CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213464Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Tentative Approval
☒ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213464
Assessment #1 -Addendum

Drug Product Name	Nifurtimox
Dosage Form	Tablet
Strength	30mg and 120mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Bayer Healthcare Pharmaceuticals, Inc.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0001	Dec 06, 2019	All
eCTD 0014	Feb 11, 2020	Quality
eCTD 0016	Feb 27, 2020	Quality
eCTD 0018	March 11, 2020	Quality
eCTD 0026	April 03, 2020	Quality
eCTD 0033	May 15, 2020	Quality
eCTD 0046	July-15, 2020	All (quality related information)

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Katherine Windsor	Ali Al Hakim
Drug Product & Labeling	Peter Guerrieri	Thomas Oliver
Manufacturing	Jiao Yang	Steven Frisbee
Biopharmaceutics	Mathew John	Elsbeth Chikhale
Regulatory Business Process Manager	Anh-Thy Ly	
Application Technical Lead	Shalini Anand	
OTR	NA	
Environmental	Refer drug product review document	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs: None

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	109901	Referenced IND

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH-ODE	NA			
CDRH-OC	NA			
Clinical	NA			
Other	NA			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ). The Overall Manufacturing Inspection recommendation was entered as Approve on Aug 05-2020.

Bayer agreed to a post marketing commitment (PMC) for conducting an in-use stability study for Nifurtimox 30 mg tablets (submission dated 07-15-2020)

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Refer to Review #1 for the complete details of the drug product.

The CMC Integrated Quality Review #1 on 05/06/2020 recommended this NDA for a CR due to OAI status of drug substance (DS) (b) (4) facility, Bayer AG (FEI# 3002806462, Leverkusen, Germany). Also, the response to a post-marketing commitment was pending for the in-use stability studies of Nifurtimox 30 mg tablets.

The OAI alert of Bayer, Germany facility was removed as a result of follow up inspection conducted between 07/20/2020~07/27/2020. The OMIR is recommended as approval on Aug-05-2020, to support this application. An addendum to manufacturing review was completed.

The applicant agreed to the PMC on May-15-2020 and July-15-2020. An addendum to the drug product review was completed.

This NDA is now recommended for approval from a CMC perspective.

B. Quality Assessment Overview

Drug Substance: Adequate

Refer to Review #1.

Drug Product: Adequate

Refer to Review #1 for the complete details of the drug product assessment.
At the time of Review #1, there was a pending issue related to the agreement of post-marketing commitment for in-use stability studies of Nifurtimox 30 mg tablets.

The DP batch of Nifurtimox 30 mg strength (batch # KM6012C) marginally failed the dissolution criteria (NLT (b) (4)% (Q) in 60 minutes). However, a human PK study 16007 had demonstrated bioequivalence between a batch with (b) (4)% dissolved in 60 min to a batch with (b) (4)% dissolved in 60 min. So, the in-use stability results for Nifurtimox 30 mg tablets were not concerning from biopharm (release) perspective.

A post-marketing commitment (PMC) was requested for conducting a repeat in-use stability study. The applicant agreed to the post marketing commitment and proposed timelines (submission dated May-15-2020 and July-15-2020).

This NDA is currently recommended for Approval from a drug product perspective. For additional details, refer to the drug product review by Peter Guerrieri.

Labeling: Adequate

Refer to Review #1.

Manufacturing: Adequate

Refer to Review #1 for the complete details of the manufacturing assessment.
At the time of Review #1, the facility assessment for drug substance (DS) (b) (4) facility, Bayer AG, FEI# 3002806462, located in Leverkusen, Germany, was found inadequate due to the OAI status concluded from last surveillance inspection in 2019 (inspection ID #1084360).

A follow-up inspection (Inspection ID: 1125538) was conducted between 07/20/2020~07/27/2020. A 5-item FDA 483 was issued at the completion of inspection. A final classification of VAI was concluded for the inspection on 08/04/2020. The OAI alert was thus removed from the facility. As a result, the facility is deemed acceptable for the proposed operation. Therefore, the OMIR is recommended as approval to support this application.

This NDA is currently recommended for Approval from a manufacturing perspective. For further details, refer to the manufacturing review addendum by Jiao Yang.

Biopharmaceutics: Adequate

Refer to Review #1.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Eval.**	**Lifecycle Considerations & Comments**
Assay, Stability	Process, formulation, raw materials	**Medium**	(b) (4)	Acc	
Physical stability (solid state)	Process, formulation, raw materials	**Low**		Acc	
Content uniformity	Process	**Low**		Acc	
Microbial limits	Process, formulation, raw materials	**Low**		Acc	
Dissolution – BCS Class II & IV	Process, formulation, raw materials	**Medium**		Acc	
Patient Use Considerations (split tablet content uniformity)	Process, formulation, raw materials	**Low**		Acc	
Split tablet (Friability)	Process, formulation, raw materials	**Medium**		Acc	

D. List of Deficiencies for Complete Response - None

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

Application Technical Lead Name and Date:
Shalini Anand, Ph.D.

NDA/BLA #: 213464

Product Name: Lampit (Nifurtimox) Tablets, 30 mg and 120 mg

Submission: SD# 0034; Date: 05/15/2020

Final review recommendation: Adequate

Drug Product Review Final Assessment Memo – PMC # 3868

The original proposed release and shelf life specification limit for dissolution was NLT (b)(4)% (Q) in 60 min. During the review cycle, Biopharm requested that the acceptance limits be tightened to Q = (b)(4)% in 60 min. The applicant initially proposed to tighten the release acceptance limit accordingly (response dated 04/03/20) but declined to tighten the shelf life specification, as dissolution values for in-use stability studies of the 30 mg tablets at 30°C/75% RH fell slightly below (b)(4). Upon discussion with CMC, Biopharm again requested that the Q = (b)(4)% in 60 min be implemented for shelf life testing. In the response dated 04/29/20, the applicant accepted the FDA recommended dissolution acceptance criterion of NLT (b)(4)% (Q) in 60 minutes for batch release and stability testing of the drug product.

A human PK study 16007 had demonstrated bioequivalence between a batch with (b)(4)% dissolved in 60 min to a batch with (b)(4)% dissolved in 60 min. Based on these results, the 30 mg in-use stability results were not concerning from a biopharm (release) perspective. The in-use stability results for the 30 mg tablets (batch # KM6012C) showed approximately a (b)(4)% decrease over 67 days. This decrease was not observed for the 120 mg tablets. The release testing for the 30 mg batch used for the in-use stability studies (3.2.P.5.4, p. 7 of 30 mg results) showed an initial value of (b)(4)%, lower than the initial values reported at the start of the in-use stability study. This batch's initial dissolution results were also lower than the release result for most of the other development batches as well as the commercial site batches, which were generally (b)(4)%.

The stability results for the commercial scale/site batches through nine months at 30°C/75% RH and six months under accelerated conditions (40°C/75% RH) showed no change in the dissolution for both strengths over the course of the studies to-date. In addition, development/pilot scale batches for both strengths also showed no change over 24 months at 30°C/75% RH. These above results mitigate efficacy risk to the patient, and therefore additional pre-approval data commitment is not necessary.

