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RESEARCH**

APPLICATION NUMBER:

218860Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA IQA Template Title Page-EXEC SUMMARY		
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Template Revision: 03

Office of Pharmaceutical Quality

New Drug Application (NDA) Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	NDA 218860
Applicant Name	Ipsen Biopharmaceuticals, Inc.
Drug Product Name	IQIRVO (elafibranor) Tablets, 80 mg
Dosage Form	Tablet
Proposed Strength(s)	80 mg
NDA Classification	Type 1 - NME
Route of Administration	Oral
Maximum Daily Dose	80 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.
Drug Product Description	Ipsen Biopharmaceuticals, Inc. has submitted this 505(b)(1) application for IQIRVO (elafibranor) tablets, 80 mg for oral administration indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. Patients are to orally take one 80 mg tablet once daily. The drug substance elafibranor and its main active metabolite GFT1007 are dual peroxisome proliferator-activated receptor (PPAR)α/δ agonists. Elafibranor has not been previously approved or marketed in the United States and therefore, it is classified as a New Molecular Entity (NME). IQIRVO (elafibranor) is available as round orange, approximately 8 mm, film-coated tablets, debossed

	with 'ELA 80' on one side. Each tablet contains 80 mg of elafibranor as the active ingredient and microcrystalline cellulose, povidone, croscarmellose sodium, (b) (4) colloidal silica, and magnesium stearate as inactive ingredients. The film coating consists of polyvinyl alcohol (b) (4) titanium dioxide (b) (4) talc, iron oxide yellow and iron oxide red. All inactive ingredients including the tablet coating components are compendial materials. The quantity of each inactive ingredient is at or below the limit listed in the Agency's IID for approved oral drug products. IQIRVO tablets will be packaged as 30-count tablets in high density polyethylene (HDPE) bottle with a white child-resistant (b) (4) cap (b) (4) (b) (4) (b) (4) This drug product should be stored at 15°C to 30°C (59°F to 86°F) with an expiration dating period of 24 months.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	Store at 15°C to 30°C (59°F to 86°F)		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Friedrich Burnett, Ph.D.	Lawrence Perez, Ph.D.
	<i>Drug Product/ Labeling</i>	Craig Bertha, Ph.D.	Hamid Shafiei, Ph.D./Julia Pinto, Ph.D.
	<i>Manufacturing</i>	Wei Yang, Ph.D.	Jean Tang, Ph.D.
	<i>Biopharmaceutics</i>	Kamrun Nahar, Ph.D.	Tapash Ghosh, Ph.D.
	<i>Microbiology</i>	Wei Yang, Ph.D.	Jean Tang, Ph.D.
	<i>Environmental Assessment</i>	Craig Bertha, Ph.D.	Hamid Shafiei, Ph.D.

	<i>RBPM</i>	Megan Nguyen
	<i>ATL</i>	Hamid Shafiei, Ph.D.
Consults		

2. Final Overall Recommendation - Approval

This application is recommended for approval from all OPQ review disciplines and the final agreed labeling that has been communicated through the clinical team to the applicant will be submitted to this application prior to PDUFA action date.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, elafibranor and the drug product, IQIRVO (elafibranor) Tablets, 80 mg.
- The Office of Pharmaceutical Manufacturing Assessment has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC recommended changes to the labeling have been communicated to the Clinical Review Team and the proposed CMC revisions have been accepted.
- The applicant request for categorical exclusion from the preparation of environmental assessment has been found adequate and is granted.

Therefore, this applicant is recommended for approval from the OPQ perspective with an expiration dating period of 24 months.

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

Although, in the labeling chapter, the labeling was recorded as inadequate, the CMC labeling deficiencies/revisions have been communicated through the clinical team to applicant and the applicant has accepted the recommended CMC labeling changes/revisions. Therefore, the labeling is now considered adequate from the OPQ perspective, and the final agreed labeling will be submitted to the application closer to PDUFA action date.

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): Yes

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments: None

Application Technical Lead Name and Date:

Hamid Shafiei, Ph.D.

Senior Pharmaceutical Quality Assessor

DPQA VII/OPQA II/OPQ



Hamid
Shafiei

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Title:	NDA IQA Template CHAPTER IV- LABELING		
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Template Revision: 03

Important: Do Not Change the Header or Footer

CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide \(OPQ-ALL-WI-0006\)](#)

NDA Number	218860
Assessment Cycle Number	1
Drug Product Name	Elafibranor Tablets

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate (“N/A” otherwise)
Prescribing Information Labeling	Inadequate	
Patient Information	Inadequate	
Instruction for Use (IFU)	Inadequate	
Container Labels	Inadequate	
Carton Labeling	Inadequate	

Brief Description of Outstanding Issues:

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
eCTD 0001, SDN 1	10/10/2023	Original application with labeling

1.0 PRESCRIBING INFORMATION¹

Assessment of Product Quality Related Aspects of the Prescribing Information:

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)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)



Item	Item in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights² [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	

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>

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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	
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

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)

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>

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)⁹



(b) (4)

Item	Item in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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 crush or chew extended-release tablets, instructions for mixing with food).	N/A	
For parenteral products: include statement: <i>“Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.”</i> ¹¹	N/A	

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*

¹¹ §201.57(c)(3)(iv)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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 " <i>DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.</i> ^x " with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: Adequate.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)¹³

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly state	N/A	

¹² USP General Notices 2.30 Legal Recognition

¹³ See § 201.57(c)(4); [Labeling Review Tool \(March 2022, page 29\)](#)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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.		
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.

