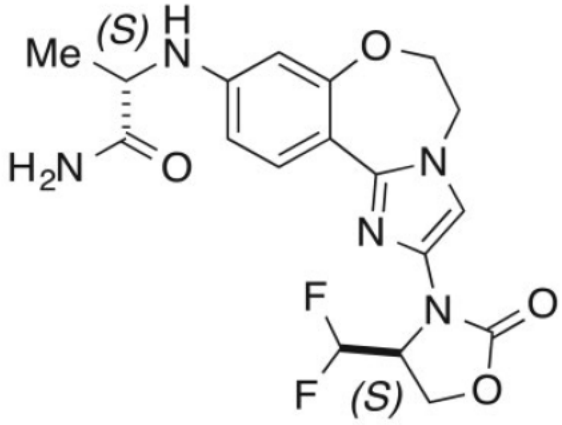
Item	Item in Proposed Labeling	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Change to 'Tablets'
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	N/A	

Assessment: *Adequate*

Minor change to dosage form recommended.

1.2.3 Section 11 (DESCRIPTION)[14]

TRADENAME contains (b) (4) inavolisib (b) (4) a kinase inhibitor. The chemical name of inavolisib is (2S)-2-[[2-[(4S)-4-(difluoromethyl)-2-oxo-oxazolidin-3-yl]-5,6-dihydroimidazo[1,2-d][1,4]benzoxazepin-9-yl]amino]propanamide. Inavolisib is a white to off-white, greyish pink, greyish orange, or greyish yellow powder. The molecular formula for inavolisib is $C_{18}H_{19}F_2N_5O_4$ and the molecular weight is 407.37 g/mol. The chemical structure of inavolisib is shown below:



TRADENAME are ~~film-coated~~ tablets ~~are~~ supplied for oral administration with two strengths that contain 3 mg and 9 mg of inavolisib. The tablets also contain lactose, magnesium stearate, microcrystalline cellulose, (b) (4) and sodium starch glycolate.

Item	Item in Proposed Labeling	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§	N/A	

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)
[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item in Proposed Labeling	Assessor's Comments
201.57(c)(12)(i)(C)].		
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	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. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

Item	Item in Proposed Labeling	Assessor's Comments
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Inadequate	Include chemical and physical properties of the inavolisib drug substance
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: *Inadequate*

Several editorial changes recommended; chemical/physical description of the drug substance is needed.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

TRADENAME is supplied in the following strengths and package configurations:

Package Configuration	Tablet Strength	NDC	Tablet Description
Bottle of 30 (b) (4) tablets	3 mg	50242-084-01	Red and round convex-shaped with an "INA 3" (b) (4) on one side
Bottle of 30 (b) (4) tablets	9 mg	50242-079-01	Pink and oval-shaped with an "INA 9" (b) (4) on one side

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F) [see USP Controlled Room Temperature].

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)
[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item in Proposed Labeling	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	Revise to 'Tablets'
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral 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 (see USP <659>).	N/A	

Item	Item in Proposed Labeling	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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	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."*[21]	N/A	
Include information about child-resistant packaging[22] (if chosen by manufacturer).	N/A	

Assessment: *Adequate*

Minor editorial change to 'tablets'

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

1.2.5 Other Sections of Labeling

NA

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling	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.	Adequate	

Assessment: *Adequate*

2.0 PATIENT LABELING

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

Item	Item in Proposed Labeling	Assessor's Comments about Labeling
Established name[24]	Adequate	
Special preparation instructions (if applicable).	N/A	
Storage and handling information (if applicable).	Inadequate	Instructions for applicant to reverse the order of Celsius and Fahrenheit storage conditions.
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	Adequate	(b) (4)
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Inadequate	Instructions for applicant to alphabetize
Name and location of business	Adequate	

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)
[24] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling	Assessor's Comments about Labeling
(street address, city, state, and zip code) of manufacturer, distributor, and/or packer.		