However, to confirm that the 30 mg tablets studied for in-use stability will pass the shelf-life acceptance limit for dissolution, Q = (b)(4)% in 60 min, the applicant was requested to provide a post-marketing commitment (PMC) and agreed. The PMC provides for conducting a follow-up in-use stability study per a submitted protocol (submitted by October 28, 2020) on an expired 30 mg batch under the same conditions for the initial studies submitted. The results may also provide additional insight into whether the (b)(4)% decrease in dissolution over the in-use period for the 30 mg tablets is observed consistently. The results will be provided in a prior approval supplement by February 28, 2021. **Based on this commitment, the drug product review is deemed adequate.**

Peter Guerrieri

Digitally signed by Peter Guerrieri
Date: 6/24/2020 12:56:45PM
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Thomas Oliver

Digitally signed by Thomas Oliver
Date: 6/24/2020 01:36:17PM
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/s/

SHALINI ANAND
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U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Tentative Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 213464
Assessment #1

Drug Product Name	Nifurtimox
Dosage Form	Tablet
Strength	30mg and 120mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Bayer Healthcare Pharmaceuticals, Inc.
US agent, if applicable	

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Application Technical Lead	Shalini Anand	
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Pharmacology/Toxicology	NA			
CDRH-ODE	NA			
CDRH-OC	NA			
Clinical	NA			
Other	NA			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has not provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for a Complete Response by the Office of Pharmaceutical Quality (OPQ) at this time.

The drug substance (DS) (b) (4) facility, Bayer AG, FEI# 3002806462, located in Leverkusen, Germany, was found inadequate due to the concluded OAI status from last surveillance inspection in 2019 (inspection ID #1084360). Due to the Covid-19 pandemic travel restriction, the follow-up inspection originally scheduled for March 2020 was postponed, and is currently rescheduled to start on July 06, 2020. Thus, the facility remains out of compliance and is recommended as Withhold, at this time.

Nifurtimox 30 mg tablets did not meet the updated dissolution criterion (NLT (b) (4)% (Q) in 60 minutes) for the in-use stability studies. The applicant has been asked to submit a PMC (post marketing commitment) to conduct an identical in-use stability study on an appropriately aged batch (PMC language issued on May 6, 2020)

An addendum will be written to this IQA following review of the applicant's response of the PMC request and facility inspection (as appropriate).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Nifurtimox is a nitrofuran antiprotozoal agent developed for the treatment of Chagas disease (caused by Trypanosoma cruzi), in pediatric patients less than 18 years of age.
LAMPIT (Nifurtimox) tablets (30 mg and 120 mg) are for oral use and are administered three times a day with food. For patients who are unable to swallow whole or half tablets, tablets can be dispersed in water. The tablets are formulated as a round, biconvex yellow immediate release tablets. The tablets are functionally scored and are designed for splitting solely by hand. The tablets are supplied in a 90 mL white opaque HDPE bottle with 3 g desiccant capsule and child resistant screw cap (PP/PP) in 100s counts packaging configuration.
The CMC information (including environmental assessment) for the nifurtimox tablet formulation is submitted in NDA 213464 (Module 3). The labeling information for is provided in the Module 1 of the NDA.

Proposed Indication(s) including Intended Patient Population	For the treatment of Chagas disease (American Trypanosomiasis) caused by Trypanosoma cruzi (T.cruzi.) in pediatric patients less than 18 years of age.
Duration of Treatment	60 days
Maximum Daily Dose	Tablets are dosed by body weight and age of the patient. For pediatric patients ((b) (4) <18 years) (≥40 kg), total daily dose is 8 mg/kg -10 mg/kg; for pediatric patients (b) (4) (<40 kg), total daily dose is 10 mg/kg -20 mg/kg.
Alternative Methods of Administration	Tablets can be dispersed in water (half teaspoon) for patients who cannot swallow tablets

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance (DS) related information is submitted in the NDA. No separate DMF has been referenced for DS related information.

(b) (4)

Specified and unspecified organic impurities are controlled at the ICH Q3A qualification and identification threshold, respectively. The control strategies for impurities – including potential mutagenic impurities – are acceptable, particularly given that nifurtimox is considered genotoxic.

(b) (4)

Starting material designation was agreed upon in previous interactions with the Agency and starting material specifications include sufficient impurity controls to minimize any impact on the impurity profile of the drug substance.

The retest period for nifurtimox drug substance is (b) (4) months when stored at or below (b) (4)

For additional details, refer to drug substance review by Katherine Windsor.

Drug Product: Inadequate

Nifurtimox tablets 30 mg and 120 mg are formulated as a round, biconvex yellow immediate release tablets. The tablets are functionally scored for division into two equal halves. The tablets are designed for splitting solely by hand.

The 30 mg and 120 mg tablets have a score line on the top side and are de-bossed with the marking “30” and “120” on the bottom side, respectively. The commercial drug product will be packaged in a 90 mL white opaque HDPE bottle with 3 g desiccant capsule and child resistant screw cap (PP/PP) in 100s counts packaging configuration.

Long-term stability results of 24 months were provided for the primary stability batches, which support the proposed shelf life of 36 months. Nine months of long-term and six months of accelerated stability data is also provided for a total of three commercial site batches (manufactured at (b) (4) site). A minor formulation change (addition of (b) (4) magnesium stearate) was implemented for the commercial site/scale batches, however, this formulation change is not expected to impact product performance. The long-term and intermediate studies are ongoing for DP batches manufactured at the commercial drug product manufacturing site.

The proposed 36-month expiration dating period is appropriate, with labeling to “Store at controlled room temperature 20°C to 25°C (68°F to 77°F)”.

The applicant has also provided the in-use stability study for Nifurtimox 30 mg and 120 mg split tablets. Nifurtimox 120 mg tablets passed the in-use stability study criteria, however 30 mg dosage strength did not meet the updated dissolution recommendations (Q = Not less than (b) (4)% at 60 min). The original proposed dissolution acceptance criterion was NLT (b) (4)% (Q) in 60 min for drug product release and stability specifications. During the review cycle, Biopharm requested that the acceptance limits be tightened to Q = (b) (4)% at 60 min.

The DP batch of Nifurtimox 30 mg strength (batch # KM6012C) used for the in-use stability study is a development batch and showed slower dissolution (Q = (b) (4)% at 60 mins for drug product release) than other development and registration stability batches, which showed (b) (4)% release at 60 mins.

A human PK study 16007 had demonstrated bioequivalence between a batch with (b) (4)% dissolved in 60 min to a batch with (b) (4)% dissolved in 60 min. Based on these results, the 30 mg in-use stability results were not concerning from biopharm (release) perspective.

The applicant will be requested to provide a post-marketing commitment (PMC) for conducting a follow-up in-use stability study, as per a submitted protocol on an appropriately aged drug product batch of Nifurtimox 30mg tablets under the same conditions, as used for the initial in-use studies (PMC request issued on May 06, 2020).

The drug product review outcome is inadequate at this time. The response to PMC request will be evaluated and drug product review document will be updated accordingly. The request for a PMC for in-use stability would not have been a CR issue.

For additional details, refer to the drug product review by Peter Guerrieri.

