CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208078Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVE

NDA 208078
Review 1

Drug Name/Dosage Form	Amifampridine Tablets
Strength	10 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Catalyst Pharmaceuticals
US agent, if applicable	N/A

Quality Review Team

Discipline	Primary Reviewer	Secondary Reviewer
Drug Substance	Sithamalli Chandramouli	Charles Jewell
Product and Labeling	Dan Berger	Wendy Wilson-Lee
Process	Kejun Cheng	Nallaperumal Chidambaram
Microbiology	N/A	--
Facility	Wayne Seifert	Ruth Moore
Biopharmaceutics	Akm Khairuzzaman	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia Walters	--
Application Technical Lead	Martha Heimann	--
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental	N/A	

Submissions Reviewed	Document Date	Disciplines Affected
SD-01, Original submission	12/16/2015	All
SD-09, Resubmission after Refuse to File	03/28/2017	All
SD-15, Response to IR	04/30/2018	Biopharmaceutics
SD-22, Labeling/PI	06/22/2018	Labeling
SD-23, Labeling/Container	05/03/2018	Labeling
SD-24, Response to IR	07/06/2018	Drug Substance, Product
SD-25, Response to IR	07/13/2018	Process
SD-28, Response to IR	08/06/2018	Product

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

Fs:

	Type			Status [1]	Date Review Completed [1]	Comments
(b) (4)	III		(b) (4)	N/A	--	
	III			N/A	--	
	III			N/A	--	
	III			N/A	--	
	III			N/A	--	
	III			N/A	--	
	III			N/A	--	
	III			N/A	--	
	III			N/A	--	

te inform e not reviewed.

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

Document	Application Number	Description
IND	106263	Sponsor: Catalyst Development of amifampridine phosphate for treatment of LEMS
IND		(b) (4)
NDA		(b) (4)

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

The OPQ review team recommends APPROVAL of NDA 208078 for Firdapse (amifampridine tablets).

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) Including Intended Patient Population	(b) (4) treatment of Lambert-Eaton myasthenia syndrome (LEMS)in adults
Duration of Treatment	Chronic
Maximum Daily Dose	80 mg
Alternative Methods of Administration	None

Lambert-Eaton Myasthenia Syndrome (LEMS) is a rare autoimmune disorder caused by antibodies to presynaptic voltage-gated calcium channels located on the presynaptic membrane of the neuromuscular junction. Inhibition of calcium entry into the nerve, and impaired release of acetylcholine from nerve terminals into the synapse results in a loss of neuromuscular transmission. LEMS is frequently associated with lung cancer, small cell carcinoma, and symptoms include weakness of proximal limb muscles and eye muscles, and disruption of the autonomic nerve system. In advanced stages, respiratory disorders may occur. LEMS generally occurs in patients older than 40 years. There is no approved treatment.

Amifampridine (also known as 3,4-diaminopyridine or 3,4-DAP) is a voltage-dependent calcium channel blocker that enhances neuromuscular transmission, providing improved muscle function. Amifampridine tablets formulated from amifampridine base have been used under compassionate use INDs for treatment of LEMS since the early 1990s. The current applicant, Catalyst Pharmaceuticals (Catalyst), is not involved in the manufacture of the product used under most of the compassionate use INDs but has provided their drug to some sponsors.

Catalyst Pharmaceuticals Catalyst seeks approval of a tablet formulation containing amifampridine, as the phosphate salt, for treatment of LEMS. The tablet formulation is marketed as Firdapse in the European Union by Biomarin Pharmaceuticals. Catalyst has licensed US rights to the formulation and the Firdapse tradename. However, the manufacturing and supply chain for the Catalyst product is independent of the European product.

B. Quality Assessment Overview

As the applicant cross-references an approved application for the CMC information to support the to-be marketed product, the OPQ review team focused on evaluation of information to support the new indication, verification that there are no outstanding regulatory activities under the (b) (4) ANDA that would preclude approval of the current NDA, evaluation of manufacturing and testing facilities, and CMC-related labeling.

Drug Substance

Amifampridine is a well-characterized simple molecule that is commercially available from non-pharmaceutical suppliers (e.g., Sigma-Aldrich) as a (b) (4) (b) (4) (b) (4) The active ingredient in Firdapse, amifampridine phosphate, is manufactured from (b) (4) (b) (4) (b) (4) The typical scale of the commercial drug substance synthesis produces approximately (b) (4) kilograms of amifampridine phosphate.