Assessment: *Adequate*

3.0 CONTAINER AND CARTON LABELING[25]

3.1 Container Labels[26]

(b) (4)

[redacted]

[25] Carton and Container Labeling Resources

[26] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

3.2 Carton Labeling

(b) (4)

Item	Item in Proposed Carton Labeling	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	

[27] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Carton Labeling	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	Yes	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Yes	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-	N/A	Yes	

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling
use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).			
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Adequate	Yes	
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Yes	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Yes	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	Yes	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[31]	N/A	Yes	
And others if space is available.	N/A	Yes	

Assessment of Carton Labels and Container Labeling: *Adequate*

[31] USP General Notices 3.20 Indicating Conformance

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

Highlights:
Change dosage form to 'Tablets'.
Section 3:
Change dosage form to 'Tablets'.
Section 11:
Change introduction to "TRADENAME contains inavolisib," where describing the drug substance
Change dosage form to 'Tablets'
Include chemical and physical properties of the inavolisib drug substance
Section 16:
Change dosage form to 'Tablets'
Patient Information:
Reverse the Celsius and Fahrenheit storage conditions.
Alphabetize the excipient list.

Primary Labeling Assessor Name and Date: Olen Stephens 5/21/2024

Secondary Assessor Name and Date: David Claffey 7/26/2024

Xing Wang

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Olen Stephens

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	INAVOLISIB TABLETS
NDA Number	NDA-219249-ORIG-1
Assessment Cycle Number	1
Drug Product Name/ Strength	INAVOLISIB TABLETS, 3 mg and 9 mg
Route of Administration	ORAL
Applicant Name	GENENTECH, Inc.
Therapeutic Classification/ OND Division	ONCOLOGY/OND/OOD/DO1
RLD/RS Number	New Molecular Entity (NME)
Proposed Indication	Selective inhibitor of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) catalytic subunit alpha isoform protein (p110α; encoded by the PIK3CA gene) for treatment of breast cancer

Assessment Recommendation: **Adequate**

Assessment Summary:
NDA 219249 is an original Type 1 application for New Molecular Entity (NME) seeking approval of immediate release drug product, Inavolisib Tablets, 3 mg and 9 mg. Inavolisib drug substance is a highly potent and selective inhibitor of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) catalytic subunit alpha isoform protein (p110 α; encoded by the PIK3CA gene) as a potential treatment for patients with breast cancer.

The proposed commercial formulation is an immediate-release, (b) (4) film coated tablet (FCT) for oral administration presented in two strengths of 3 mg and 9 mg. The dosage strengths are proposed to allow for accurate, convenient dosing regimen requirements of 9 mg using one 9 mg Tablet, or dose reductions to 6 mg or 3 mg using the 3 mg tablets.

This Biopharmaceutics review is focused on the 1) Evaluation and acceptability of the proposed dissolution method and acceptance criterion for the proposed test product, and the 2) Evaluation of the need for any formulation bridging.

In Vitro Dissolution Method and Acceptance Criterion:
The following dissolution method and acceptance criterion are deemed adequate and acceptable based on the totality of the information and data provided by the Applicant.

Dissolution Method and Acceptance Criterion for Inavolisib Tablets, 3 mg and 9 mg for immediate release (IR)				
Apparatus	**Speed**	**Volume/ Temp**	**Medium**	**Acceptance Criterion**
USP Apparatus II	50 rpm	500 mL for 3 mg and 900 mL for 9 mg / 37°C	0.1 N HCl	Q = (b) (4)% at 30 min

Bridging of formulation changes made throughout the clinical development:
Series of formulations for the proposed drug product labeled as F01-F17 were developed by the Applicant throughout the clinical development phase. The Applicant conducted in vitro dissolution studies to bridge these various formulation changes made during clinical development studies. From the early formulations (F01) up to the Phase III and primary stability formulations (F19), the tablets exhibit comparable drug release at pH 1.1 to pH 6.8 consistent with drug release behavior for immediate release products.

The Applicant's proposed dissolution method and test conditions (500 mL of 0.1 N HCl for 3 mg and 900 mL for 9 mg using USP Apparatus 2 (paddle) at 50 rpm at 37 ± 5°C) with dissolution acceptance criterion of Q = (b) (4)% in 30 minutes for both strengths used for batch release and stability testing of Inavolisib FCT is found adequate.