1.2.3 Section 11 (DESCRIPTION)¹⁴

(b) (4)



Item	Item in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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	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 (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
of drug-x hydrochloride)” [§ 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)].	Inadequate	The inactive ingredients are listed, but not in alphabetical order. The inactive ingredient name (b) (4) (b) (4) changed to <i>colloidal silicon dioxide</i> to be consistent with the USP/NF. The inactive ingredient name (b) (4) (b) (4) changed to <i>polyvinyl alcohol</i> . The inactive ingredient name (b) (4) (b) (4) changed to <i>polyethylene glycol</i> .
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	

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.

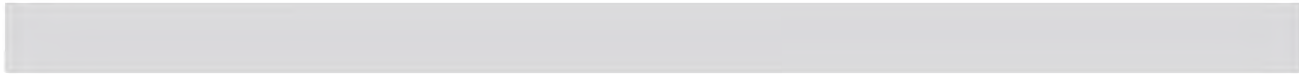
Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Chemical name ¹⁸ , structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Inadequate	The IUPAC chemical name should be used in the proposed labeling.
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	N/A	
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. The following comments should be sent to the applicant:

1. We recommend that you order the list of inactive ingredients in the DESCRIPTION section and MEDICATION GUIDE of the labeling in alphabetical order. In addition, revise (b) (4) *colloidal silicon dioxide* (b) (4) (b) (4) *polyvinyl alcohol*, and (b) (4) *polyethylene glycol*, to be consistent with the USP/NF.
2. Revise the chemical name of the drug in the DESCRIPTION section so that it is as per the IUPAC nomenclature, i.e., 2-(2,6-Dimethyl-4-{3-[4-(methylsulfanyl)phenyl]-3-oxoprop-1-en-1-yl}phenoxy)-2-methylpropanoic acid, as in the USP Dictionary.

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).

¹⁹ Draft guidance: [Gluten in Drug Products and Associated Labeling Recommendations \(December 2017\)](#)



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

(b) (4)



Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	
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	

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 (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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	
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.” with x numerical citation to “OSHA Hazardous Drugs.” [§ 201.57(c)(17)(iv)]	Inadequate	The labeling states the following: “Store in the original package.” No additional statements are made as to the reason why this should be done.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	The long term stability studies were performed with 30°C/75%RH storage conditions.
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: “ <i>Not made with natural rubber latex.</i> ”	N/A	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
<i>Avoid statements such as "latex-free."²¹</i>		
Include information about child-resistant packaging ²² (if chosen by manufacturer).	Adequate	The labeling indicates that the package is child-resistant.

Assessment: Inadequate.

1. Revise the HOW SUPPLIED/STORAGE AND HANDLING section of the labeling to indicate why the drug product is to be stored in its original package (i.e., to protect it from light and moisture).
2. Remove the statement to [REDACTED] (b) (4) from the HOW SUPPLIED/STORAGE AND HANDLING section of the labeling.

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

[REDACTED] (b) (4)

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)

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

Item	Item in Proposed Labeling (choose “Adequate” or “Inadequate”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Inadequate	Revise to include the street address of Ipsen Biopharmaceuticals, Inc.

Assessment: *Inadequate.*

1. Revise the labeling (package insert and MEDICATION GUIDE) to also include the street address for Ipsen Biopharmaceuticals, Inc.

2.0 PATIENT LABELING

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

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²³ § 201.1(h)(5) and 201.1(i); [Labeling Review Tool \(March 2022, page 74\)](#)

(b) (4)



Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²⁴	Adequate	
Special preparation instructions (if applicable).	Adequate	
Storage and handling information (if applicable).	Adequate	
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	Note that desiccant is enclosed in the child resistant closure, thus a warning is not needed.
Active ingredient(s) (if applicable).	Adequate	
Alphabetical listing of inactive ingredients (if applicable).	Inadequate	The inactive ingredients are listed, but not in alphabetical order. The inactive ingredient name (b) (4) (b) (4) changed to <i>colloidal silicon dioxide</i> to be consistent with the USP/NF. The inactive ingredient name (b) (4) (b) (4) changed to <i>polyvinyl alcohol</i> . The inactive ingredient name (b) (4) (b) (4) changed to <i>polyethylene glycol</i> .
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Inadequate	The street address is not included.

Assessment: Inadequate. See deficiencies above regarding the street address for the applicant and the alphabetical listing and names of inactive ingredients.