The analytical methods to control the quality of the drug substance are adequately described and validated to ensure quality control. No related impurities are observed above (b) (4) Potentially mutagenic impurities were adequately qualified in nonclinical studies or are controlled at limits consistent with the proposed maximum daily dose of amifampridine. The drug substance stability studies support a retest period of (b) (4) years.

Product

The drug product is an immediate-release, scored tablet containing 10 mg amifampridine (as 18.98 mg amifampridine phosphate). The inactive ingredients, microcrystalline cellulose, silicon dioxide and calcium stearate, comply with compendial requirements. The formulation and manufacturing process for tablets used in clinical studies are the same as the proposed commercial formulation. Clinical supplies for early studies were manufactured by a firm that will not be used for commercial production; however, supplies for the last pivotal study were manufactured at one of the two proposed commercial sites. Additional information requested during the review was provided by the applicant and is deemed adequate to support the second site.

The tablet manufacturing process consists of (b) (4) (b) (4) The critical process steps and material attributes are controlled to ensure that the product maintains its target quality attributes.

Two commercial packaging configurations, HDPE bottles with child-resistant polypropylene closures, and (b) (4) Aluminum blisters, are proposed. Both

packaging configurations are suitable for pharmaceutical use and adequately supported by the information provided.

The product specification was revised, per Agency request, to tighten the dissolution acceptance criteria. All analytical methods are straightforward and adequately validated to ensure the quality of the final drug product. In primary stability studies, no new impurities or degradants were identified, and no significant changes were observed under long-term (25°C/60% R.H.) or intermediate (30°C/65% R.H.) storage conditions. (b) (4) (b) (4) Based on the overall stability data submitted, a 24-month shelf-life is granted for product stored at 25°C/60% RH conditions.

Facilities

All facilities that will be involved in commercial manufacture and testing of amifampridine phosphate and Firdapse (amifampridine) tablets are currently acceptable.

Environmental Assessment

The applicant submitted a claim for categorical exclusion under 21 CFR § 25.31 (b). Assuming all U.S. patients use the product and no metabolism occurs, the expected introduction concentration (EIC aquatic), would be significantly below 1 ppb. The applicant states that, to their knowledge, no extraordinary circumstances exist. Thus, the claim for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations

There are no special labeling recommendations.

D. Final Risk Assessment

From Initial Risk Identification			ssessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	(b) (4)	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale • Equipment • Site	**L**		**Adequate**	
Physical stability, solid state		**L**		**Adequate**	
Functionally scored tablets: content uniformity		**M**		**Adequate**	
Functionally scored tablets: friability		**M**		**Adequate**	
Content uniformity		**L**		**Adequate**	
Microbial limits		**L**		**Adequate**	
Dissolution		**L**		**Adequate**	

Martha Heimann

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LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Adequate (FIRDAPSE® (amifampridine)
Dosage form, route of administration	Adequate (tablet, oral)
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Adequate (10 mg tablet)

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	NA

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Adequate
Strengths: in metric system	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Adequate

4. ***Section 11 Description***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Adequate
Dosage form and route of administration	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Adequate
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Adequate
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	Adequate with edits made.
Chemical name, structural formula, molecular weight	Adequate with edits made.
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	Adequate with edits made.

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Adequate with edits made.
Available units (e.g., bottles of 100 tablets)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Adequate
Special handling (e.g., protect from light)	Adequate
Storage conditions	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Adequate

Reviewer's Assessment of Package Insert: ***Adequate***
Sections 11 and 16 have been edited to add the following information: 1) pharmacological/ therapeutic class, 2) molecular weight, 3) physical properties, 4) strength of dosage form. With these edits, the prescribing information meets all regulatory requirements from a CMC perspective.

II. Labels:

(b) (4)

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

Reviewer's Assessment of Labels: ***Adequate***
The labels comply with all regulatory requirements from a CMC perspective.

List of Deficiencies: None

Overall Assessment and Recommendation:

All labeling deficiencies have been addressed. The Prescribing Information and labels comply with all regulatory requirements from a CMC perspective.