BIOPHARMACEUTICS OVERALL RECOMMENDATION
From the Biopharmaceutics perspective, NDA-219249-ORIG-1 for the proposed Inavolisib, Tablets, 3 mg, and 9 mg is recommended for **Approval.**

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #1	Comments
Dissolution	Very Low	Based on the pH solubility studies, drug substance meets the ICH M9 BCS guidance criteria for high solubility	Very Low	Applicant is proposing (b) (4) dissolution method and dissolution acceptance criterion which is deemed adequate

List Submissions Being Assessed:

Document(s) Assessed	Date Received	SDN#
Original	03/27/2024	1
Quality Information Response	06/03/2024	14

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed)*: N/A

B.1 BCS DESIGNATION

Assessment: N/A

Solubility: As shown in Table 1, the drug substance, inavolisib exhibits pH-dependent solubility, (b) (4)

Table 1. Aqueous Solubility of Inavolisib Drug Substance in Aqueous Media across the Physiological pH Range (pH 1 to pH 6.8) at 37 °C

Medium	Initial pH	Solubility in mg/mL after 4 h	Solubility in mg/mL after 24 h	pH after 24 h
0.1N HCl, pH 1.1	1.09	2.41	8.14	1.17
50 mM Acetate pH 4.5	4.50	0.06	0.05	4.47
50 mM Phosphate pH 6.8	6.80	0.05	0.04	6.78
FaSSIF pH 6.5	6.50	0.06	0.05	6.45
FeSSIF pH 5.0	5.00	0.10	0.09[a]	4.97

[a] (b) (4)

Permeability: The passive permeability of Inavolisib is considered as medium by the Applicant (P_{app} 1.9 x 10^{-6} cm/sec MDCK cell assay; P_{eff} 0.9 x 10^{-4} cm/sec)

Dissolution: The proposed Inavolisib Tablets, 3 mg and 9 mg show rapid dissolution (b) (4) using the proposed dissolution testing parameters of 0.1 N HCl using USP Apparatus II at 50 rpm paddle speed without use of any surfactant in dissolution medium. (b) (4)

(b) (4)

(b) (4) therefore 500 mL of 0.1 N HCl was used as the volume for dissolution media.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: ADEQUATE.

Background

Inavolisib is categorized as a highly aqueous soluble molecule with a moderate permeability. The inavolisib formulation is designed as an immediate release tablet. Inavolisib shows a linear dose-exposure relationship following single and multiple administration. As per the Applicant, the absolute bioavailability of inavolisib following a single 9 mg oral capsule dose of [14C] inavolisib was 76 % (90% CI: 69-83%), suggesting inavolisib has a high absolute bioavailability (Clinical Summary Module 2.7.1). Due to the rapidly dissolving behavior ((b) (4)% drug release in 30 minutes) of the proposed drug product the drug release rate is expected to have minimal impact on the overall drug absorption rate.

Dissolution Method

The solubility data of inavolisib (Table 2) demonstrated that Inavolisib exhibits a pH dependent solubility, (b) (4) inavolisib can be classified as highly soluble molecule according to according to the Biopharmaceutics Classification System.

Based on this assessment the Applicant adopted the dissolution testing conditions (b) (4) (b) (4) for the proposed test product based on the 2018 FDA guidance for Industry titled "Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances" for routine quality control test of the drug product upon manufacture and throughout the shelf life of the drug product. As both Inavolisib FCT strengths (3 mg and 9 mg) are dose proportional and are manufactured with the same process (b) (4) (b) (4) the same in vitro dissolution method and testing conditions were applied initially. The Applicant's proposed dissolution method and acceptance criterion are shown in Table 2.

Table 2. Proposed Dissolution Method and Acceptance Criterion for Inavolisib Tablets, 3 mg and 9 mg

Apparatus	Speed	Medium/Temperature	Volume	Acceptance Criterion
USP Apparatus 2 (Paddle)	50 rpm	0.1 N HCl / 37°C	500 mL for 3 mg 900 mL for 9 mg	Q = (b) (4)% in 30 minutes

Based on the IR response dated June, 3, 2024 use of 900 mL dissolution media for 9 mg strength was justified and found acceptable.