²⁴ Established name = [Drug] [Route of Administration] [Dosage Form]

3.0 CONTAINER AND CARTON LABELING²⁵

3.1 Container Labels²⁶



3.2 Carton Labeling



Item	Item in Proposed Carton Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Is item in Container Labels same as that of Carton Labeling?	Assessor’s Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name ²⁷ , (font size and prominence) [§ 201.10(g)(2)].	Inadequate	Yes	The established name does not have prominence in accordance with the regulations, as the font size is not at least half the size of the type of the proprietary name (ratio of 0.35/1.0). The boldness of the proprietary name font is significantly more prominent than that of the established name.
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	No	
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	Choose an item.	
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	

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.

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

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 (choose “Adequate”, “Inadequate”, or “N/A”)	Is item in Container Labels same as that of Carton Labeling?	Assessor’s Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
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).	Inadequate	No	The carton label does indicate that the drug product should be stored in the original package to protect it from light. But since there is a desiccant in the cap, the label should also indicate that keeping the drug product in the original bottle is also for protection from moisture.
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, and these products require a “Not for direct infusion” statement. (See USP <659>).	N/A	Choose an item.	
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)].	N/A	Choose an item.	
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the	N/A	Choose an item.	

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
name and statement of effect. [§ 201.100(b)(5)(iii)].			
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	Choose an item.	
Linear Bar code [§ 201.25(c)(2)]. ³⁰	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	No	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	No	
"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.	Adequate	No	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Choose an item.	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Choose an item.	

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 (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
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	Choose an item.	
And others if space is available.	N/A	Choose an item.	

Assessment of Carton Labels and Container Labeling: *Inadequate.*

1. As there is a desiccant in the cap, revise the carton label to also indicate that keeping the drug product in the original bottle is for protection from moisture, in addition to light.
2. Revise the carton and container labeling such that it is in compliance with 21 CFR 201.10(g)(2), i.e., the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

1. We recommend that you order the list of inactive ingredients in the DESCRIPTION section and MEDICATION GUIDE of the labeling in alphabetical order. In addition, revise (b) (4) colloidal silicon dioxide (b) (4) to polyvinyl alcohol, and (b) (4) polyethylene glycol, to be consistent with the USP/NF.
2. Revise the chemical name of the drug in the DESCRIPTION section so that it is as per the IUPAC nomenclature, i.e., 2-(2,6-Dimethyl-4-{3-[4-

³¹ USP General Notices 3.20 Indicating Conformance

(methylsulfanyl)phenyl]-3-oxoprop-1-en-1-yl}phenoxy)-2-methylpropanoic acid, as in the USP Dictionary.

3. Revise the HOW SUPPLIED/STORAGE AND HANDLING section of the labeling to indicate why the drug product is to be stored in its original package (i.e., to protect it from light and moisture).
4. Remove the statement to [REDACTED] ^{(b) (4)} from the HOW SUPPLIED/STORAGE AND HANDLING section of the labeling.
5. Revise the labeling (package insert and MEDICATION GUIDE) to also include the street address for Ipsen Biopharmaceuticals, Inc.
6. As there is a desiccant in the cap, revise the carton label to also indicate that keeping the drug product in the original bottle is for protection from moisture, in addition to light.
7. Revise the carton and container labeling such that it is in compliance with 21 CFR 201.10(g)(2), i.e., the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

Primary Labeling Assessor Name and Date: Craig M. Bertha (1/31/2024)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Julia Pinto



Craig
Bertha

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Julia
Pinto

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QUALITY REVIEW



BIOPHARMACEUTICS

NDA: NDA 218860

Drug Product Name / Strength: IQIRVO (Elafibranor) film coated tablets, 80 mg

Route of Administration: Oral

Applicant Name: Ipsen Biopharmaceuticals, Inc.

Indication: For the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

Submission date: 10/08/2023

Primary Reviewer: Kamrun Nahar, Ph.D.

Secondary Reviewer: Tapash Ghosh, Ph.D.

Recommendation: Adequate

BACKGROUND:

The Applicant is seeking approval under 505(b)(1) regulatory pathways for IQIRVO (Elafibranor) film coated tablets, 80 mg, for oral administration, indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting: 1) the proposed dissolution method and acceptance criteria, and 2) formulation bridging throughout product development. Summary of the key findings are presented below, based on the review of the provided information/data:

Dissolution Method and Acceptance Criteria: Adequate

The proposed dissolution method and acceptance criterion for quality control and stability testing of the proposed IQIRVO (Elafibranor) film coated tablets, 80 mg at release and stability:

Apparatus	Rotation Speed (rpm)	Medium	Volume (mL)	Temperature	Dissolution acceptance criterion
USP Apparatus 2 (Paddle)	50	0.1% sodium dodecyl sulfate (SDS) in phosphate buffer, pH 6.8	900	37±0.5°C	(b)(4)% in 30 minutes

1) Bridging of Formulations: Acceptable

The Applicant manufactured Elafibranor 80 mg white film-coated tablets (Formulation 5) in Delpharm (b)(4) and used in Phase 2 and phase 3 clinical study of primary biliary cholangitis (PBC). To commercialize, they manufactured formulation 6 (orange film-coated tablets) at Delpharm (b)(4) which is the final drug product. Formulation 6 (Elafibranor

80mg orange film coated tablets) was then transferred to another facility of Delpharm in Milano (Italy), the site for commercial manufacturing. Formulation 5 and formulation 6 are same except for the coloring agent in the coating (b) (4). To bridge the formulation 5 (clinical batch 211089, formulation 5 used in PBC phase III Study 319-1) and formulation 6 (registration batches# M0006, M0007, and M0008 manufactured at Delpharm Milano, the proposed commercial site) they conducted comparative dissolution in QC dissolution method. No formal BE between the PBC clinical and to-be-marketed formulations of Elafibranor tablets, 80 mg. Dissolution data showed that dissolution rate of both clinical and registration batches (to-be-marketed formulations) have similar drug release from the tablets. Similarity factor (f2) analysis between the clinical and registration batches showed that $f_2 > 50$, indicating dissolution profile sameness between the formulations.