Primary Labeling Reviewer Name and Date:

Dan Berger July 26, 2018

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

Wendy Wilson July 26, 2018

Dan Berger

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Wendy Wilson- Lee

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BIOPHARMACEUTICS

NDA: 208078
Drug Product Name/Strength: FIRDAPSE® (amifampridine phosphate)® Tablets, 10 mg
Route of Administration: Oral
Applicant Name: Catalyst Pharmaceuticals, Inc.
Regulatory Path: 505 b(1), rare disease designated

Background: Catalyst Pharmaceuticals, Inc. is seeking approval for FIRDAPSE® (amifampridine phosphate) Tablets; 10 mg to be administered orally for the treatment of treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) under the 505(b)(1) path. It is to be noted that the drug product is approved in European Union (b) (4) The proposed drug product is an immediate release scored tablet containing the active ingredient, amifampridine phosphate. Inactive ingredient used in the formulation are microcrystalline cellulose (b) (4) colloidal silicon dioxide (b) (4) and calcium stearate (b) (4) The drug product is manufactured by (b) (4)

The clinical package in support of this NDA through 505(b)(1) pathway includes the results of five phase I studies evaluating safety and tolerability, food effect on bioavailability, and pharmacokinetics (including relative bioavailability study between salt and base). The primary clinical support of this NDA is supported by one Phase 3 study.

REVIEW SUMMARY

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, **2)** bridging throughout product development, **3)** the biowaiver request, and **4)** split tablet dissolution data.

Based on the review of the provided information/data, Biopharmaceutics has the following comments:

1) ***Dissolution Method and Acceptance Criteria:*** The Applicant's proposed dissolution method [*USP apparatus II (Paddle) at 75 rpm; 900 mL of 0.01N HCl at 37°C*] was fully validated and is considered ***acceptable***. As part of an Information Amendment to the NDA, the Applicant proposed to tighten the dissolution limit from Q= (b) (4) to Q= (b) (4)% in 30 minutes. The **revised** acceptance criteria of "NLT (b) (4)% (Q) in 30 minutes" is ***acceptable*** for release and on stability.

2) ***Bridging of Formulations:*** The formulation of the drug product used in the pivotal clinical studies is reported to be the same as that of the commercial drug product, except for the manufacturing process was transferred from (b) (4) site with no change in the manufacturing process (except for the change in (b) (4)). (b) (4) is the commercial manufacturing facility. All three registration batches were manufactured at the (b) (4) site. The provided dissolution profile data from both sites meet the proposed acceptance criterion and thus support the bridging between drug

products manufactured at (b) (4) sites. Since there is no formulation change, bridging between the clinical and commercial formulation-products is not needed. The bridging is ***Acceptable.***

3) ***Biowaiver Request:*** There is only one proposed strength, thus no biowaiver request in the application.

4) ***Split Tablet Dissolution:*** For the tablets manufactured at the proposed one of the commercial sites (b) (4), dissolution profiles of the manually and mechanically split tablets versus whole tablets were considered as different for the (b) (4) site only, but not for the (b) (4) site, based on calculation of the simulation factor (f_2). In response to the Information Request, the Applicant acknowledged the Reviewer's findings and attributed the issue to variability in dissolution at early time points, i.e., some product batches had (b) (4)% drug release in 30 minutes and some batches (including split tablets) were (b) (4)% dissolved in (b) (4) minutes. Such early time point variability in dissolution of the proposed drug product is deemed to have insignificant clinical relevance. Results of the study support the functional scoring of the proposed drug product.

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 208078 for FIRDAPSE® (amifampridine phosphate)® Tablets 10 mg, is recommended for **APPROVAL**.

The approved dissolution method and dissolution acceptance criterion are as follows:

USP Apparatus	Speed (RPMs)	Medium	Volume/Temp (mL/°C)	Analytical Method	Proposed Acceptance Criterion
II (Paddle)	75	0.01N HCl (pH 1.9)	900/37	HPLC	NLT (b) (4)% (Q) in 30 min

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:

Akm Khairuzzaman, PhD ***08/14/2018***
Division of Biopharmaceutics
Office of New Drug Products, OPQ

Secondary Biopharmaceutics Reviewer Name and Date:

Ta-Chen Wu, PhD 0***8/14/2018***
Division of Biopharmaceutics
Office of New Drug Products, OPQ

BIOPHARMACEUTICS ASSESSMENT

LIST SUBMISSIONS BEING REVIEWED:

eCTD # (SND #)	Received date	Document
0007 (7)	03/28/2018	Re-submission after refuse to file (not due to biopharmaceutics related issue)
0013 (13)	04/30/2018	Information Amendment
0014 (14)	05/03/2018	Information Amendment
0022 (24)	07/06/2018	Information Amendment