Selection of the Dissolution Testing Conditions

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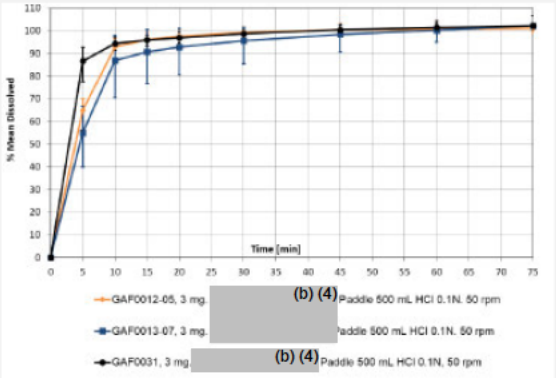
(b) (4)

Discriminating Ability

The Applicant evaluated the discriminating ability of the proposed dissolution testing conditions toward intentional variations in unit formula and demonstrated no impact on dissolution towards drug substance particle size distribution (PSD). Dissolution profiles of 3 mg tablets manufactured with mean particle sizes of D_{10} of (b) (4) µm, D_{50} of (b) (4) µm, and D_{90} of (b) (4) µm representing fine, standard, and coarse formulations of the drug substance respectively is shown in Figure 9 A. Dissolution profiles of 9 mg tablets manufactured with mean particle sizes of D_{10} of (b) (4) µm, D_{50} of (b) (4) µm, and D_{90} of (b) (4) µm representing standard, and coarse formulations of the drug substance respectively is shown in Figure 9 B.

A



B

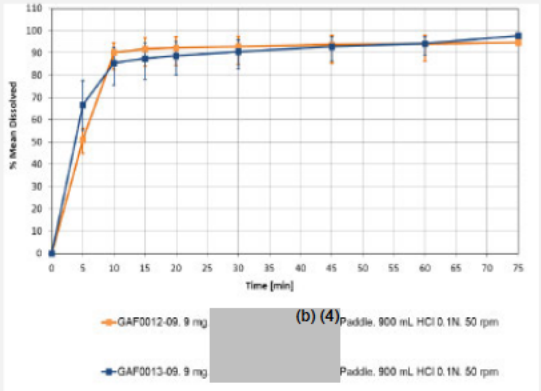


Fig. 9. Dissolution profiles of Inavolisib Tablets 3 mg (A) and 9 mg (B) in 0.1 N HCl at 50 rpm (n = 6) manufactured with API Batches of different PSD

The impact of tablet hardness on the dissolution (b) (4) was also studied by the Applicant. (b) (4) Dissolution data (Fig 10 A and B) indicates that the proposed dissolution method was able to discriminate

between tablets manufactured with different hardness (b) (4)

(b) (4)

(b) (4)