CONCLUSION AND RECOMMENDATION:

Form a Biopharmaceutics perspective, NDA 218860 IQIRVO (Elafibranor) film coated tablets, 80 mg is **adequate** for approval.

BIOPHARMACEUTICS ASSESSMENT:**List Submissions being reviewed:**

1. 0001 10/08/2023 Original submission

Solubility:

The Applicant claimed that Elafibranor is a low soluble compound. Solubility data across the physiological pH range 1.2-6.8 in aqueous media showed that Elafibranor is a low soluble compound.

Table 1: Solubility data of Elafibranor in the pH range 1.2-7.1

Aqueous Buffer Solubility	Buffer	Solubility (µg/mL) Mean	USP/Ph.Eur Solubility
	USP HCl buffer, pH 1.2	<0.2 (NQ)	Practically insoluble
	Citrate buffer 0.1 M, pH 3.9	<0.2 (NQ)	Practically insoluble
	USP Acetate buffer, pH 4.5	<0.2 (NQ)	Practically insoluble
	USP Phosphate buffer, pH 6.7	78.9	Practically insoluble
	Phosphate-buffered saline (PBS), pH 7.1	729.1	Very slightly soluble

Description and composition of the drug product

The Elafibranor 80 mg drug product consists of a round, orange film-coated tablet, approximately 8 mm diameter, debossed with “ELA 80” on one side. Each tablet contains the (b) (4) drug substance formulated with conventional excipients.

Formulation development

Elafibranor capsule formulations, at different dosage strengths from 5 mg to 60 mg capsules (Formulation 1 to 4), were first developed and used for Phase 1 and Phase 2 clinical program in the treatment of non-alcoholic steatohepatitis (NASH). After that Elafibranor 80 mg and 120 mg white film-coated tablets were developed (b) (4) (Formulation 5) and transferred to Delpharm (b) (4) keeping the process to their equipment unmodified. Several clinical batches of Elafibranor white coated tablets (Formulation 5) have been manufactured for NASH Phase 3 clinical study and primary biliary cholangitis (PBC) Phase 2 and Phase 3 clinical studies. To commercialize, formulation 6 (orange film-coated tablets) has been manufactured at Delpharm (b) (4) which is the final drug product. Formulation 6 (Elafibranor 80 mg orange film coated tablets) was then transferred to another facility of Delpharm in Milano (Italy), the site for commercial manufacturing. Formulation 5 and formulation 6 are same except for the coloring agent in the coating (b) (4).

Bridging between the formulations

The Applicant bridged the clinical batch 211089 (Formulation 5 used in PBC phase III Study 319-1), manufactured at Delpharm (b) (4) with the three registration industrial scale batches (batches# M0006, M0007, and M0008) manufactured at Delpharm Milano via dissolution test using QC dissolution method. No formal BE between the PBC clinical and to-be-marketed formulations of Elafibranor tablets, 80 mg. Dissolution data showed that dissolution rate of both clinical and to-be-marketed formulations have similar drug release from the tablets. Similarity

factor (f_2) analysis between the clinical and registration batches showed that $f_2 > 50$, indicating dissolution profile sameness between the formulations.