Labeling: Adequate

The labelling recommendations have been conveyed to OND PM for consideration. For additional details, refer to the quality labelling review by Peter Guerrieri.

Manufacturing: Inadequate

The drug product manufacturing process includes (b) (4) Applicant proposed adequate control strategy for the manufacturing process to ensure drug product critical quality attributes are maintained.

The facility assessment for (b) (4) drug product manufacturing facility located in (b) (4) and Bayer AG, FEI# 3003229486, drug substance manufacturing facility located in Wuppertal, Germany, revealed that both facilities have considerable manufacturing experience with proposed responsibilities and acceptable compliance history. However, drug substance (DS) (b) (4) facility, Bayer AG, FEI# 3002806462, located in Leverkusen, Germany, was found inadequate due to the OAI status concluded from last surveillance inspection in 2019 (inspection ID #1084360). Due to the Covid-19 pandemic travel restriction, the follow-up inspection originally scheduled for March 2020 was postponed, and is currently rescheduled to start on July 06, 2020. Thus, as of the date of this review, the facility remains out of compliance and is recommended as Withhold. Since this DS (b) (4) facility is currently inadequate, the OMIR is recommended Withhold for this application.
The manufacturing review will be updated with an addendum (as appropriate), to capture updates in the facility status after the scheduled inspection.
For further details, refer to the manufacturing review by Jiao Yang.

Biopharmaceutics: Adequate

Bayer proposed a change to the clinical formulation (adding (b) (4) magnesium stearate), a change to the tablet image, and a change in the drug product manufacturing site (from Bayer to (b) (4)) between the clinical and the to-be-marketed drug product. The Applicant provided dissolution profile comparisons and conducted a BE study for a drug product with fast dissolution profile and a drug product with slow dissolution profile to support the bridging between the clinical formulation/image/DP manufacturing site (Bayer) and the commercial formulation/image/DP manufacturing site (b) (4).

To support reliance on published literature references, the Applicant has submitted adequate information to establish a bridge between the proposed drug product and the drug products used in the clinical studies described in the key relied upon published literature, which used the Bayer 2502 Lampit drug product.

The Biopharmaceutics review evaluated the data supporting the proposed dissolution method, acceptance criterion and the bridging. The following dissolution method and revised acceptance criterion for drug product batch release and stability were found acceptable:

USP Apparatus	Rotation Speed	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
USP II (Paddle)	100 RPM	Acetate buffer pH 4.5 with 1% SDS for 30 mg Tablet and 1.5 % SDS for 120 mg Tablet	900 mL	NLT (b) (4)% (Q) in 60 minutes for batch release and stability.

For more details, refer the Biopharmaceutics review by Mathew John.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations & Comments

Assay, Stability	Process, formulation, raw materials	**Medium**	(b) (4)	Acc	
Physical stability (solid state)	Process, formulation, raw materials	**Low**		Acc	
Content uniformity	Process	**Low**		Acc	
Microbial limits	Process, formulation, raw materials	**Low**		Acc	
Dissolution – BCS Class II & IV	Process, formulation, raw materials	**Medium**		Acc	
Patient Use Considerations (split tablet content uniformity)	Process, formulation, raw materials	**Low**		Acc	Nifurtimox 30 mg tablets did not meet the updated dissolution criterion (NLT (b) (4)% (Q) in 60 minutes) for the in-use stability studies. The applicant has been asked to submit a PMC (post marketing commitment) to conduct an identical in-use stability study an appropriately aged batch (PMC language issued on May 6, 2020)
Split tablet (Friability)	Process, formulation, raw materials	**Medium**		Acc	

D. List of Deficiencies for Complete Response - None

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	LAMPIT tablets	Adequate.
Established name(s)	Nifurtimox	Adequate.
Route(s) of administration	Oral	Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 30 mg (functionally scored) Tablets: 120 mg (functionally scored)	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Functionally scored	Adequate.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		

APPEARS THIS WAY ON ORIGINAL

Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Section 2.1 • LAMPIT tablets (30 mg and 120 mg) are functionally scored tablets which can be split into one-half (15 mg and 60 mg respectively) at the scored lines. • For patients who cannot swallow tablets, LAMPIT tablets 30 mg and 120 mg can be made into slurry as an alternative method of administration [see Dosage and Administration (2.3) Section 2.2 • LAMPIT is provided in a special tablet format. Do not break LAMPIT tablets mechanically with a tablet splitting device. A functional score line is used to divide the tablet by hand: o To split the tablet, place the tablet on a flat surface with the score line facing up. With the tablet resting on the flat surface, apply enough downward pressure with the index finger centered on the top of the tablet to break it along the score line Section 2.3 Preparation of Slurry as an Alternate Method of Administration For patients who are unable to swallow whole or half tablets, LAMPIT can be dispersed in water. • Place approximately 2.5 mL of water into a spoon. • Place the prescribed dose into the water.	Adequate.

	• Allow the tablet(s) to disintegrate (typically less than 30 seconds). • A slurry (liquid suspension) is formed. • Take immediately with food.	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

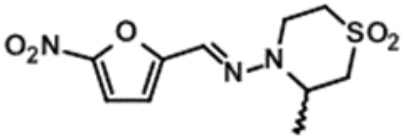
APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	LAMPIT Tablets are available as: • 30 mg, yellow, round, biconvex tablets, functionally scored on one side for division of the tablet into equal doses and marked with '30' on the other side. • 120 mg, yellow, round, biconvex tablets, functionally scored on one side for division of the tablet into equal doses and marked with '120' on the other side	Adequate.
Strength(s) in metric system	mg (see above)	Adequate.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	See above.	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Functionally scored.	Adequate.
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	LAMPIT (nifurtimox) tablets are yellow round, biconvex tablets, each containing 30 mg or 120 mg of nifurtimox, intended for oral use. The 30 mg tablets are functionally scored on one side and marked with '30' on the other side. The 120 mg tablets are functionally scored on one side and marked with '120' on the other side.	Adequate.
Dosage form(s) and route(s) of administration	See above.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The inactive ingredients of the tablets are calcium hydrogen phosphate dehydrate, magnesium stearate, maize starch, silica colloidal anhydrous and sodium lauryl sulfate.	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.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	

Pharmacological/ therapeutic class	Yes.	Adequate.
Chemical name, structural formula, molecular weight	LAMPIT contains nifurtimox, an antiprotozoal. The chemical name is (E)-N-(3-Methyl-1,1-dioxidothiomorpholin-4-yl)-1-(5-nitro-2-furyl)methanimine. The molecular weight is 287.29 and the molecular formula is $C_{10}H_{13}N_3O_5S$. The structural formula is: 	Adequate.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement 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	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	LAMPIT Tablets are supplied as follows: • 30 mg, yellow, round, biconvex tablets, functionally scored on one side and marked with '30' on the other side. • 120 mg, yellow, round, biconvex tablets, functionally scored on one side and marked with '120' on the other side.	Adequate.
Strength(s) in metric system	mg (see above)	Adequate.
Available units (e.g., bottles of 100 tablets)	LAMPIT Tablets 30 mg are supplied as bottles of 100 tablets with child-resistant caps (NDC 50419-750-01) LAMPIT Tablets 120 mg are supplied as bottles of 100 tablets with child-resistant caps (NDC 50419-751-01)	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See above.	Adequate.