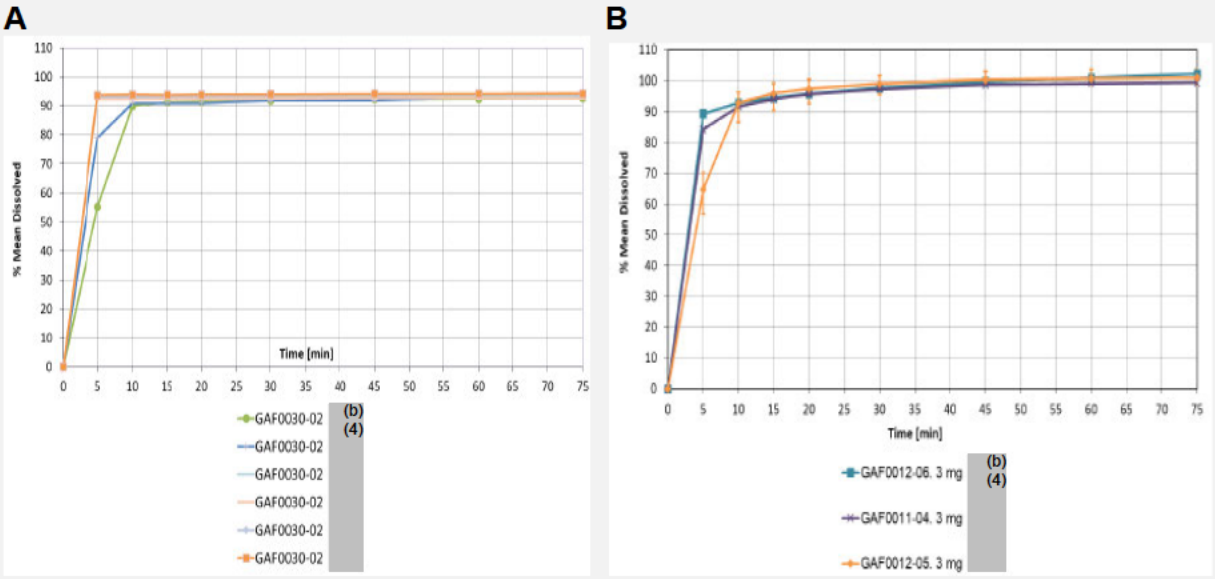


Fig. 10. Dissolution profiles of Inavolisib Tablets 3 mg (A) and 9 mg (B) manufactured at different hardness in 0.1 N HCl at 50 rpm (n = 6)

In addition to the PSD and tablet hardness, the Applicant also studied and demonstrated the discriminating ability of the proposed dissolution method against various storage and stress conditions (varying temperature and humidity (b) (4)

(b) (4)

(b) (4)

Reviewer's Assessment: Based on the overall information provided by the Applicant, the Reviewer finds the dissolution testing conditions (Apparatus 2, using 500 mL 0.1 N HCl for 3 mg and 900 mg of 0.1 N HCl for 9 mg at 50 rpm at 37 ± 5 °C), proposed for this drug product is found **Acceptable** by considering the following supportive information:

1. The proposed product is an immediate release dosage form intended to rapid drug release within gastric transit time and pH range.
2. The drug substance Inavolisib is highly soluble drug substance across gastric pH range as per the BCS classification system.
3. The API particle size distribution which is identified as the critical material attribute (CMA) have no significant impact on the drug release. The drug substance particle size is adequately controlled (b) (4) .
4. The proposed dissolution method demonstrated discriminating ability against the tablet hardness, storage and stress conditions.
5. Due to high solubility of Inavolisib across physiological pH conditions, dissolution identified as one of the CQA of drug product has very low initial biopharmaceutics risk and therefore minimal impact on the bioavailability of the proposed drug product.

6. The proposed dissolution method and test conditions (USP Apparatus II, in 500 mL/900 mL of 0.1 N HCl at 50 rpm) are in accordance with the 2018 Dissolution Guidance[1] for drug products containing highly soluble drug substance, and 2021 Guidance M9 Biopharmaceutics Classification System Based Biowaivers[2] are found adequate.
7. Dissolution acceptance criterion Q = (b) (4)% in 30 min (b) (4) (b) (4) (b) (4) are found adequate.
8. Dissolution specifications ensure complete drug release (b) (4) (b) (4).

Dissolution Acceptance criterion

The acceptance criterion for dissolution of Inavolisib Tablets, 3 mg and 9 mg is set by the Applicant to ensure that sufficient in-vitro release can be achieved with adequate discriminating ability. The proposed strengths of Inavolisib Tablets (3 mg, and 9 mg) demonstrate very rapid and complete dissolution. Based on a risk-based approach indicating low risk and the provided overall dissolution and clinical information, this Reviewer considers that the proposed dissolution acceptance criterion with the dissolution testing conditions proposed will adequately control the product's quality and ensures its clinical performance. Therefore, the proposed acceptance criterion of Q = (b) (4)% in 30 min is found adequate and **Acceptable** for both strengths of Inavolisib Tablets at release and on stability.

Biopharmaceutics Risk Assessment and Mitigation

Based on the pH solubility studies, drug substance meets the ICH M9 BCS guidance criteria for high solubility and initial risk determination is very low. The Applicant is proposing (b) (4) dissolution method and dissolution acceptance criterion, which is deemed adequate.

B.12 BRIDGING OF FORMULATIONS

Assessment: Adequate

The proposed commercial formulation for Inavolisib Tablet 3 mg and 9 mg has evolved from several iterations of clinical formulations, wherein Applicant has made minor adaptations to address dosage strengths (b) (4) as shown in Figure 11. A film-coat was introduced (b) (4) The color of the intended commercial formulation has been optimized for adequate market acceptance.