DRUG PRODUCT:

The proposed drug product is an immediate release scored tablet containing the active ingredient, amifampridine phosphate. Inactive ingredient used in the formulation are microcrystalline cellulose (b) (4) colloidal silicon dioxide (b) (4) and calcium stearate (b) (4). The drug product is manufactured by (b) (4)

BCS DESIGNATION

No formal BCS designation request was submitted. The drug substance is freely soluble in water. From clinical study, it was found that Amifampridine was rapidly absorbed with T_{max} between 20 min to 1 hr. The Applicant classified this drug as a BCS class 3 product. However, results from a human mass-balance study (IND # 106263, protocol # LMS-001, module 5.3.1.1) showed that the mean total recovery of parent drug and metabolites eliminated in the 0 to 24-hour urine samples represents 93.2% to 100% of the administered amifampridine dose. Therefore, these data suggest that permeability appears not to be an issue for the amifampridine absorption.

- ***Solubility***: amifampridine phosphate amifampridine phosphate is a highly soluble drug.
  Table 1. Solubility data provided by the applicant is as follows:

Solvent	Solvent required for 1 g of solute (mL)	Solubility
Water	8	Freely Soluble
Dimethyl sulfoxide	187	Slightly soluble
Glacial acetic acid	250	Slightly soluble
Methanol	750	Slightly soluble
Ethanol	1000	Very slightly soluble
N,N-Dimethylformamide	1500	Very slightly soluble

The following table and graph (provided by the Applicant) represent the proportion of protonated freebase, free base and deprotonated freebase of the drug in various pH media. As seen from the given graph below, the predominant moiety in solution at phyiologic pH is the free base.

Table 2. Proportion of moiety in solution:

Proportion (Percent) of Moiety in Solution	Solution pH				
	1.2	1.9	4.5	6.8	7.2
Protonated Freebase	(b) (4)				
Freebase					
Deprotonated Freebase					

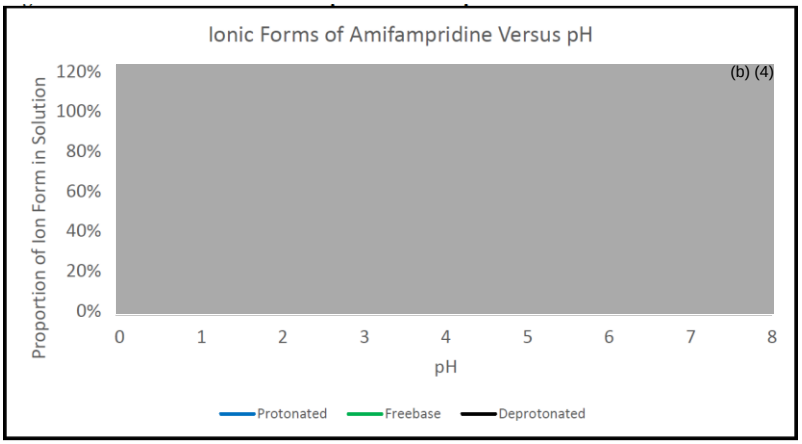

Figure. 1. Solubility profile: Ionic Forms of Amifampridine Versus pH

- ***Permeability:*** Permeability information for amifampridine phosphate was not provided in the submission. However, from the human mass-balance data it appears that permeability might not be an issue for absorption. Additionally, the Applicant reported (through Information Amendment dated 07/06/2018) that the oral bioavailability is estimated 93-100%.
- ***Dissolution***: Multi-media dissolution profile data were provided (Figure 2). Refer to the dissolution data below (Tables 3 and 4). The drug product has rapid dissolution characteristics.

➢ ***DISSOLUTION INFORMATION:***

Proposed Dissolution Method and Acceptance Criteria:

Table 2. Proposed dissolution method and dissolution acceptance criterion

USP Apparatus	Speed (RPMs)	Medium	Volume/Temp (mL/°C)	Analytical Method	Proposed Acceptance Criterion
II (Paddle)	75	0.01N HCl (pH 1.9)	900/37	HPLC	Original: NLT (b) (4) % (Q) in (b) (4) Revised: NLT (b) (4) % (Q) in 30 min

➢ ***DISSOLUTION METHOD DEVELOPMENT***

(b) (4)

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***Reviewer's Assessment:* ADEQUATE**