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	Functionally scored.	Adequate. Instructions are included in section 2.2 and Patient Information for the tablet splitting. Instructions and a pictorial representation of the tablet splitting are also included in the IFU.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

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

Item	Information Provided in the NDA	Assessor’s Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Store tablets in the original bottle with child-resistant caps and do not remove the desiccant. Keep bottle with child-resistant caps tightly closed and protect from moisture.	Adequate.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	Yes. Desiccant canister includes the statement: “DANGER: DO NOT EAT”	Adequate.
Storage conditions. Where applicable, use USP	Yes, see above.	Adequate.

storage range rather than storage at a single temperature.		
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.”	N/A	
Include information about child-resistant packaging	Yes, see above.	

1.2.5 Other Sections of Labeling

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981 USA Manufactured in (b) (4)	Adequate

2.0 PATIENT LABELING

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

The applicant provided instructions for the tablet splitting in the Patient Information and Instructions for Use (IFU). A pictorial representation of the tablet splitting in the IFU was requested during the review process and provided.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Lampit (nifurtimox) tablets; oral use	Adequate.
Dosage strength	30 mg; 120 mg	Adequate.
Route of administration	Oral	Adequate.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	100 tablets	Adequate.
"Rx only" displayed on the principal display	Yes	Adequate.
NDC number	30 mg: 50419-750-01 120 mg: 50419-753-01	Adequate.
Lot number and expiration date	Yes	Adequate.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]. Keep bottle tightly closed and protect from moisture.	Adequate.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes	Adequate.

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981 Manufactured in (b) (4)	Adequate.
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	Yes	Adequate.
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.	N/A	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: Adequate.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

The PI and container/carton labels are adequate.

Primary Labeling Assessor Name and Date:

Pete Guerrieri, PhD

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

Peter Guerrieri

Digitally signed by Peter Guerrieri
Date: 4/30/2020 08:24:12PM
GUID: 54eb8ba100062ea99cbaab7c64143df3

Thomas Oliver

Digitally signed by Thomas Oliver
Date: 5/01/2020 06:55:03AM
GUID: 508da71f00029ed4697700cee3d31ca0
Comments: Just signed

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	213464
Assessment Cycle Number	01
Drug Product Name/ Strength	Nifurtimox Immediate Release Tablets / 30 mg and 120 mg
Route of Administration	Oral
Applicant Name	Bayer Healthcare LLC
Therapeutic Classification/ OND Division	OID / DAI
RLD/RS Number	N / A
Proposed Indication	For the treatment of Chagas disease (American Trypanosomiasis) caused by Trypanosoma cruzi (T.cruzi.)
Primary Assessors	Mathew John, Ph. D
Secondary Assessors	Elsbeth Chikhale, Ph. D.
Assessment	**Adequate**
Recommendation	Recommended for Approval from a Biopharmaceutics perspective.

Background:

The proposed drug product, Lampit® (nifurtimox) Immediate Release Tablets 30 mg and 120 mg, is indicated in pediatric patients 0 to less than 18 years of age for the treatment of Chagas disease (American Trypanosomiasis) caused by Trypanosoma cruzi. This 505(b)(2) application relies on one pivotal phase 3 clinical study and several phase 1 clinical studies conducted by the Applicant, as well as literature publications to support the safety and efficacy of the proposed drug product.

Assessment Summary:

The Applicant conducted one Phase 3 pivotal clinical study to support the safety and efficacy of the proposed drug product, using the clinical drug product formulation manufactured at Bayer. The Applicant is proposing a change to the clinical formulation (adding (b) (4) magnesium stearate), a change to the tablet image, and a change in the drug product manufacturing site (from Bayer to (b) (4) between the clinical and the to-be-marketed drug product. The Applicant provided dissolution profile comparisons and conducted a BE study (b) (4) to support the bridging between the clinical formulation/image/DP manufacturing site (Bayer) and the commercial formulation/image/DP manufacturing site (b) (4)). The Applicant also relies on literature publications to support the safety and efficacy of the proposed drug product. A bridge has been established between the proposed drug product and the drug

products used in the clinical studies described in the key relied upon published literature.

This review evaluates the data supporting the proposed dissolution method, acceptance criterion and the bridging.

Dissolution method and acceptance criterion:
The following dissolution method and revised acceptance criterion for drug product batch release and stability are found acceptable:

USP Apparatus	Rotation Speed	Medium	Volume	Cumulative % of Drug Dissolved (Label Claim)
USP II (Paddle)	100 RPM	Acetate buffer pH 4.5 with 1% SDS for 30 mg Tablet and 1.5 % SDS for 120 mg Tablet	900 mL	NLT (b) (4)% (Q) in 60 minutes for batch release and stability.

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

Concise Description of Outstanding Issues: None

B.1 DRUG SUBSTANCE SOLUBILITY

Table 1: Solubility of the drug substance in aqueous solutions with and without sodium dodecyl sulfate (SDS) at 37°C[1]

Medium Buffer system	Surfactant level (SDS) [%]	Dissolved at 37 °C [mg/L]
HCl pH 1.2	--	60 [a]
HCl pH 2	--	41 [a]
Acetate buffer pH 4.5 (USP)	--	83 [a]
Acetate buffer pH 4.5 (USP)	0.5	115 [a]/196 [b]
Acetate buffer pH 4.5 (USP)	0.8	161[a]
Acetate buffer pH 4.5 (USP)	1.0	196 [a]/294 [b]
Acetate buffer pH 4.5 (USP)	1.5	284 [a]/415 [b]
Acetate buffer pH 4.5 (USP)	2.0	553 [b]
Phosphate buffer pH 6.8 (USP)	--	59 [a]
Phosphate buffer pH 6.8 (USP)	1.0	280 [b]
Phosphate buffer pH 6.8 (USP)	1.5	386 [b]
Phosphate buffer pH 6.8 (USP)	2.0	493 [b]

a Solubility determined for NDA submission, refer to General information - general properties (S.1.3.01).
b Solubility data determined during development.

The Applicant uses (b) (4) drug substance for the manufacture of the drug product. The particle size is controlled as follows: X_{10} ((b) (4) µm), X_{50} ((b) (4) µm) and X_{90} ((b) (4) µm).[2]

Reviewer's Assessment: The drug substance has low solubility across the physiological pH. The Applicant did not provide permeability data. The Applicant's claim that Nifurtimox is a BCS class 2 compound (low solubility and high permeability) is supported by the solubility data.