Table 2: Comparison of Elafibranor 80 mg clinical and registration tablets

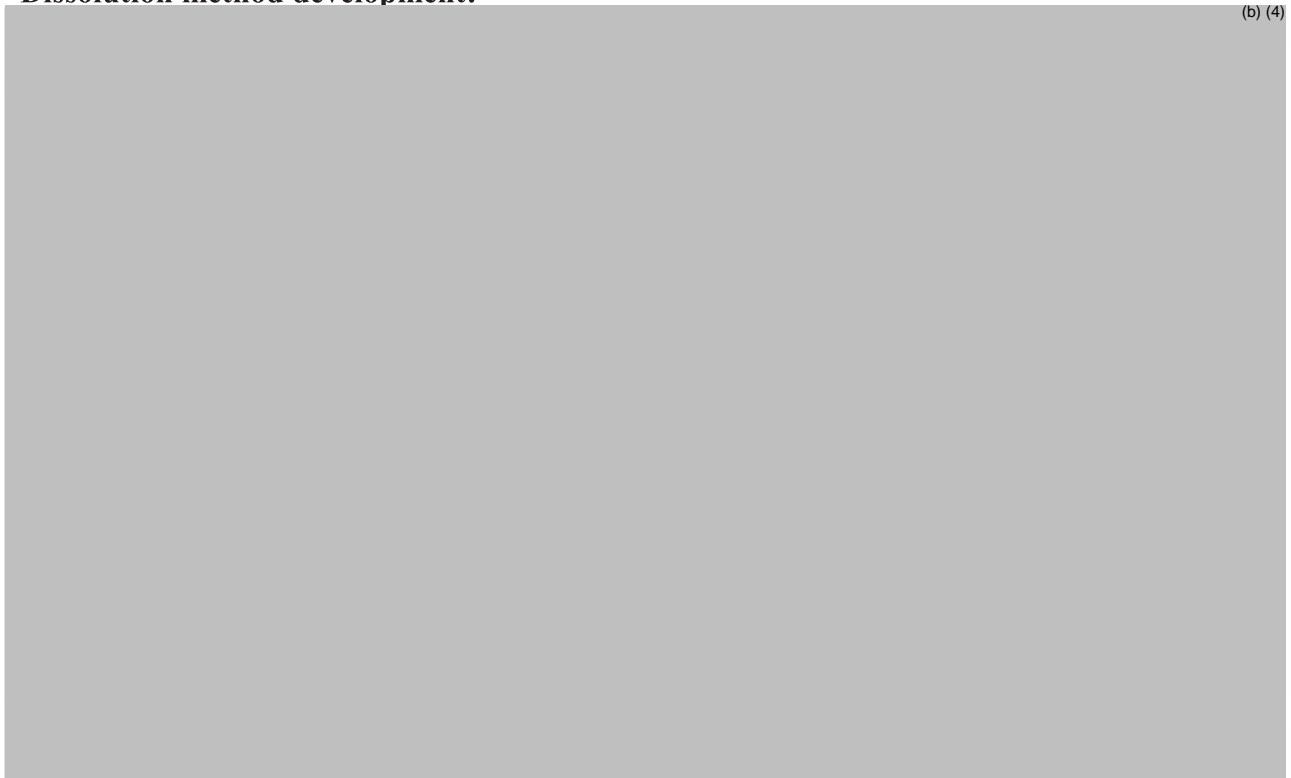
	Clinical tablet batches Formulation 5 80 mg	Registration tablet batches Formulation 6 80 mg
Tablet description	White to off-white round film-coated tablets	Orange round film-coated tablets debossed with ELA and 80 on 1 side
Manufacturing site	Delpharm (b) (4)	Delpharm Milano
Batch size	(b) (4) tablets	(b) (4) tablets

Data Source: Section 3.2.P.2.3, Appendix I.

Table 3: Similarity factor results reported by the Applicant between the Elafibranor 80 mg clinical and registration tablets.

Reference Drug product	Test Drug Product	Similarity factor (f_2) value
211089	M0006	66
211089	M0007	83
211089	M0008	96

Dissolution method development:



(b) (4)

Table 4: Comparison of initial and quality control dissolution methods

(b) (4)

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Dissolution method development:

(b) (4)

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Discriminatory ability of the method:

To evaluate the discriminating ability of the dissolution method, the Applicant manufactured several aberrant formulations by modifying the composition and manufacturing process of the Elafibranor commercial formulation (orange round tablets) and compared to the Elafibranor clinical formulation (white round tablets) which is considered as reference formulation.

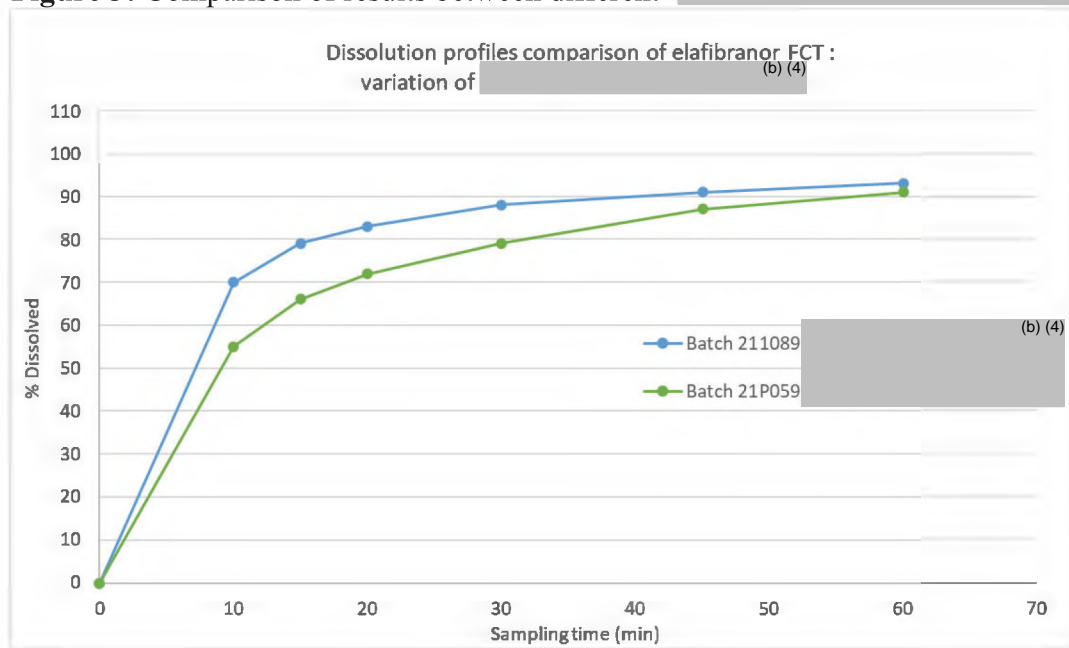
The modifications applied to the manufacturing process parameters were the following:



Variation of [redacted] (b) (4) :

The Applicant manufactured a batch# 21P059 with [redacted] (b) (4) and compared the dissolution rate with the target batch# 211089 with [redacted] (b) (4). Dissolution rate of the batch with th [redacted] (b) (4) showed slightly lower drug release compared to the target batch up to 30 minutes time points. Similarity factor (f2) analysis showed that $f_2 < 50$ (47.72) indicating dissolution profile differences between the aberrant and target batches.

Figure 3: Comparison of results between different [redacted] (b) (4)



Variation in amount of [redacted] (b) (4) :

The Applicant manufactured four batches of aberrant formulations with various amount of [redacted] (b) (4). Formulations with increased amount of [redacted] (b) (4) showed slower drug release from the tablets compared to the target

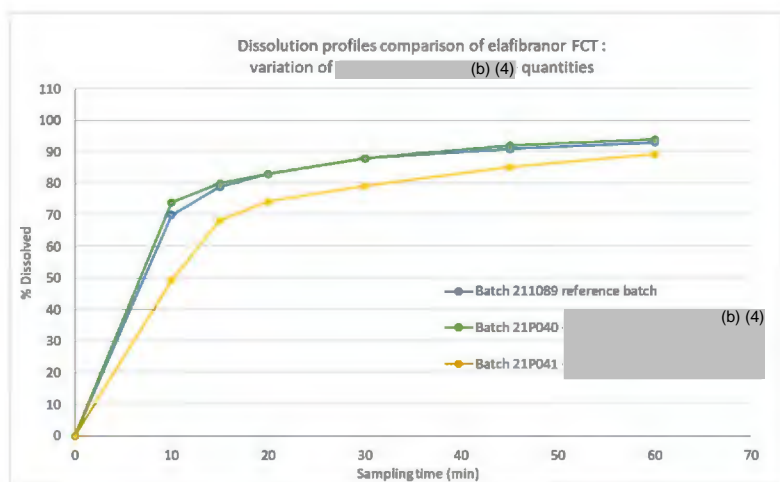
formulation with a similarity factor, $f_2 < 50$, indicating dissolution profiles differences between the aberrant batches (b) (4)

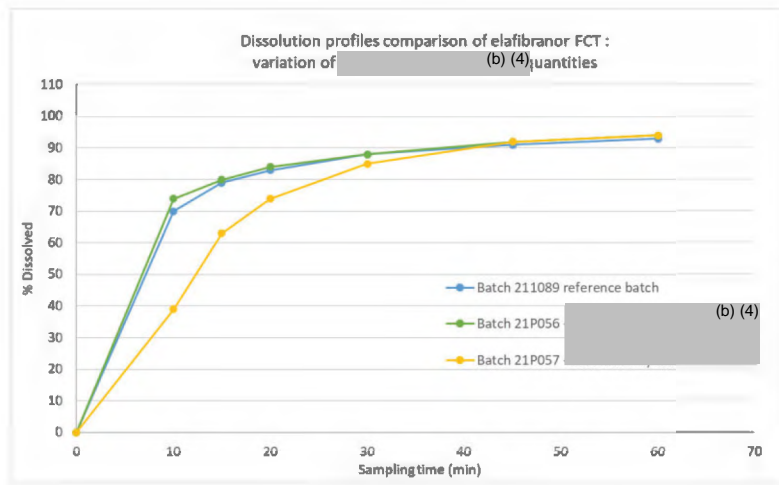
Table 8: Formula of the Drug Product with different quantities of (b) (4)

	Component	Batch 211089 (reference)		Batch 21P040		Batch 21P041		Batch 21P056		Batch 21P057 (b) (4)	
		Unit formula		Unit formula		Unit formula		Unit formula		Unit formula	
		(mg)	(%)	(mg)	(%)	(mg)	(%)	(mg)	(%)	(mg)	(%)
(b) (4)	Elafibranor	80.0	(b) (4)	80.0	(b) (4)	80.0	(b) (4)	80.0	(b) (4)	80.0	(b) (4)
	Cellulose Microcrystalline (b) (4)	(b) (4)									
	Povidone (b) (4)										
	Sodium Croscarmellose (b) (4)										
	colloidal silica										
	Sodium Croscarmellose										
	Magnesium stearate										
(b) (4)	Film coating (b) (4)	(b) (4)									
	Total film coated tablet weigh										

Figure 4: Dissolution profile comparison of Elafibranor film coated tablets (FCT) with variation in the amount of (b) (4)