[1] https://www.fda.gov/media/92988/download
[2] https://www.fda.gov/media/148472/download

Fig. 11. Drug product formulation development overview

A qualitative and quantitative comparison of all clinical formulations and the formulations used for the primary stability studies is given in Module 3.2.P.2. Table 4 shows comparison of formulations used for Phase 1, Phase 3, Primary Stability study and the Proposed Commercial drug product

Pivotal clinical batches (formulations F08/09 and F14/15) were tested with the proposed dissolution method using (b) (4) rpm paddle speed. Representative pivotal batches were also tested using the proposed QC method at 50 rpm during formulation bridging study.

The Applicant conducted in vitro dissolution studies in different pH conditions (pH 1.1, pH 4.5, and pH 6.8) to bridge these formulations that are used throughout the various clinical development stages as shown in Figures 12 A, B and C.

Table 4. Comparison of formulations used for Phase 1, Phase 3, Primary Stability study and the Proposed Commercial drug product.

Phase I (Early Clinical Development)	Phase III (Pivotal Clinical Trials)	Primary Stability	Commercial
First generation of drug product: • Formulations F01 (b) (4) and F02 (b) (4) (b) (4) Second generation of drug product: • Formulations F04 (3 mg) and F05 (b) (4) • Coated (b) (4) film coating (b) (4) • These formulations were developed in a dose-proportional manner for 3 mg (F04) and 9 mg (F05) dose strengths. (b) (4) • These formulations were used to resupply Phase I trials	Third generation of drug product: • Formulations F08/ F14 (9 mg) and F09/ F15 (3 mg) (b) (4) • Coated: (b) (4) film coating (b) (4) • Formulations F14 (3 mg) and F15 (9 mg) were manufactured with drug substance (b) (4)	Fourth generation of drug product: • Formulations F12 (9 mg) and F13 (3 mg) • Used for primary stability studies. • Coated: Red film coating for the 3 mg and a pink film coating for the 9 mg (b) (4)	Fifth generation of drug product: • Represents the intended commercial formulation F16 (9 mg) and F17 (3 mg). • Includes commercial debossing and represent the final commercial trade dress. • The formulation components are qualitatively and quantitatively identical compared to Fourth generation