B.2 DISSOLUTION METHOD

The Applicant provided the following data and justifications for the selection of the dissolution methodology:

[1] \\cdsesub1\evsprod\nda213464\0001\m3\32-body-data\32p-drug-prod\nifurtimox-tablets-bayer\32p5-contr-drug-prod\32p53-val-analyt-proc\32p53-7.pdf
[2] \\cdsesub1\evsprod\nda213464\0001\m2\23-qos\drug-substance.pdf

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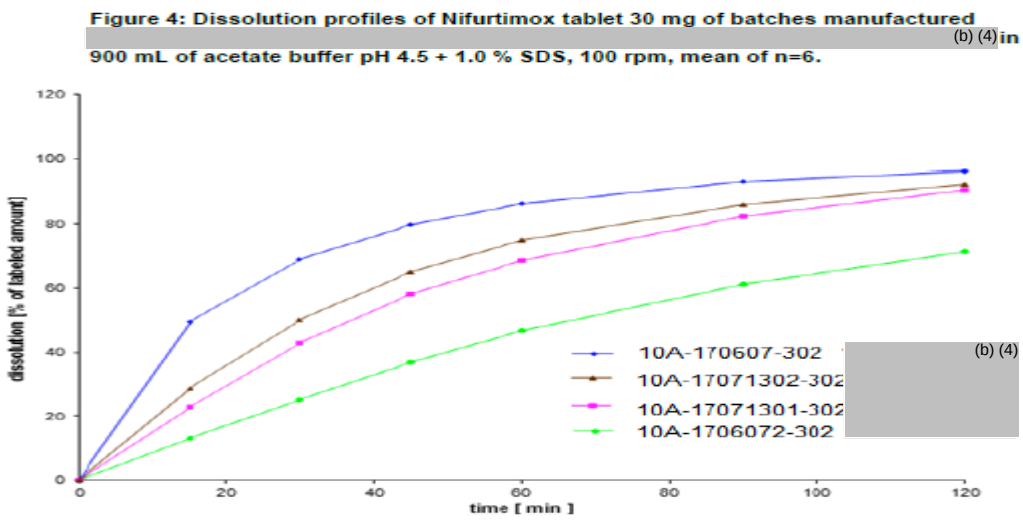
(b) (4)

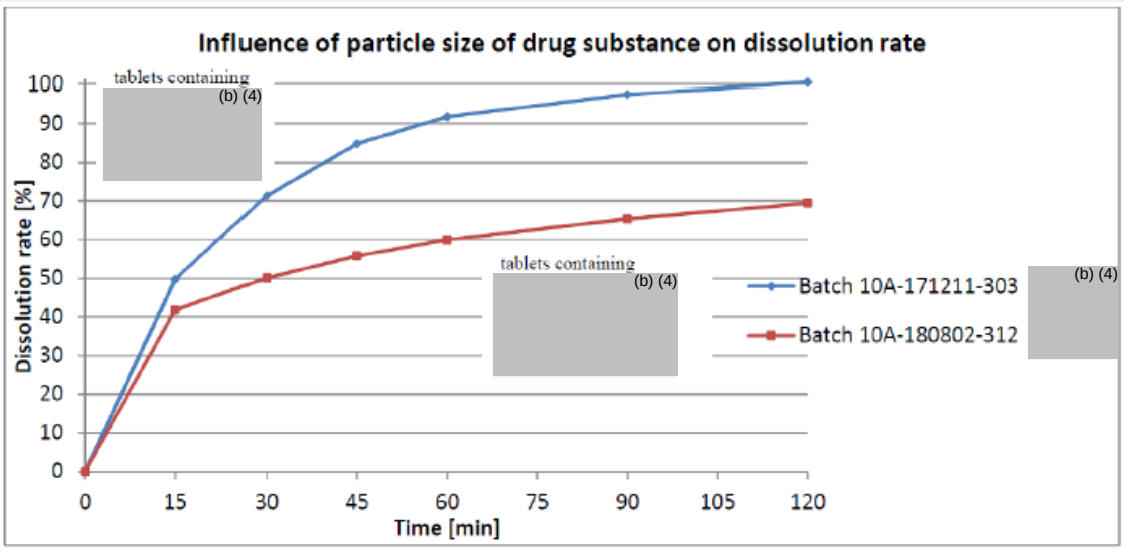
Discriminatory ability of the proposed dissolution method:
The Applicant has demonstrated the discriminating ability of the proposed dissolution method (b) (4)



(b) (4)

The Applicant has demonstrated the discriminating ability of the proposed dissolution method in terms of critical material attributes (b) (4)

Figure 5: Dissolution profiles of Nifurtimox tablet 30 mg, influence of different particle sizes of the drug substance, using the proposed dissolution method for the 30 mg tablets (Apparatus 2, 900 mL of acetate buffer pH 4.5 + 1.0 % SDS, 100 rpm), mean of n=12 (b) (4), mean of n=6 (b) (4).



[3] \\cdsesub1\evsprod\nda213464\0001\m2\23-qos\drug-substance.pdf

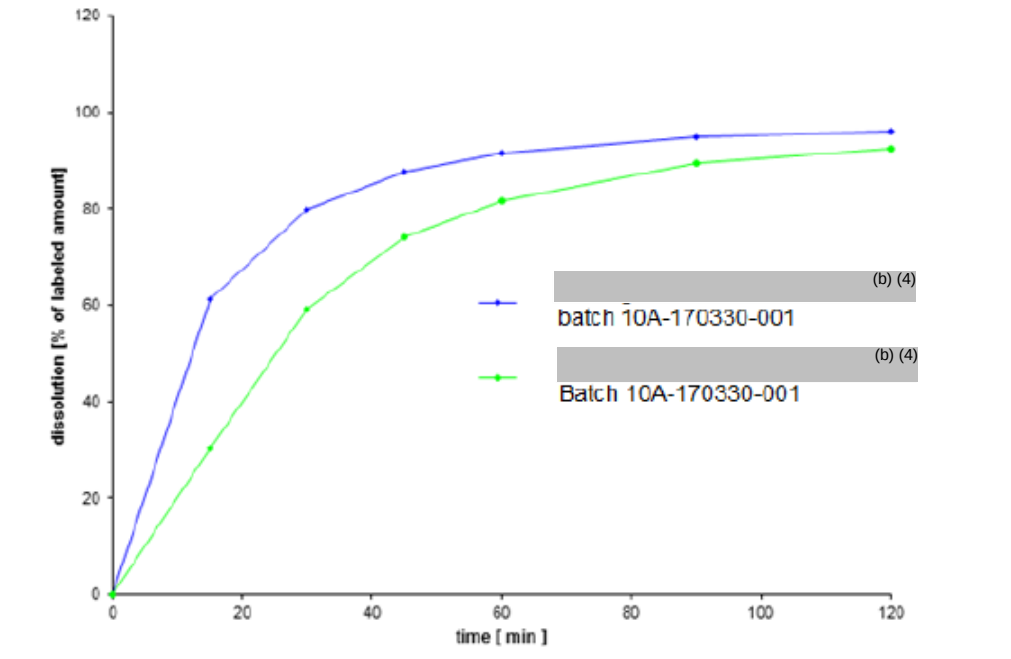
The Applicant mentioned that the drug substance particle size is controlled as X_{10} (b) (4) µm), X_{50} (b) (4) µm) and X_{90} ((b) (4) µm).

The Applicant has also demonstrated the discriminating ability of the proposed dissolution method in terms of critical processing parameters (b) (4)

(b) (4)

The dissolution profiles are as follows,

Figure 6: Dissolution profiles of the two 30 mg tablet batches manufactured with (b) (4) Experiments were performed using the proposed dissolution method for 30 mg tablets (900 mL of acetate buffer pH 4.5 + 1.0 % SDS, 100 rpm), mean of n=3.