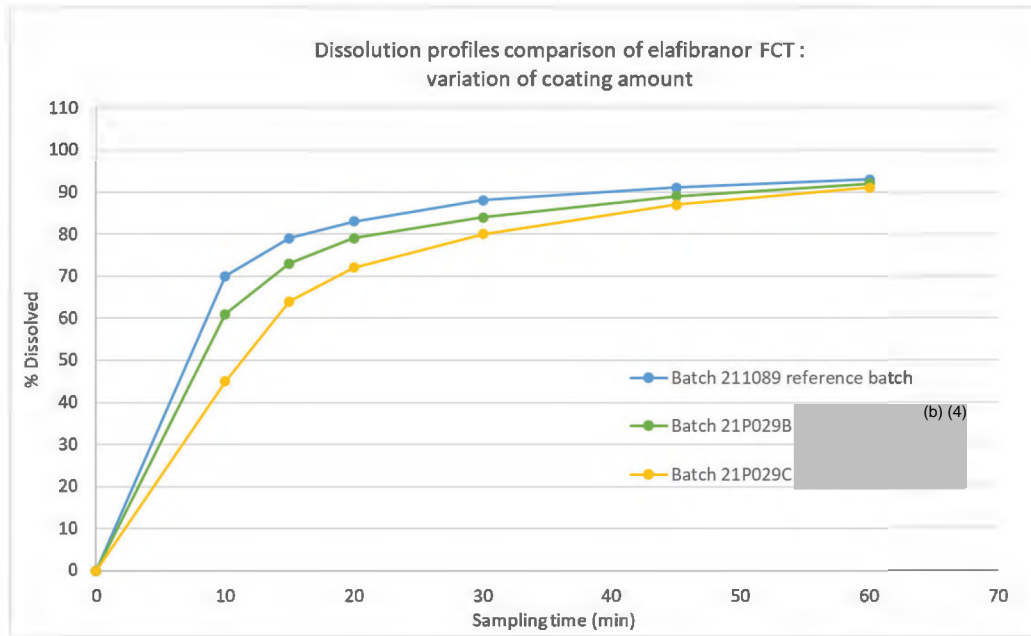
a. Batch 211089 (target batch) vs batches# 21P040 and 21P041 (aberrant batches)



b. Batch 211089 (target batch) vs batches# 21P056 and 21P057 (aberrant batches)**Variation in amount of film coating:**

To evaluate the effect of the amount of film coating on drug dissolution rate, the Applicant manufactured two aberrant formulations with two times, batch 21P029B (b) (4) coating – target value x2 times) and three times, batch 21P029C (b) (4) - target value x 3 times) increased in the amount of film coating. Dissolution data showed that formulations with three times film coating has lower drug release compared to the target formulation (batch 211089 with (b) (4) coating) with a f_2 value less than 50, indicating dissolution rate dissimilarity between the formulations. Although there is difference in dissolution rate, discriminating ability is not giving meaningful information since the amount of change in film coating is beyond the $\pm$ (b) (4)% limit generally recommend by the Agency. Dissolution rate of the target formulation and formulation with two times film coating showed similar drug release. In conclusion, changing in the amount of film coating did not show discriminating ability of the dissolution method.

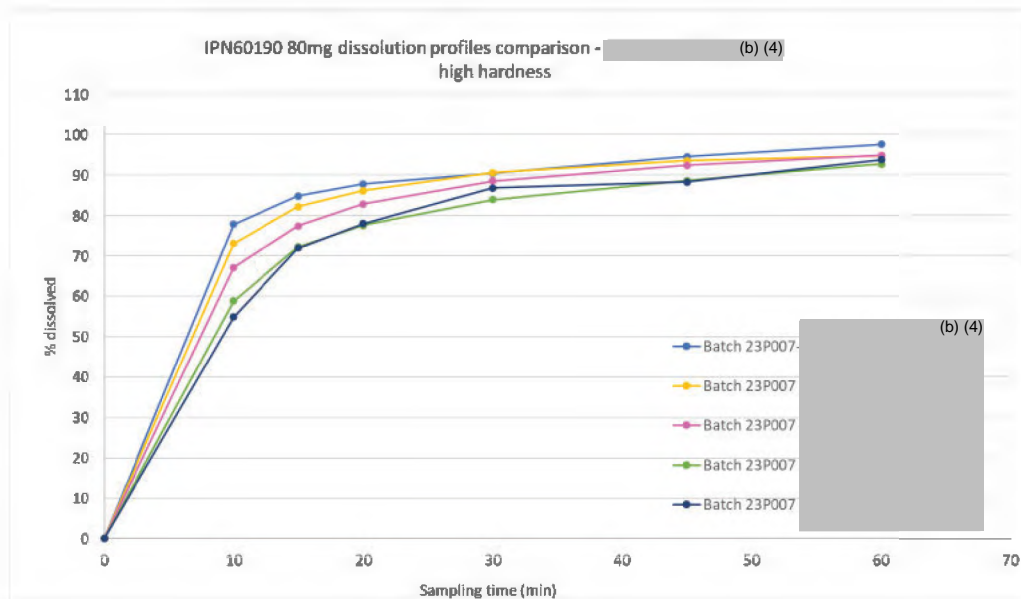
Figure 5: Comparison of results between quantities coating



Variation in tablet hardness:

The Applicant manufactured several batches of tablets with deviated hardness (tablet hardness (b) (4)) and compared the dissolution rate with the target formulation (tablet hardness (b) (4)). dissolution rate of formulations with hardness of (b) (4) and (b) (4) showed slower drug release compared to the target formulation with a $f_2 < 50$, indicating dissolution rate dissimilarity.