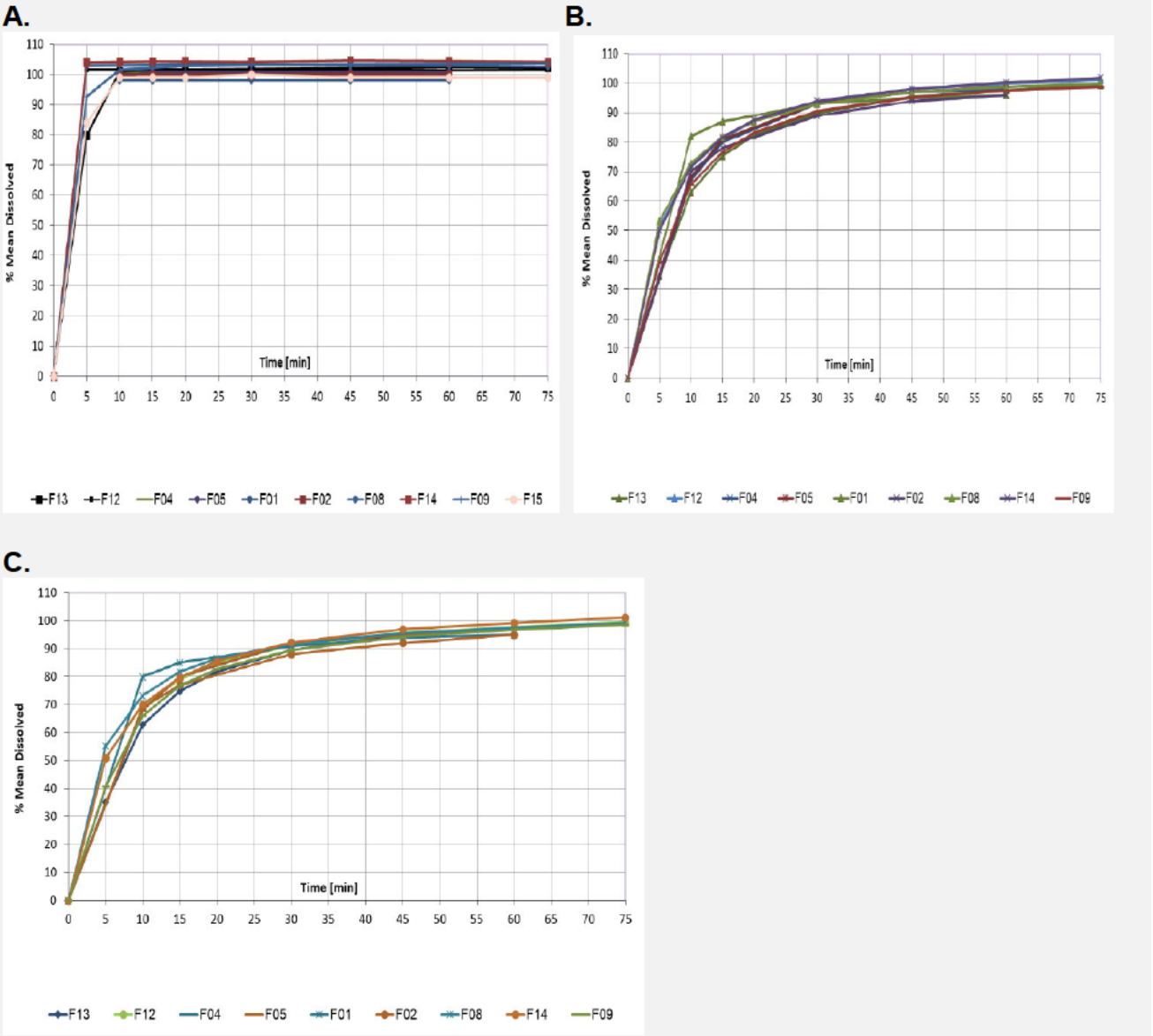


Fig. 12. Dissolution profile comparison of Inavolisib Tablets 3 mg and 9 mg from Phase I to Phase III in: A. 0.1 N HCl, B. Acetate buffer, pH 4.5, C. Phosphate buffer, pH 6.8, using USP Apparatus 2 (Paddle) at (b) (4) rpm (n=12)

From the early formulations up to the Phase III and primary stability, tablets exhibit similar dissolution behavior within pH 1.1 to pH 6.8 that are consistent with immediate release products.

In addition, a dissolution profile comparison of the Phase III batches and primary stability batches using the commercial method (USP apparatus 2 (paddle) at 50 rpm) in 0.1 N HCl as well as pH 4.5. acetate buffer and pH 6.8 phosphate buffer are shown in Figures 13 A, B and C respectively (Note: Formulation F15 was not tested at 50 rpm. F15 has the same formulation as F09 therefore the dissolution profile is expected to be the same).