(b) (4)

The Applicant has performed a dissolution study using the proposed dissolution method and a pharmacokinetic study (16007) using three different drug product batches of 30 mg tablets (KM601B0, KM6013R and KM60192) (b) (4)

(b) (4)

The Applicant explains that the three batches exhibited equivalent pharmacokinetic parameters such as AUC and $C_{max.}$ The BE study was evaluated by the Office of Clinical Pharmacology and was deemed adequate.

Robustness of the proposed dissolution method:
The Applicant has investigated the robustness of the dissolution method by performing the dissolution with small changes in temperature, pH and presence or absence of air bubbles on the surface of the tablet (Figure 11 through 13 of the method development report). The provided data support the robustness of the proposed dissolution method.

Reviewer's Assessment: Adequate
The provided data support the Applicant's claims that the dissolution method is over discriminating based on the fact that the three batches with fast medium and slow dissolution exhibits equivalent pharmacokinetic parameters such as AUC and $C_{max.}$ Based on the totality of the provided data regarding the suitability (the selection of dissolution medium and the surfactant concentration to achieve sink conditions) discriminating ability (b) (4)) and robustness of the dissolution method, the proposed dissolution method is adequate.

B.3 DISSOLUTION ACCEPTANCE CRITERIA

The Applicant's originally proposed dissolution acceptance criterion of Q= (b) (4)% in 60 minutes is permissive based on the dissolution data of the clinical batches and the registration batches of both 30 mg (batch # M0022M1 and M0023M1) and 120 mg (batch # M0004M1) tablets manufactured at (b) (4). Therefore, the Applicant was recommended (IR dated 03/27/2020) to tighten the dissolution acceptance criterion to Q= (b) (4)% in 60 minutes for batch release and stability testing of both 30 mg and 120 mg strengths of this immediate release drug product. In the response (04/03/2020), the Applicant stated that the in-use stability data of the 30 mg tablet (batch # KM6012C), in which they kept the drug product in the proposed container closure system at 30 °C and 75 % RH and opened the cap daily for 67 days, does not support the recommended dissolution acceptance criterion of NLT (b) (4)% (Q) in 60 minutes as the amount of drug dissolved is (b) (4)% at the 60 minutes time point after opening the bottle daily for 67 days. The Applicant also argued that the proposed dissolution acceptance criterion of NLT (b) (4)% (Q) in 60 minutes was derived from human pharmacokinetic study 16007. Based on the overall submitted dissolution data, and upon discussion with the CMC review team regarding the in-use and regular stability studies, the Applicant was again recommended (second IR dated 04/28/20) to implement NLT (b) (4)% (Q) in 60 minutes as the dissolution acceptance criterion for batch release and stability testing for both strengths of the proposed drug. In the response dated 04/29/20, the Applicant accepted the FDA recommended dissolution acceptance criterion of NLT (b) (4) (Q) in 60 minutes for batch release and stability testing of the drug product.

Reviewer's Assessment:
As the Applicant accepted the FDA recommended dissolution acceptance criterion of NLT (b) (4)% (Q) in 60 minutes for batch release and stability testing of the drug product in the response (dated 04/29/20) and committed to update all relevant sections of the NDA accordingly, the Applicant's response is adequate.

B.4 BRIDGING

Justification of reliance on literature publications:

The Applicant relies in part, on literature publications to support the safety and efficacy of the proposed drug product. The Applicant has submitted a list of literature publications on which this NDA relies. Four key publications describing partially controlled clinical studies (Bustos et al. 1969; Cichero et al. 1969; Ferreira HO 1990; and Schmunis et al 1978) all used drug products manufactured by Bayer. In the publications, the drug product used in the described clinical studies is referred to as "Bay 2502", "Bayer 2502", "Lampit", and/or "Nifurtimox manufactured at Leverkussen by Bayer"). It is likely that most of the other publications also used the original Bayer drug product. The Applicant was asked in an information request dated 03/27/20 to provide a comparison between the proposed drug product and the drug products used in the key literature references that are relied upon in terms of dosage form, formulation (including excipients), strength, manufacturing site, dosage, route of administration, etc. and to justify the differences, if any, to support reliance on the key literature reference. In the response dated 04/03/20, the Applicant explained that the 120 mg tablet formulation of Lampit was registered in Germany since 1970 and the only change in the qualitative and quantitative composition is the addition of (b) (4) magnesium stearate for the proposed drug product in this NDA. Since the addition of (b) (4) magnesium stearate is supported by comparative dissolution data and dissolution data of two bioequivalent BE batches (see below), the Applicant has provided sufficient justification to support reliance on literature publications which used the Bayer 2502 Lampit drug product.

Bridging to support formulation, image and manufacturing site change:

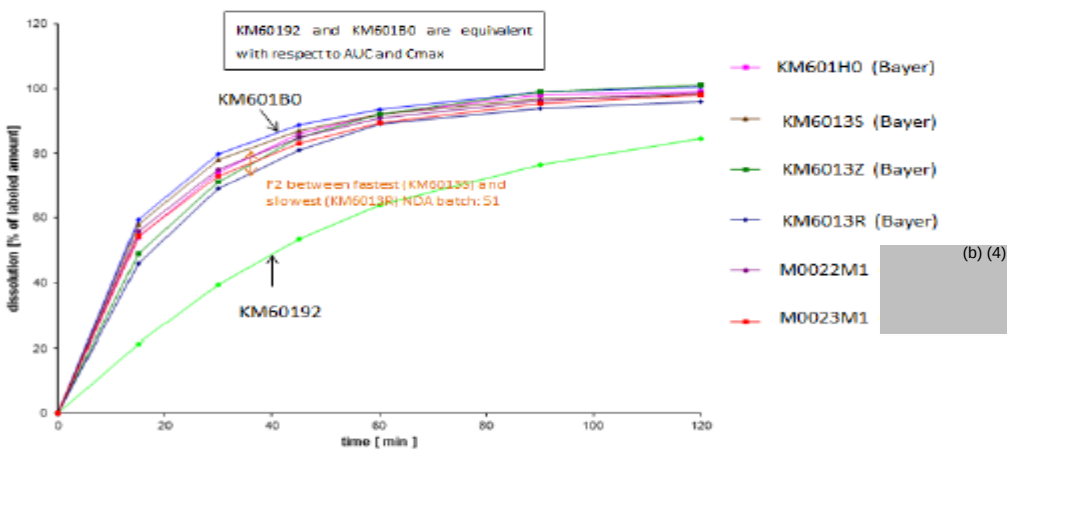
The Applicant is proposing to make the following changes to the pivotal clinical formulation for both 30 mg and 120 mg strengths:

- Addition of (b) (4) magnesium stearate in the commercial formulation.
- The commercial drug product will be debossed on one side with 30 or 120 respectively for 30 mg and 120 mg strengths, whereas the clinical drug product is not debossed.
- The drug product manufacturing site will be changed from Bayer for the clinical drug product to (b) (4) for the commercial, to-be-marketed drug product.