Figure 6: Comparison of results between different hardness

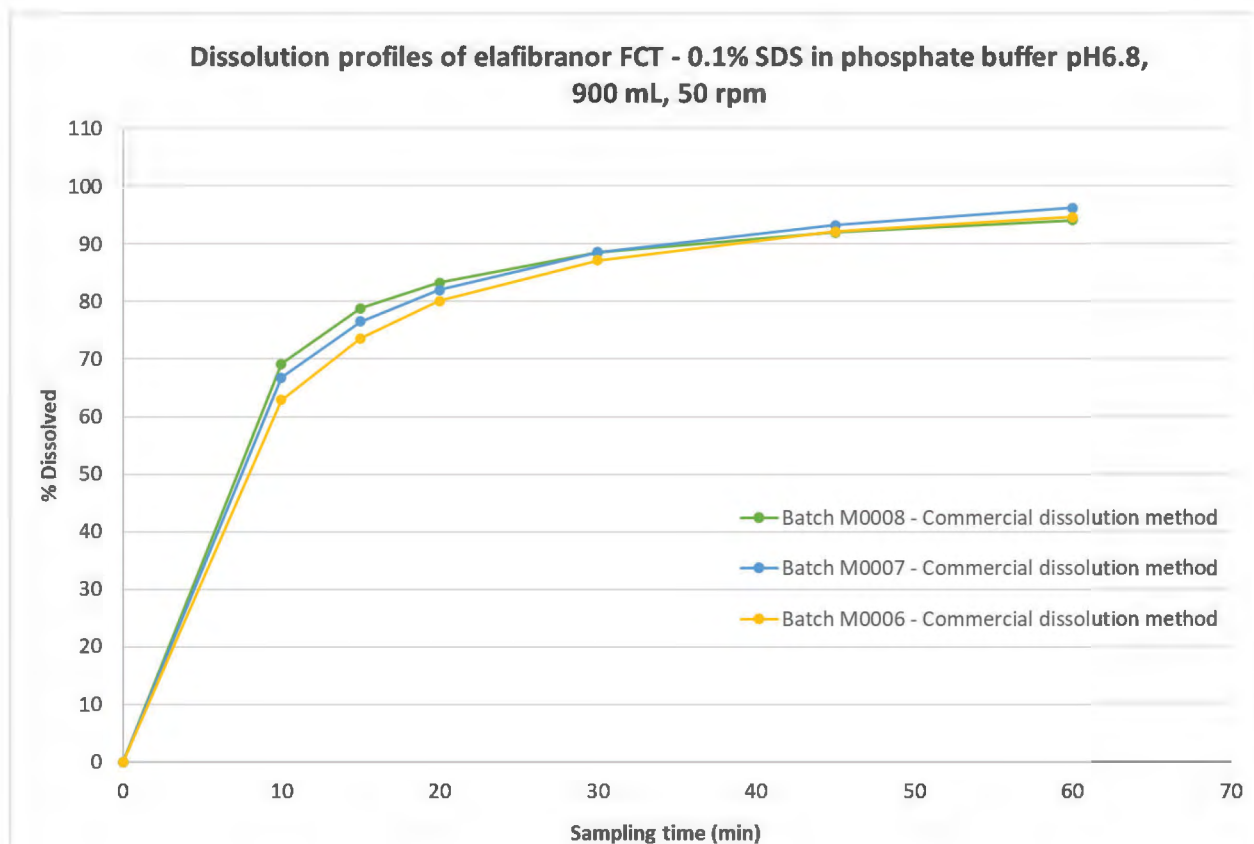


In conclusion, Elafibranor is a low soluble compound. The Applicant provided dissolution method development and validation report. Dissolution method showed discriminating ability due to the differences in critical formulation and process variables, i.e. (b) (4) (b) (4), variation o (b) (4) (b) (4) proportion in the formulation, variation in tablet hardness. The Applicant used (b) (4) drug substance and controlled the drug substance (DS) particle size distribution (PSD), i.e., D50% (b) (4) D90% (b) (4) (b) (4). Therefore, based on the totality of the information, dissolution method is deemed adequate.

Dissolution acceptance criterion:

The Applicant proposed dissolution acceptance criterion as “Q (b) (4)% in 30 minutes” which is supported by dissolution data provided for the clinical formulation and registration batches, the. Therefore, the Applicant’s proposed dissolution acceptance criterion of “Q (b) (4)% in 30 minutes” is deemed adequate.

Figure 7: Dissolution profiles: using quality control dissolution method.





Appendix 1. Dissolution Data

Dissolution data:

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Ghosh

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