Dissolution method development report was found to be adequate by the reviewer. Biorelevance of the selected method is reasonable and found to be acceptable. Although no formal study on the methods discriminating capability was conducted, differences in dissolution were observed from accelerated stability samples. Since the drug has high solubility and bioavailability is calmed to be 93-100%, the overall **risk** with respect to biopharmaceutics is **low**. Therefore, the overall method is acceptable and found to be suitable as a quality control test for batch release and stability. Besides that, other in process control are in place adding further assurance to dissolution. As for example, there is a in (b) (4) (b) (4)

➢ *DISSOLUTION ACCEPTANCE CRITERIA*

Based on the manufacturing experience, dissolution profile data of BE and pivotal clinical batches, and stability data, the Applicant proposed to tighten the dissolution acceptance criterion from Q= (b) (4) (b) (4) to Q= (b) (4)% in 30 minutes for batch release and stability testing (Information Amendment dated 07/06/2018) as follows:

Q=NLT (b) (4)% in 30 min

***Reviewer's Assessment:* ADEQUATE**

The dissolution profile data (b) (4) collected from all the clinical and registration batches at release are summarized in **Table 3 & 4**. Based on the provided dissolution data, the proposed **revised** dissolution acceptance criteria of Q=NLT (b) (4)% in 30 min is acceptable. It is also to be noted that the T_{max} times appears to be very short (also discussed under biorelevance of the dissolution method earlier) and therefore a limit of Q=NLT (b) (4)% in 30 min would be more clinically relevant and would represent the dissolution profiles of the lots tested in the clinical trials.

Long term stability provided in the application shows that the recommended dissolution limit can be met in such condition. However, significant downward trend in dissolution from accelerated stability samples were observed. No explanation for such trend in dissolution was provided. Therefore, the following clarifying question were sent out to the Applicant (dated 06/26/2018).

IR Comment communicated: We noticed significant decreases in the dissolution results at (b) (4) for some lots stored under accelerated stability conditions. (b) (4) (b) (4) (b) (4)

Response: The Applicant has acknowledged it and explained that [redacted] (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Split tablet dissolution data are comparable (near overlapping) with whole tablets from (b) (4) site (Figure 4) but showed a faster profile compared to the whole tablet from (b) (4) site (Figure 3). Note that the difference is significant (f_2 is (b) (4) for manually and mechanically split, respectively) for the product made at the commercial site, but insignificant (f_2 is (b) (4) for manually and mechanically split, respectively) for the product made at the clinical site (b) (4).

(b) (4)

[redacted]

For the tablets manufactured at the proposed commercial site [redacted] (b) (4), dissolution of the manually and mechanically split tablets versus whole tablets were different (f_2= (b) (4)), but not at the clinical site, (b) (4) (f_2= (b) (4)). The Applicant attributes the observed differences to relatively slower dissolution of the whole tablet manufactured at the [redacted] (b) (4) site compared to that at the (b) (4) site. Information Request was sent out on 06/26/2018 to request further explanation. In an Information Amendment on 07/06/2018, the Applicant acknowledged the issues and explained that some batches had (b) (4)% release in 30 minutes and some product batches (or split tablets) are (b) (4)% dissolved in (b) (4) minutes. Such early time point variability in dissolution has no clinical relevance since the bioavailability is estimated 93-100%. Additionally, the Applicant proposed to tighten the dissolution limit from Q= [redacted] (b) (4) to Q= (b) (4)% in 30 min (refer to "*DISSOLUTION ACCEPTANCE CRITERIA*" section).

- ***BRIDGING OF FORMULATIONS***

The formulation of the drug product used in the pivotal clinical studies is reported to be the same as that of the commercial drug product, except for the addition of another manufacturing site, (b) (4) without any significant change in the process. (b) (4) will be the commercial drug product manufacturer.

Reviewer's Assessment: ADEQUATE

All three registration batches were manufactured at the (b) (4) site. Since it is an immediate release product and there is no formulation and manufacturing process change, in-vivo bridging between the two sites (b) (4) is not needed. Dissolution data submitted from both manufacturing sites met the revised limit of Q= (b) (4)% in 30 min.

- ***BIOWAIVER REQUEST***

None/not applicable

- **OVERALL RECOMMENDATION:**

From a Biopharmaceutics perspective, NDA 208078 for FIRDAPSE® (amifampridine phosphate)® Tablets, 10 mg, is recommended for **APPROVAL**.

Akm Khairuzzaman

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Ta-Chen Wu

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Martha Heimann

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