To support the changes, the Applicant submitted dissolution profiles of 30 mg primary stability batches manufactured at Bayer (KM6013S, KM6013Z and KM6013R) without magnesium stearate and without debossing and 30 mg registration batches manufactured at (b) (4) (batch # M0022M1 and M0023M1) which contain (b) (4)

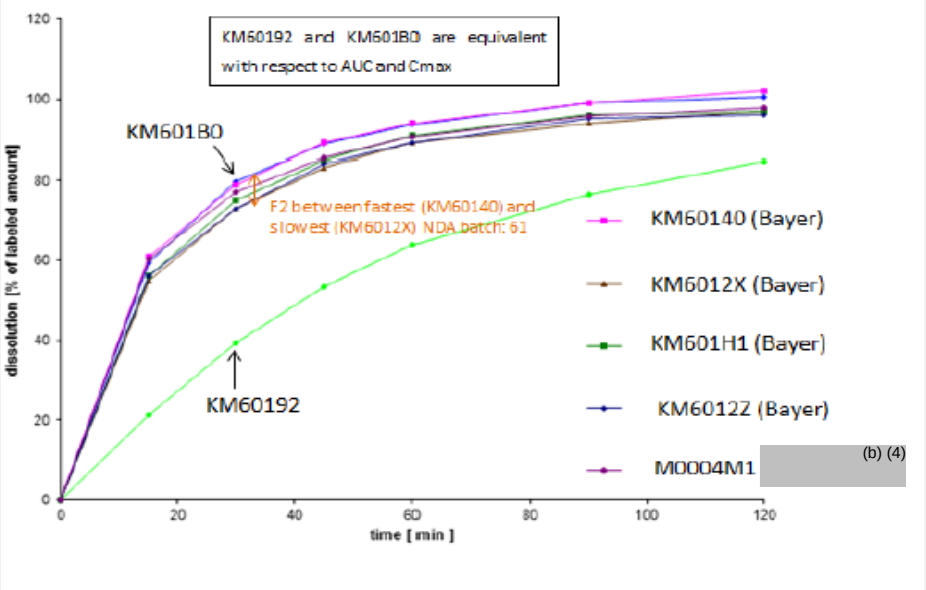
magnesium stearate and are debossed. The Applicant has compared the dissolution profiles of these before and after change batches to the dissolution profiles of two 30 mg tablet drug product batches (batch KM601B0 with fast dissolution and batch KM60192 with slow dissolution), that were shown to be bioequivalent in BE study #16007. The BE study was evaluated by the Office of Clinical Pharmacology and was deemed adequate. The dissolution profile comparisons are as follows,

Figure 8: Comparison of Nifurtimox tablet 30 mg batches manufactured at Bayer and (b) (4) (mean of n=6), and their relation to batches KM601B0 and KM60192 (n=12) which revealed equivalent AUC and Cmax in study 16007.



The Applicant has also submitted the dissolution profiles of primary stability batches of 120 mg (KM60140, KM6012X, KM601H1 and KM6012Z) manufactured at Bayer without magnesium stearate and without debossing and one 120 mg registration batch manufactured at (b) (4) (batch # M0004M1) which contains (b) (4) magnesium stearate and is debossed. For reference purpose, the 30 mg BE batches with fast dissolution (KM601B0) and slow dissolution (KM60192) are also included as follows,

Figure 9:
Comparison of Nifurtimox 120 mg tablet batches manufactured at Bayer and (b) (4) (mean of n=6), and their relation to batches KM601B0 and KM60192 (n=12) which revealed equivalent AUC and Cmax in study 16007.



The Applicant explains that the dissolution profiles of all batches of both strengths manufactured at Bayer and (b) (4), with and without magnesium stearate, and with or without debossing, fall within the dissolution profiles of the BE batches of 30 mg strength with fast dissolution (KM601B0) and slow dissolution (KM60192) which exhibited equivalent pharmacokinetic parameters such as AUC and C_{max} in BE study 16007. All comparative dissolution profiles of the before change (clinical drug product) and after change (commercial) drug product batches are bracketed between the dissolution profiles of the BE batches of the 30 mg strength drug products with fast dissolution (batch KM601B0) and slow dissolution (batch KM60192). Therefore, the provided dissolution data together with the dissolution data for the BE batches, support the bridge between the pivotal clinical non-debossed drug product manufactured at Bayer and the commercial debossed drug product manufactured at (b) (4)

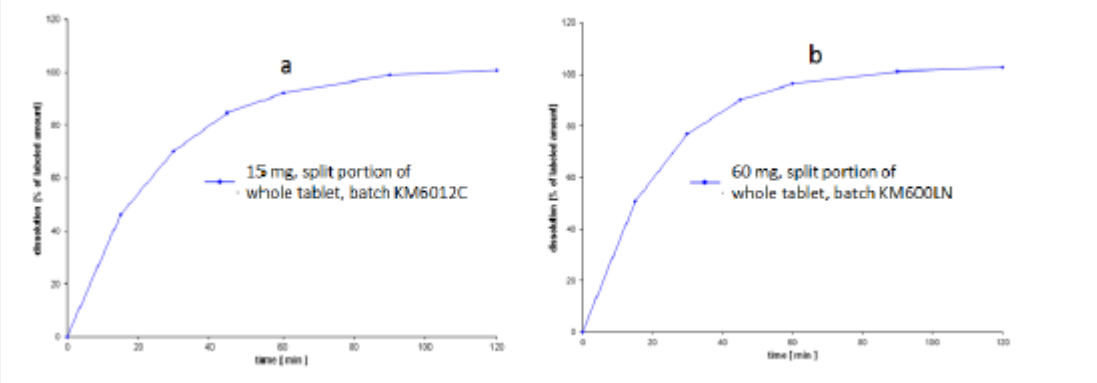
Reviewer's Assessment:

- The Applicant has provided sufficient justification to support reliance on literature publications which used the Bayer 2502 Lampit drug product.
- The provided dissolution data together with the dissolution data for the BE batches, support the bridge between the pivotal clinical non-debossed drug product manufactured at Bayer and the commercial debossed drug product manufactured at (b) (4)

B.5 DISSOLUTION DATA TO SUPPORT THE FUNCTIONAL SCORE

Both 30 mg and 120 mg Tablets have a functional score allowing to split the Tablet in two equal halves. The Applicant has submitted dissolution data and profiles of whole and split tablets of the pilot scale batches (KM6012C and KM600LN)[4].

Figure 9: Dissolution profiles of 30 mg and 120 mg Nifurtimox tablet halves (15 mg and 60 mg, respectively). One tablet half was applied per vessel using the proposed dissolution methods for the whole 30 mg tablet (a mean of n=12) and for the whole 120 mg tablet (b mean of n=12)



The Applicant is proposing to make a change to the formulation (with addition of (b) (4) % magnesium stearate) and the drug product manufacturing site (from Bayer to (b) (4)) for the to be marketed drug product. The Applicant originally did not provide dissolution data on split tablets of the registration batches of 30 mg strength (batch # M0022M1 and M0023M1) and 120 mg strength (batch # M0004M1) with the final to-be-marketed formulation, image and manufacturing site. Therefore, an IR was sent to the Applicant on 03/27/20 requesting the split tablet dissolution data for the registration batches. In the response on 04/03/2020, the Applicant has provided the comparative dissolution data (full profiles) of the split Tablets (half tablet per vessel) vs. whole Tablets for one registration batch of each strength in module 3 pharmaceutical development section[5] (page 64 and 65 of the referenced document.)