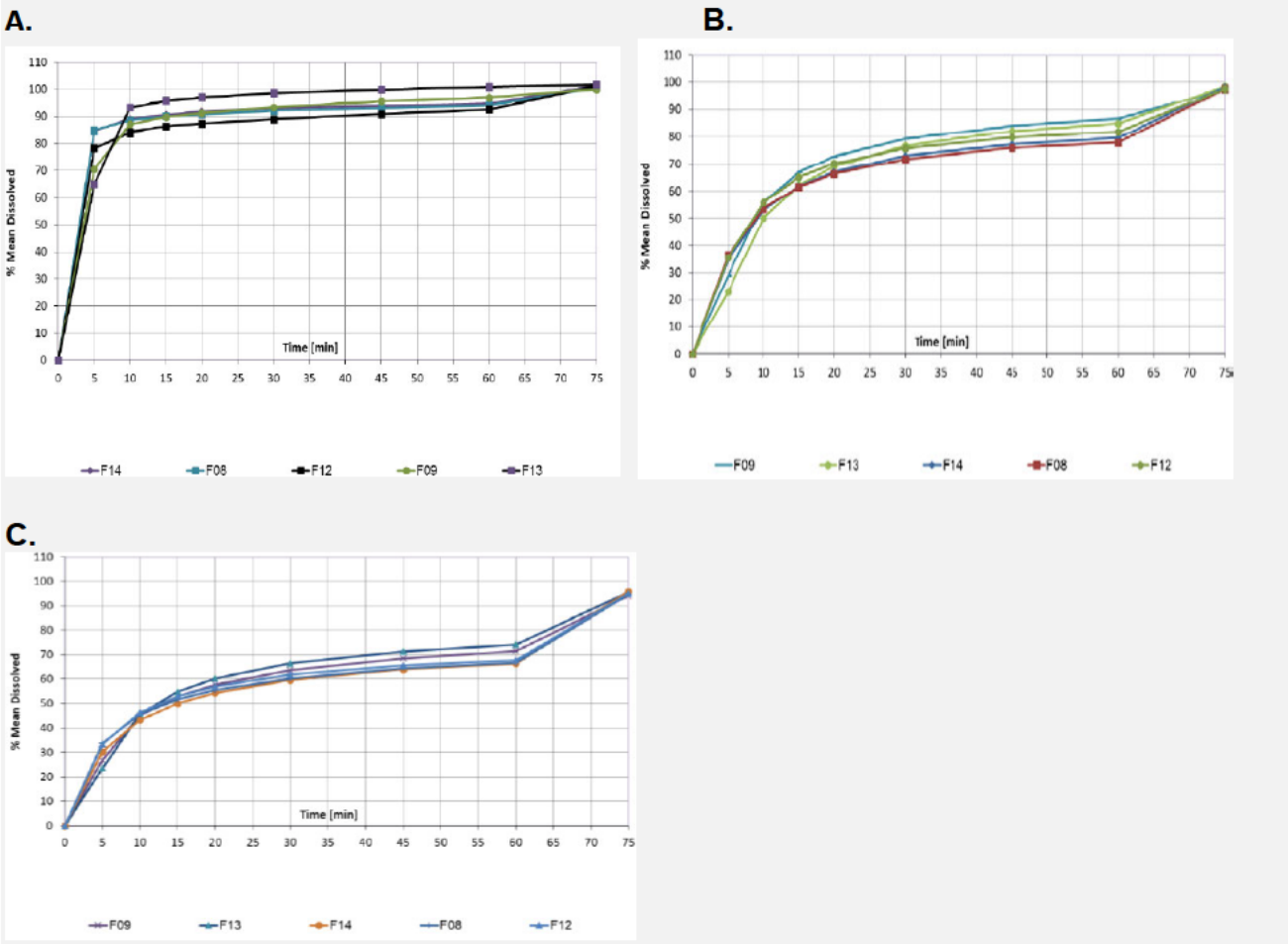


Fig. 13. Dissolution profile comparison of Inavolisib Tablets 3 mg and 9 mg from Phase III Batches (F08, F09 and F14) and Primary Stability Batches (F12/F13) in: A. 0.1 N HCl, B. Acetate buffer, pH 4.5, C. Phosphate buffer, pH 6.8 using USP Apparatus 2 (Paddle) at 50 rpm (n=12)

In 0.1 N HCl, all formulations exhibit similar very rapid dissolution behavior, with (b) (4)% dissolved (b) (4) In pH 4.5 acetate buffer and pH 6.8 phosphate buffer, all formulations exhibit similar dissolution behavior (f2 > 50).

Conclusion: The Applicant conducted comparative in vitro dissolution testing to adequately bridge the drug product formulation changes made throughout the clinical development phases, demonstrating similarity ((b) (4)% release in (b) (4) minutes) amongst the various formulations.

OVERALL BIOPHARMACEUTICS RECOMMENDATION: Based on totality of information submitted, from a Biopharmaceutics perspective, the proposed dissolution method using USP Apparatus 2 with 500 mL of 0.1 N HCl for 3 mg and 900 mL of 0.1 N HCl for 9 mg strength at 50 rpm and acceptance criterion of Q = (b) (4)% in 30 minutes for both strengths for batch release and stability testing for Inavolisib Tablets, 3 mg and 9 mg is deemed acceptable for NDA 219249 and recommended for **APPROVAL.**

B. 13 BIOWAIVER REQUEST

Assessment: N/A

Pivotal clinical studies were conducted using both 3 mg and 9 mg strengths of the proposed Inavolisib Tablets.

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: N/A

Post-Approval Commitments

Assessment: N/A

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

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