Reviewer's Assessment:

The dissolution profiles between the split tablets and the whole tablets are comparable (based on the bootstrapping analysis result: $f_2 = 72$) and therefore, the provided dissolution data are adequate to support the functional score of the proposed drug product.

[4] \\cdsesub1\evsprod\nda213464\0001\m3\32-body-data\32p-drug-prod\nifurtimox-tablets-bayer\32p2-pharm-dev\pharmaceutical-development-dissolution-profiles-tablet-30-mg.pdf

[5] \\cdsesub1\evsprod\nda213464\0026\m3\32-body-data\32p-drug-prod\nifurtimox-tablets-bayer\32p2-pharm-dev\pharmaceutical-development-dissolution-profiles-p22020205898.pdf

APPENDIX I

Biopharmaceutics Information Request dated 03/27/2020

1. *Provide a comparison between the proposed drug product and the drug products used in the key literature references that you rely on in terms dosage form, formulation (including excipients), strength, manufacturing site, dosage, route of administration, etc. Justify the differences, if any, to support your reliance on the key literature reference.*

   Response from the Applicant dated 04/03/2020[6]: *The Applicant explained that the 120 mg tablet formulation of Lampit was registered in Germany since 1970 and there is no other qualitative and quantitative change in the formulation apart from the addition of* (b) (4) *magnesium stearate for the proposed drug product in this NDA.*

2. *You have provided split Tablet dissolution data for pilot scale batches (KM6012C and KM600LN). However, you did not provide split tablet dissolution data for the registration batches. Provide comparative dissolution data (full profiles) of the split Tablets (half tablet per vessel) vs. whole Tablets for one registration batch of each strength.*

   Response from the Applicant dated 04/03/2020: *The Applicant has provided the comparative dissolution data (full profiles) of the split Tablets (half tablet per vessel) vs. whole Tablets for one registration batch of each strength in module 3 pharmaceutical development section[7] (page 64 and 65 of the referenced document.)*

3. *Based on the provided information and data, the proposed dissolution method (USP II (Paddle) at 100 rpm in 900 mL / 37°C of pH 4.5 acetate pH 4.5 with 1% SDS for 30 mg Tablet strength and 1.5 % SDS for 120 mg Tablet strength is deemed adequate for quality control testing of the proposed drug product. However, the provided dissolution data of the clinical batches and the registration batches of both 30 mg (batch # M0022M1 and M0023M1) and 120 mg (batch # M0004M1) tablet strengths manufactured at* (b) (4) *support a tighter dissolution acceptance. Implement the following dissolution acceptance criterion for batch release and stability testing for both strengths of the proposed drug product:*

   "NLT (b) (4)% (Q) in 60 minutes"

   Response from the Applicant dated 04/03/2020*: The Applicant states that the in-use stability data of the 30 mg tablet (batch # KM6012C) does not support the recommended dissolution acceptance criterion of NLT* (b) (4)*% (Q) in 60 minutes as*

[6] \\cdsesub1\evsprod\nda213464\0026\m1\us\12-cover-letters\bayers-response-to-fda-request-for-information.pdf

[7] \\cdsesub1\evsprod\nda213464\0026\m3\32-body-data\32p-drug-prod\nifurtimox-tablets-bayer\32p2-pharm-dev\pharmaceutical-development-dissolution-profiles-p22020205898.pdf

the average values are (b) (4)% after 60 minutes. The Applicant further argued that their proposed dissolution acceptance criterion of NLT (b) (4)% (Q) in 60 minutes was derived from human pharmacokinetic study 16007. The Applicant accepts FDA recommended dissolution acceptance criterion of NLT (b) (4)% (Q) in 60 minutes for batch release. However, the Applicant proposes to retain the originally proposed dissolution acceptance criterion of NLT (b) (4)% (Q) in 60 minutes for stability of the drug product.

Biopharmaceutics Information Request communicated to the Applicant on 04/28/2020:

Based on the primary stability data, all registration batches exhibit a minimum of more than (b) (4)% dissolved at 60 minutes and therefore, supports the previous FDA recommended dissolution acceptance criterion of NLT (b) (4)% (Q) in 60 minutes. It is noted that the in-use stability study was performed on Batch KM6012C, which is a development batch and not a registration batch. It appears that Batch KM6012C exhibited a slow dissolution profile even at batch release. Therefore, the dissolution acceptance criterion for your proposed drug product cannot be based on the in-use stability study for Batch KM6012C. As a result, your proposal to retain a shelf life dissolution acceptance criterion of NLT (b) (4)% (Q) in 60 minutes for stability testing of the drug product is not acceptable. Implement the following dissolution acceptance criterion for batch release and stability testing for both strengths of the proposed drug product and update all relevant sections of your NDA accordingly:

"NLT (b) (4)% (Q) in 60 minutes".

Response from the Applicant dated 04/29/20: *The Applicant accepted the recommendation to implement dissolution acceptance criterion of NLT (b) (4)% (Q) in 60 minutes for batch release and stability testing for both strengths of the proposed drug product and committed to update all relevant sections of the NDA.*

APPENDIX II

The dissolution data of the slowest stability batch of 30 mg tablet strength at 60 minutes (batch # KM6013R) is tabulated below[8]

Table 1: Batch no. KM6013R

Test Acceptance criterion	Storage duration [months]	25 °C/60 % RH	30 °C/75 % RH	40 °C/75 % RH
Dissolution after 60 minutes	Initial	89	89	89
Stage testing according to	1	-	-	92
Ph. Eur., USP, Ph. Jap.	3	88	91	90
	6	92	95	94
Q= (b) (4)%	9	89	92	-
	12	91	91	-
	18	89	89	-
	24	91	93	-
	36			
	48			
	60			

The dissolution data of the slowest stability batch of 120 mg tablet strength at 60 minutes (batch # KM6012X) is tabulated below[9]

Table 2: Batch no. KM6012X

Test Acceptance criterion	Storage duration [months]	25 °C/60 % RH	30 °C/75 % RH	40 °C/75 % RH
Dissolution after 60 minutes	Initial	89	89	89
Stage testing according to	1	-	-	89
Ph. Eur., USP, Ph. Jap.	3	90	91	93
	6	90	91	93
Q= (b) (4)%	9	87	87	-
	12	91	92	-
	18	90	93	-
	24	93	94	-
	36			
	48			
	60			

[8] \\cdsesub1\evsprod\nda213464\0026\m3\32-body-data\32p-drug-prod\nifurtimox-tablets-bayer\32p2-pharm-dev\pharmaceutical-development-dissolution-profiles-p22020205898.pdf (Page # 32 of the document)

[9] \\cdsesub1\evsprod\nda213464\0026\m3\32-body-data\32p-drug-prod\nifurtimox-tablets-bayer\32p2-pharm-dev\pharmaceutical-development-dissolution-profiles-p22020205898.pdf (Page # 58 of the document)

Mathew John

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Elsbeth Chikhale

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